A Phase 3 Randomized, Double-Blind Study of Nivolumab Monotherapy or Nivolumab Combined with Ipilimumab vs Placebo in Participants with Localized Renal Cell Carcinoma Who Underwent Radical or Partial Nephrectomy and Who Are at High Risk of Relapse

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Primary ObjectivePart A: To compare disease-free survival (DFS) per Blinded Independent Central Review (BICR) of nivolumab combined with ipilimumab versus placebo infusions in participants with localized RCC, with a predominantly clear cell...

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

Summary

ID

NL-OMON53133

Source
ToetsingOnline

Brief title
CA209-914: Nivolumab and Ipilimumab in Renal Cell Carcinoma

Condition

- Renal and urinary tract neoplasms malignant and unspecified

Synonym
RCC, renal cell carcinoma

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Ipilimumab, Nivolumab, Renal Cell Carcinoma

Outcome measures

Primary outcome

The primary endpoint is DFS. The primary endpoint of DFS will be programmatically determined based on the disease recurrence date provided by the BICR. DFS is defined as the time from randomization to development of local disease recurrence (ie, recurrence of primary tumor in situ or occurrence of a secondary RCC primary cancer), distance metastasis, or death, whichever came first.

Secondary outcome

- OS, defined as the time between the date of randomization and the date of death. For participants without documentation of death, OS will be censored on the last date the participants were known to be alive.

-Safety and tolerability endpoint: type, incidence, severity (graded by the

National Cancer Institute [NCI] Common Terminology Criteria for Adverse

Events [CTCAE, Version 4.0], timing, seriousness, and relatedness, and

laboratory abnormalities in all treated participants

-DFS and OS in contemporaneously randomized combination and monotherapy

participants.

Study description

Background summary

This study is a multi-centre phase 3 study involving investigational drugs Nivolumab and Ipilimumab in patients 18 years or older who have had a partial or complete nephrectomy (removal of some or all of the kidney) but are at high risk of the tumor coming back. Approximately 2000 patients will be enrolled and 1600 treated across with world with approximately 39 in the Netherlands.

Renal cell cancer is the eighth most common cancer in the world with the incidence increasing. Despite the early detection and surgical removal of small kidney tumors, death rate is increasing suggesting the need to optimise early management. The purpose of this study is to find out if treatment with a combination of Nivolumab plus Ipilimumab and Nivolumab monotherapy given as adjuvant therapy will improve the outcomes of patients who have had a partial or full nephrectomy. To understand if the drugs improve the outcome 50% of the patients in Part A and 25% of the patients in Part B and will receive a dummy drug (placebo). The study treatment is blinded so neither you nor your doctor will know which treatment you will receive.

Cancer immunotherapy is based on the knowledge that tumors can be tumors can be recognized as foreign rather than as self and can be effectively attacked by an activated immune system. Nivolumab ad 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 serval tumor types, including melanoma, NSCLC and renal cell cancer. Ipilimumab is approved for the treatment of melanoma (alone or in combination with Nivolumab). The safety profile of Nivolumab plus ipilimumab is

characterized by immune-related toxicities such as diarrhoea, rash, liver toxicity. Most adverse events are low level with relatively few higher-grade events.

Study objective

Primary Objective
Part A: To compare disease-free survival (DFS) per Blinded Independent Central Review (BICR) of nivolumab combined with ipilimumab versus placebo infusions in participants with localized RCC, with a predominantly clear cell histology who have undergone a nephrectomy.

Part B: To compare disease-free survival (DFS) per Blinded Independent Central Review (BICR) of nivolumab versus placebo infusions in participants with localized renal cell carcinoma, with a predominantly clear cell histology, who have undergone a nephrectomy.

Secondary Objectives
Part A: To compare OS, including the 5- year OS rates, of nivolumab combined with ipilimumab versus placebo infusions in participants with localized RCC with a predominantly clear cell histology who have undergone a nephrectomy.

Part B: To compare overall survival (OS), including the 5-year OS rates, of nivolumab combined with ipilimumab vs versus placebo infusions in participants with localized renal cell carcinoma with a predominantly clear cell histology who have undergone a nephrectomy.

Part B: To evaluate differences in disease-free survival (DFS) per Blinded Independent Central Review (BICR) and overall survival (OS) of contemporaneously randomized nivolumab combined with ipilimumab participants versus nivolumab participants with localized renal cell carcinoma, with a predominantly clear cell histology, who have undergone a nephrectomy.

To describe the safety and tolerability of nivolumab combined with ipilimumab and nivolumab monotherapy.

Study design

This is a double blind, randomized trial of Nivolumab monotherapy or Nivolumab combined with Ipilimumab versus placebo infusions in patients with localized renal cell carcinoma with predominantly clear cell histology who underwent radical or partial nephrectomy. Approximately 2,000 patients will be screened, and approximately 1600 patients will be randomized globally.

Patients will be randomized between 2 parts of the study (part A or B) to

receive one of the below treatments.

Part A Treatments (Number of subjects ~ 800) in 1:1 ratio
A1.Nivolumab/Ipilimumab combination therapy (nivolumab 240 mg every 2 weeks and ipilimumab 1 mg/kg every 6 weeks (or every third nivolumab dose if dosing is delayed)
A2.Placebo (Placebo infusions at the same frequency of nivolumab and ipilimumab infusions)

Part B Treatments (Number of subjects ~ 800) in 2:1:1
B1.Nivolumab/Ipilimumab combination therapy (Nivolumab 240 mg every 2 weeks and ipilimumab 1 mg/kg every 6 weeks (or every third nivolumab dose if dosing is delayed)
B2.Placebo (Placebo infusions at the same frequency of nivolumab and ipilimumab infusions)
B3.Nivolumab monotherapy Nivolumab 240 mg every 2 weeks and ipilimumab Placebo every 6 weeks (or every third nivolumab dose if dosing is delayed)

Randomisation will be done by an automated system and patients will be assigned treatment based on their tumor pathology and by type of nephrectomy procedure (partial versus radical).

The nephrectomy must be done no less than 4 weeks and no more than (or equal to) 12 weeks prior to randomization.

Tumor tissue obtained within 3 months prior to enrolment, preferably at the time of the nephrectomy, must be provided for biomarker analyses.

Screening/baseline imaging should be performed at least 4 weeks post nephrectomy and submitted to the radiology vendor for BICR (blinded independent central review committee) confirmation of disease-free status. Pre-nephrectomy images are also requested, if available. Patient eligibility must be confirmed by BICR prior to randomization. As a result, pre-nephrectomy scans, if available, and baseline scans are encouraged to be submitted to BICR within 8 weeks of the nephrectomy to allow for timely return of the decision from the BICR.

Treatment must be completed within 36 weeks after the first dose; any cycles not received within 36 weeks after the first dose will be omitted, and the patient will enter the Follow-up Phase.

Tumor assessments will occur in accordance with the Schedule of Activities or until recurrence has been identified by the investigator and is confirmed by BICR. PK and immunogenicity samples, biomarker assessments, and Quality of life questionnaires will be collected according to the Schedule of Activities. Adverse event assessments will be documented at each clinic visit.

The Follow-up Phase begins at the completion of 12 cycles, when the decision to discontinue a patient from study therapy is made (no further treatment with study therapy), or at Week 36, whichever comes first. Patients will have 2 follow-up visits (FU1 and FU2) for safety within approximately 30 and 100 days, respectively, from the last dose of study therapy. Any ongoing treatment related AEs will be followed until the toxicities resolve, return to baseline, or are deemed irreversibly. After the Follow-up 2 Visit, all patients will be followed for overall survival status every 12 weeks (±1 week) until death, withdrawal of consent, lost to follow-up, or end of study.

Intervention

Part A Treatments
A1.Nivolumab/Ipilimumab combination therapy (nivolumab 240 mg every 2 weeks and ipilimumab 1 mg/kg every 6 weeks (or every third nivolumab dose if dosing is delayed)
A2.Placebo (Placebo infusions at the same frequency of nivolumab and ipilimumab infusions)

Part B Treatments
B1.Nivolumab/Ipilimumab combination therapy (Nivolumab 240 mg every 2 weeks and ipilimumab 1 mg/kg every 6 weeks (or every third nivolumab dose if dosing is delayed)
B2.Placebo (Placebo infusions at the same frequency of nivolumab and ipilimumab infusions)
B3.Nivolumab monotherapy Nivolumab 240 mg every 2 weeks and ipilimumab Placebo every 6 weeks (or every third nivolumab dose if dosing is delayed)

Each cycle will be 2 weeks (14 days). Patients will receive study drug until the end of 12 cycles (12 nivolumab doses and 4 ipilimumab doses), recurrence

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. Blood will also be collected at certain visits for research purposes (PK, immunogenicity and biomarker studies).
If there is no archival tissue available, or the sample was taken too long ago (more than 3 months), patients will be required to have a biopsy in order to participate. A biopsy of tumor tissue at progression is optional.
In addition, patients will undergo radiographic assessment (by CT or MRI) 23, 36 and 52 weeks after their first dose. These will then continue every 6 months until year 6 and then after every year until year 10.

The frequency of visits and number of procedures carried out in the 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 threating. An Independent Data Monitoring Committee (DMC) will be utilised in this trial to ensure that the safety data is reviewed during the trial. New immune system targeted therapy such as Nivolumab and ipilimumab could potentially provide clinical benefit and improvement in the outcomes for patients with this disease. However, with all experiential drugs and clinical trials, there are unknown risks. Study medication ad 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

a) Kidney tumor has been completely resected with negative surgical margins obtained. The
randomization must occur greater than 4 weeks and less than (or equal to) 12 weeks from
the date of nephrectomy. Partial nephrectomy is allowed provided all inclusion criteria are
met.
b) Post-nephrectomy tumor shows RCC with a predominately clear cell histology, including participants with sarcomatoid features.
c) Pathological TNM staging per AJCC staging version 2010:
i) pT2a, G3 or G4, N0M0
ii) pT2b, G any, N0M0
iii) pT3, G any, N0M0
iv) pT4, G any, N0M0
v) pT any, G any, N1M0
d) Participants must have no clinical or radiological evidence of macroscopic residual disease or distant metastases (M0) after nephrectomy
i) Baseline tumor assessment, performed 4 to approximately 12 weeks after nephrectomy, shows no metastasis or residual tumor lesions per local review and as confirmed by Blinded Independent Central Review (BICR). Results of BICR of the baseline tumor assessment confirming absence of metastasis or residual tumor lesions must be received before randomization.
Note: participants with one or more regional lymph nodes identified with short axis 15 mm on the baseline (Post-Operative) tumor assessments are considered to have gross residual disease and are therefore ineligible.
e) Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) 0-1 (Appendix 5).
f) Either a formalin-fixed, paraffin-embedded (FFPE) tissue block or unstained tumor tissue sections, obtained within 3 months prior to enrollment, preferably from nephrectomy, with an associated pathology report, must be submitted to the central laboratory prior to randomization. FFPE block or 20 unstained slides is ideal, but a minimum of 10 unstained slides will be acceptable if tumor tissue is limited. Biopsy should be excisional, incisional, or core needle. Fine needle aspiration is unacceptable for submission.
g) Males and Females, ages *18 years or age of majority.
h) Women of childbearing potential (WOCBP) must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 72 hours prior to the start of study treatment.
i) Women must not be breastfeeding.
j) Women of childbearing potential (WOCBP) must agree to follow instructions for method(s) of contraception
k) Males who are sexually active with WOCBP must agree to follow instructions

for method(s) of contraception

Exclusion criteria

a) Any severe or serious, acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or study drug administration including ongoing or active infection requiring parental antibiotics
b) Participants with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days prior to the first dose of study drug. Topical, ocular, intra-articular, intranasal, inhaled steroids, and adrenal replacement steroid doses > 10 mg daily prednisone or the equivalent are permitted in the absence of active immune disease.
c) Uncontrolled adrenal insufficiency
d) Participants with an active known or suspected autoimmune disease. Participants with type I diabetes mellitus, hypothyroidism only requiring hormone replacement, skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enrol.

Study design

Design

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

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	20-03-2018
Enrollment:	23

Type:	Actual

Medical products/devices used

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

Ethics review

Approved WMO Date:	09-05-2017
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	20-06-2017
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	15-08-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	16-09-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	24-05-2019

Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	05-08-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	24-03-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	09-04-2020
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:	01-06-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	22-07-2021
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:	18-02-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	25-02-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	27-05-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	08-10-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	19-12-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	15-02-2023
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:	01-08-2023
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
EudraCT	EUCTR2016-004502-34-NL
CCMO	NL61087.056.17

Study results

Date completed:	23-01-2024
Results posted:	30-07-2024

Summary results
Trial ended prematurely

First publication
01-01-1900