A Phase 3, Open-label, Randomized Study of Nivolumab Combined with Ipilimumab, or with Standard of Care Chemotherapy, versus Standard of Care Chemotherapy in participants with Previously Untreated Unresectable or Metastatic Urothelial Cancer

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This study has been transitioned to CTIS with ID 2022-501784-40-00 check the CTIS register for the current data. The study aims to demonstrate that treatment with nivolumab combined with ipilimumab will improve efficacy in cisplatin-ineligible...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Bladder and bladder neck disorders (excl calculi)
Study type	Interventional

Summary

ID

NL-OMON56458

Source
ToetsingOnline

Brief title
CA209-901

Condition

- Bladder and bladder neck disorders (excl calculi)

Synonym
Bladder Cancer, Urothelial Carcinoma

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Bladder Cancer, Ipilimumab, Nivolumab, Urothelial Carcinoma

Outcome measures

Primary outcome

To compare Overall Survival (OS) of nivolumab combined with ipilimumab versus standard of care (SOC) chemotherapy in cisplatin-ineligible participants with previously untreated, unresectable or metastatic urothelial carcinoma (UC). Efficacy will be evaluated by Overall Survival in cisplatin-ineligible randomized participants.

To compare OS of nivolumab combined with ipilimumab versus standard of care (SOC) chemotherapy in PD-L1 positive (>= 1%) participants with previously untreated, unresectable or metastatic UC. Efficacy will be evaluated by Overall Survival in PD-L1 positive (>= 1%) randomized participants by immunohistochemistry.

Secondary outcome

To compare OS of nivolumab combined with ipilimumab versus SOC chemotherapy in all randomized participants with previously untreated, unresectable or metastatic UC.

To evaluate Progression-Free Survival (PFS) of nivolumab combined with ipilimumab versus SOC chemotherapy in cisplatin-ineligible randomized participants, in PD-L1 positive (>=1%) randomized participants and in all randomized participants with previously untreated, unresectable or metastatic UC.

To evaluate changes from baseline in Health-Related QOL (HRQoL) of nivolumab combined with ipilimumab versus SOC chemotherapy in all randomized participants with previously untreated, unresectable or metastatic UC.

Study description

Background summary

CA209-901 is a multi-centre, phase 3 study involving adult patients with previously untreated unresectable or metastatic urothelial carcinoma. The study will compare nivolumab combined with ipilimumab or with standard of care chemotherapy followed by nivolumab alone versus standard of care platinum doublet therapy. Approximately 1792 patients will take part in this study, approximately 70 of those will be from the Netherlands.

Urothelial carcinoma (UC) of the bladder is the ninth most common cancer in the world. Approximately 20% to 25% of all patients with UC of the bladder develop metastatic disease, for which median survival is approximately 14 months.

Cisplatin is among the most active agents in UC and the gemcitabine/cisplatin doublet has become a standard regimen for patients with metastatic UC. However, in clinical practice, more than 50% of all patients with unresectable or metastatic UC have contraindications for treatment with cisplatin. While no standard treatment has been defined for cisplatin-unfit patients, carboplatin-containing regimens are considered appropriate alternatives. Despite this, combination regimens that do not include cisplatin have never been shown to improve survival, and patients who are not candidates for cisplatin-containing chemotherapy regimens have significantly worse outcomes with regard to response to treatment and overall survival (OS).
There is thus a clear need to improve upon the established standard of care in

for all patients with metastatic UC, but especially for those who are not fit to receive a cisplatin based therapy.

Cancer immunotherapy is based on the knowledge that tumours can be recognized as foreign rather than as self and can be effectively attacked by an activated immune system. Nivolumab and ipilimumab are types of immunotherapy drugs called monoclonal antibodies that work by blocking inhibitory signalling pathways in the immune response. This results in stimulation of the body*s own immune system to help attack the cancer cells. Nivolumab has demonstrated clinical activity and been approved for the treatment of several tumour types, including melanoma, advanced renal cell cancer and advanced NSCLC. Ipilimumab is approved for the treatment of melanoma (alone or in combination with nivolumab). There is a sound biological rationale for the combination of nivolumab and ipilimumab, with existing pre-clinical data suggestive of a synergistic effect. Additionally, studies in first line metastatic NSCLC provided impressive overall survival for the combination regimen, with an acceptable safety profile.

The aim of this study is to determine if the combinations of nivolumab and ipilimumab and nivolumab and standard of care chemotherapy represents an improvement in survival (progression free and overall) compared to standard of care platinum doublet chemotherapy (gemcitabine/carboplatin) in participants with previously untreated, unresectable or metastatic urothelial carcinoma that are not eligible for treatment with cisplatin. The study will also investigate the same effect in all patients randomised, i.e. in patients both eligible and ineligible for cisplatin. Changes in Health related Quality of Life from baseline will also be compared between the immunotherapy and standard of care chemotherapy groups.

Study objective

This study has been transitioned to CTIS with ID 2022-501784-40-00 check the CTIS register for the current data.

The study aims to demonstrate that treatment with nivolumab combined with ipilimumab will improve efficacy in cisplatin-ineligible participants with previously untreated unresectable or metastatic UC and also treatment with nivolumab combined with SOC chemotherapy will improve efficacy in cisplatin-eligible participants with previously untreated unresectable or metastatic UC.

Study design

This is an open-label, randomized Phase 3 clinical trial of combination immunotherapy compared to standard of care platinum doublet therapy for first line treatment in adult participants with previously untreated unresectable or metastatic urothelial carcinoma.

Participants will undergo screening test and assessments to determine eligibility and, those eligible for the study will be randomized to a treatment arm. Randomization will be done by an automated sorting process through IVRS (a telephone based computer system) which will assign participants to a treatment based on their PD-L1 status, cisplatin eligibility and presence of liver metastasis. This ensures that both all Arms are equally balanced with subject numbers for comparison at time of analysis, while maintaining the integrity of the randomization itself.

Treated participants will be evaluated for recurrence beginning on Week 9 and then every 8 weeks (± 1 week) for 48 weeks, followed by evaluations every 12 weeks thereafter, until progression, unacceptable toxicity, withdrawal of consent, or end of treatment, whichever comes first.

A Data Monitoring Committee (DMC) will be established and meet regularly during the study to ensure that subject safety is carefully monitored and to provide oversight regarding safety and efficacy considerations.

This study will include two final analyses for the co-primary endpoints (Progression Free Survival (PFS) and Overall Survival (OS)), with each to take place once the required number of events has taken place:
• The PFS final analysis will occur when there are at least 278 events among 345 cisplatin-ineligible randomized participants. This is expected approximately 41 months after the first participant*s randomization. At this time an OS interim analysis will occur (approximately 208 deaths among the same population).
• The OS final analysis is projected to occur when there are at least 348 deaths among approximately 445 cisplatin-ineligible randomized participants, approximately 55 months after the first participant*s randomization date.

Survival follow-up may continue until end of study, which is defined as the final date on which data for the primary endpoint was or is expected to be collected.

Intervention

Participants will be randomly assigned to one of the below treatment arms. They and their study doctors will be told to which group they were allocated.

Arm A:
Part 1: nivolumab 1 mg/kg plus ipilimumab 3 mg/kg given on same day every 3 weeks for 4 cycles.
Part 2: nivolumab 480 mg every 4 weeks starting 6 weeks following the last dose of combination therapy, and continuing until confirmed disease progression, unacceptable toxicity, or participant withdrawal of consent, or 24 months - whichever comes first.

Arm B:
Up to 6 cycles of Standard of care platinum chemotherapy doublet: cisplatin & gemcitabine or carboplatin & gemcitabine (only for cisplatin-ineligible participants) given at 3-weekly cycles.
Participants assigned to receive cisplatin-gemcitabine may be eligible to switch to carboplatin-gemcitabine following a minimum of 1 cycle of cisplatin-gemcitabine, and after consultation with the medical monitor.

Arm C:
Part 1: Nivolumab (360 mg + Gemcitabine-cisplatin) every 3 weeks for up to 6 cycles.
Part 2: Nivolumab monotherapy (480 mg) every 4 weeks starting 3 weeks following the last dose of combination therapy and continuing until confirmed disease progression, unacceptable toxicity, or participant withdrawal of consent, or 24 months, whichever comes first.

• Arm D: Gemcitabine - cisplatin for 6 3-weekly cycles.

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 2 years), patients will be required to have a biopsy in order to participate.

Patients will undergo radiographic assessment of their tumours by CT or MRI at screening and then every 8 weeks for the first year and every 12 weeks thereafter until disease progression or treatment discontinuation. 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.

New Immune system targeted therapy (immunotherapies) such as Nivolumab and Ipilimumab could potentially provide clinical benefit and improvements in the outcomes for patients with this disease (improvement in progression free and overall survival). 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

Public
Bristol-Myers Squibb

Uxbridge Business Park, Sanderson Road Unit 2
Uxbridge - Middlesex UB8 1DH
GB
Scientific
Bristol-Myers Squibb

Uxbridge Business Park, Sanderson Road Unit 2
Uxbridge - Middlesex UB8 1DH
GB

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

• Histological or cytological evidence of metastatic or surgically unresectable transitional cell carcinoma (TCC) of the urothelium involving the renal pelvis, ureter, bladder or urethra. Minor histologic variants (< 50% overall) are acceptable (TCC must be the dominant histology).

• Measurable disease by CT or MRI per RECIST 1.1 criteria.
• No prior systemic chemotherapy for metastatic or surgically unresectable UC with the exception of prior intravesical therapy completed more than 4 weeks prior to initiation of study treatment or prior neoadjuvant chemotherapy, radiation or prior adjuvant platinum-based chemotherapy or radiation following radical cystectomy with recurrence >= 12 months from completion of therapy.
• Cisplatin-ineligible participants will be defined by impaired renal function, hearing loss or peripheral neuropathy
• Participants must provide a fresh tumor biopsy (<3 months) from the disease site. If the primary site is not available (ie, radical cystectomy), a fresh biopsy from a metastatic site should be submitted.
• Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) 0 or 1.
• Adequate hematologic and liver function
• Prior palliative radiotherapy must have been completed at least 2 weeks prior to study drug
administration. Participants must have measurable disease outside the radiation field to be
eligible and the tumor sample be collected before (but not after) palliative RT if it is from
the irradiated area. Participants with progression in a previously radiated field will also be
eligible.

Exclusion criteria

• Disease that is suitable for local therapy administered with curative intent.
• Presence of active brain metastases or leptomeningeal metastases
• Patients who are HIV positive
• Patients who are hepatitis B or C positive
• Prior malignancy active within the previous 3 years except for locally curable cancers
• Participants must have recovered from the effects of major surgery requiring general anesthetic or significant traumatic injury at least 14 days before randomization or treatment assignment.
• Uncontrolled adrenal insufficiency.
• Any other serious or uncontrolled medical disorder or illness that may increase the risk associated with study participation or study drug administration, impair the ability of the participant to receive protocol therapy, or interfere with the interpretation of study results.
• Participants may not have received live/attenuated vaccines within 30 days prior to first study treatment.
• Treatment with botanical preparations intended for general health support or to treat the disease under study within 2 weeks prior to first study treatment.

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:	Recruiting
Start date (anticipated):	29-05-2017
Enrollment:	70
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:	Gemzar
Generic name:	Gemcitabine
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Opdivo
Generic name:	Nivolumab
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Paraplatin

Generic name:	Cisplatin
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Yervoy
Generic name:	Ipilimumab
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	14-03-2017
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	18-04-2017
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	27-07-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	08-09-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Not approved Date:	06-10-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	13-12-2017

Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	06-03-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	18-03-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	23-04-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	18-05-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	16-07-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	04-10-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	29-11-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO Date:	10-05-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	22-05-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	02-08-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	28-11-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	11-05-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	17-09-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	05-10-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	23-05-2021
Application type:	Amendment

Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	18-06-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	15-07-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	17-11-2021
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:	01-10-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	10-03-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	02-06-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO	

Date:	04-09-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	13-09-2023
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	CTIS2022-501784-40-00
EudraCT	EUCTR2016-003881-14-NL
ClinicalTrials.gov	NCT03036098
CCMO	NL60354.056.17