A Phase 3, Randomized, Study of Neoadjuvant and Adjuvant Nivolumab Plus bempegaldesleukin (NKTR-214), Versus Nivolumab Alone Versus Standard of Care in Participants with Muscle-Invasive Bladder Cancer (MIBC) Who Are Cisplatin Ineligible

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Primary Objectives• To compare the pathologic complete response (pCR) rate of neoadjuvant nivolumab + NKTR-214 to Standard of Care (SOC, no neoadjuvant therapy) in all randomized participants• To compare the event-free survival (EFS) of neoadjuvant...

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

Summary

ID

NL-OMON55385

Source
ToetsingOnline

Brief title
CA045-009

Condition

- Renal and urinary tract neoplasms malignant and unspecified

Synonym
Muscle invasive bladdercancer

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Muscle invasive bladder cancer, Nivolumab, NKTR-214, Standard of care

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 independent pathology review

• EFS, defined as the time from randomization to any of the following events: progression of disease that precludes surgery, local or distant recurrence based on BICR assessments, or death due to any cause

Secondary 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 independent pathology review

• EFS, defined as the time from randomization to any of the following events: progression of disease that precludes surgery, local or distant recurrence based on BICR assessments, or death due to any cause

• OS, defined as the time between the date of randomization and the date of death from any cause. OS will be censored on the last date a subject was known to be alive.

• Worst grade AEs, SAEs, AEs leading to discontinuation, immune-mediation AEs

and worst grade clinical laboratory values

Study description

Background summary

Patients with muscle-invasive bladder cancer (MIBC), defined as stage T2-T4a, N0, and M0, are at a high risk for the developing metastatic disease, even after receiving SOC treatment RC. For patients with MIBC who are eligible to receive cisplatin-based chemotherapy, Level 1 evidence demonstrates a significant increase in overall survival (OS) with the use of neoadjuvant chemotherapy. The SWOG 8710 Phase 3 study, which compared neoadjuvant MVAC (methotrexate, vinblastine, doxorubicin, cisplatin) plus RC to RC alone, showed a 66% increased risk of death from bladder cancer and a 33% risk of death from all causes in patients who received RC alone compared to combination treatment. Cisplatin-ineligible patients account for 40% to 50% of the total population with MIBC. Patients with MIBC who are ineligible for cisplatin-based chemotherapy due to poor renal function (usually defined as a creatinine clearance of < 60 mL/minute), advanced age, hearing loss, peripheral neuropathy, or poor performance status represent a population with a high unmet medical need because there is currently no recommended neoadjuvant therapy (or adjuvant therapy) for this group. SOC for these patients is to proceed directly to RC, which is associated with a 50% recurrence rate at 5 years, with most of these patients dying from metastatic urothelial cancer within 1 year.
This Phase 3 study in the neoadjuvant and adjuvant treatment of MIBC for patients ineligible for cisplatin will allow for direct comparison of nivolumab plus NKTR-214 versus SOC treatment with RC alone. The study is designed with an analysis of the rate of pCR and will continue follow-up for an analysis of EFS.

Study objective

Primary Objectives
• To compare the pathologic complete response (pCR) rate of neoadjuvant nivolumab + NKTR-214 to Standard of Care (SOC, no neoadjuvant therapy) in all randomized participants
• To compare the event-free survival (EFS) of neoadjuvant nivolumab + NKTR-214 followed by adjuvant nivolumab + NKTR-214 after radical cystectomy (RC) versus SOC (no neoadjuvant or adjuvant therapy)

Secondary Objectives
• To compare the pCR rate of neoadjuvant nivolumab monotherapy to SOC (no neoadjuvant therapy) at the time of surgery

• To compare the EFS of neoadjuvant nivolumab followed by adjuvant nivolumab versus SOC
• To compare the overall survival (OS) of each experimental arm versus SOC
• To assess safety and tolerability for each treatment arm

Study design

This study is an open-label, phase 3 trial aiming to demonstrate that treatment with nivolumab combined with NKTR-214 will increase the rate of pathologic complete response and prolong event-free survival (ESF) in cisplatin ineligible participants with MIBC who undergo RC.

Approximately 540 patients will be treated globally.

Participants will be randomized (1:1:1) to one of the following 3 treatment arms:
• Treatment Arm A: NKTR-214 + nivolumab every 3 weeks for a maximum of 3 cycles as neoadjuvant therapy, followed by RC, followed by NKTR-214 + nivolumab every 3 weeks up to an additional 12 cycles (approximately 9 months of adjuvant therapy).
• Treatment Arm B: Nivolumab every 3 weeeks for a maximum of 3 cycles as neoadjuvant therapy, followed by RC, followed by nivolumab every 3 weeks up to an additional 12 cycles (approximately 9 months of adjuvant therapy).
• Treatment Arm C: SOC (cystectomy alone, without neoadjuvant or adjuvant therapy).

After treatment, all subjects will enter the follow-up phase of the study. Subjects will have 2 visits within the first 100 days after stopping treatment. The remaining follow-up visits can be conducted over the phone and will occur every 3 months.

Intervention

Participants will be randomized (1:1:1) to one of the following 3 treatment arms:
• Treatment Arm A: NKTR-214 0.006 mg/kg Q3W + nivolumab 360 mg Q3W x 3 cycles as neoadjuvant therapy, followed by RC, followed by NKTR-214 0.006 mg/kg Q3W + nivolumab 360 mg Q3W up to an additional 12 cycles (approximately 9 months of adjuvant therapy).
• Treatment Arm B: Nivolumab 360 mg Q3W x 3 cycles as neoadjuvant therapy, followed by RC, followed nivolumab 360 mg Q3W up to an additional 12 cycles (approximately 9 months of adjuvant therapy).
• Treatment Arm C: SOC (Cystectomy alone, without neoadjuvant or adjuvant therapy).
Both nivolumab and NKTR-214 are provided by the sponsor.

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, immunogenicity and biomarker studies) as well as (optional) stool samples for microbiome analysis. If there is no archival tumour tissue available or the sample was taken too long ago (>=3 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, will be surveyed for disease recurrence/progression by cystoscopy, every 3 months for the next two years and then every 6 months for 3 additional years, then once per year. 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, or until Blinded Independent Central Review confirms progression or recurrence, at intervals of every 12 weeks for up to 2 years (from the date of first neoadjuvant dose), then every 24 weeks up to a maximum of 5 years. 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 NKTR-214 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)

Inclusion criteria

• Participants with MIBC, clinical stage T2-T4a, N0 (< 10 mm on CT or MRI), M0, diagnosed at TURBT within 12 weeks of randomization
• Participant must be deemed eligible for RC by urologist. Arms A and B must agree to undergo RC after completion of neoadjuvant therapy.
• PD-L1 >= 1% or PDL1 < 1% as determined by a central laboratory during the screening period and the results must be submitted to IRT prior to randomization. Indeterminate participants are allowed in the study. Formalin-fixed, paraffin-embedded (FFPE) tissue block or 20 unstained tumor tissue sections with an associated pathology report, submitted for biomarker evaluation prior to randomization. Tumor tissue sample from a biopsy may be fresh or a recent sample (< 12 weeks old), and should be from the TURBT or biopsy that made the diagnosis of MIBC. No systemic therapy (e.g., adjuvant or neoadjuvant chemotherapy) given after the sample was obtained.

• Documented left ventricular ejection fraction (LVEF) > 45% within 60 days prior to randomization using standard echocardiogram or multigated acquisition (MUGA) scan test
• ECOG performance status 0 or 1
• Cisplatin-ineligible participants:
- Impaired renal function (GFR >= 30 but < 60 mL/min); GFR should be assessed by direct measurement or, if not available, by calculation from serum/plasma creatinine
- CTCAE version 5, >= Grade 2 hearing loss
- CTCAE version 5, >= Grade 2 peripheral neuropathy

Exclusion criteria

• Clinical evidence of pathologic 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 not permitted. Prior BCG or other intravesical treatment of NMIBC is permitted if completed at least 6 weeks prior to initiating study treatment
• Evidence of UC in upper urinary tracts (ureters or renal pelvis) or history of previous MIBC.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	29-10-2020

Enrollment:	14
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	NKTR-214
Generic name:	NKTR-214
Product type:	Medicine
Brand name:	Opdivo
Generic name:	Nivolumab
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	06-03-2019
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	25-06-2019
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	05-12-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	10-07-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	14-07-2020

Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	29-12-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	27-06-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	20-12-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	09-02-2022
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	EUCTR2018-002676-40-NL
CCMO	NL68356.056.19
Other	U1111-1216-7529

Study results

Date completed: 06-10-2021

Results posted: 06-06-2024

First publication
01-01-1900