A Phase III, Randomized, Open Label Trial of Nivolumab in combination with Ipilimumab versus Pemetrexed with Cisplatin or Carboplatin as First Line Therapy in unresectable Pleural Mesothelioma

Published: 03-11-2016
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Primary Objectives:• To compare progression free survival (PFS) as determined by blinded independent central review (BICR) and overall survival (OS) of nivolumab combined with ipilimumab to pemetrexed plus cisplatin or carboplatin regimen as first...

Ethical review	Approved WMO
Status	Completed
Health condition type	Pleural disorders
Study type	Interventional

Summary

ID

NL-OMON47222

Source
ToetsingOnline

Brief title
CA209-743

Condition

- Pleural disorders

Synonym
Mesothelioma, Unresectable

Research involving

Human

Sponsors and support

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

Intervention

Keyword: Ipilimumab, Nivolumab, Pleural Mesothelioma

Outcome measures

Primary outcome

Overall survival and the progression-free survival based on Blinded Independent Committee Review (BICR) assessment are the primary endpoints of the study.

Secondary outcome

Secondary Endpoints:

*- Objective response rate (best overall response [BOR] is either a complete response [CR] or partial response [PR] per adapted m-RECIST and/or RECIST 1.1 criteria

*- Disease control rate (BOR is CR, PR, or stable disease [SD])

*- PD-L1 expression level

Exploratory Endpoints:

*- Incidence rates of adverse events, serious adverse events, deaths, and laboratory abnormalities

*- Serum concentrations of nivolumab in combination with ipilimumab

*- The improvement of the EuroWol Group*s self-reported health status measure (EQ-5D) and EQ Vas score

*- Disease-related symptom improvement rate evaluated by mesothelioma adaption

of Lung Cancer Symptom Scale (LCSS-Meso)

Study description

Background summary

Product Development Background:
Nivolumab (Opdivo) is in clinical development for the treatment of subjects with melanoma, non-small cell lung cancer (NSCLC), renal cell carcinoma (RCC), head and neck carcinoma and other tumors (eg, gastric cancer, glioblastoma multiforme, hodgkins lymphoma, small cell lung cancer). Opdivo as monotherapy has been approved in the US in multiple indications, including, unresectable or metastatic melanoma and disease progression following Ipilimumab and a BRAF inhibitor, if BRAF V600 mutation positive; previously untreated subjects with BRAF wild-type unresectable or metastatic melanoma; NSCLC with progression on or after platinum-based chemotherapy; and advanced renal cell carcinoma who have received prior anti-angiogenic therapy. The combination of nivolumab and ipilimumab has also been approved in the US for the treatment of previously untreated metastatic melanoma. Subjects with unresectable malignant pleural mesothelioma (MPM) have poor prognosis and experience limited survival benefit with standard of care platinum based therapy. Clinical data from early trials with PD-1/PD-L1 or CTLA-4 targeted therapies has shown promising activity in pre-treated MPM. To further improve clinical outcomes in subjects with unresectable MPM in the first line treatment setting, nivolumab in combination with ipilimumab is being explored in the CA209743 clinical study.

Study objective

Primary Objectives:
• To compare progression free survival (PFS) as determined by blinded independent central review (BICR) and overall survival (OS) of nivolumab combined with ipilimumab to pemetrexed plus cisplatin or carboplatin regimen as first line treatment in patients with unresectable malignant pleural mesothelioma.

Secondary Objectives:
• To compare the objective response rate (ORR) as determined by BICR, of nivolumab combined with ipilimumab to pemetrexed plus cisplatin or carboplatin as first line treatment in patients with unresectable malignant pleural mesothelioma.

• To compare the Disease Control Rate (DCR) as determined by BICR, of nivolumab combined with ipilimumab to pemetrexed plus cisplatin or carboplatin as first line treatment in patients with unresectable malignant pleural mesothelioma.
• To evaluate whether PD-L1 expression is a predictive biomarker for ORR, PFS, and OS.

Exploratory Objectives:
• To assess safety and tolerability of nivolumab combination with ipilimumab, and pemetrexed plus cisplatin or carboplatin as first line treatment in patients with unresectable pleural mesothelioma.
• To characterize pharmacokinetics of nivolumab in combination with ipilimumab as first line in patients with unresectable malignant pleural mesothelioma (MPM).
• To characterize the immunogenicity of Nivolumab in combination with ipilimumab as first line in patients with unresectable MPM
• To assess the subject*s overall health status and health utility using the 3-level version of the EQ-5D (EQ-5D-3L) visual analog scale (VAS) and utility index, respectively.
To assess the subject*s cancer-related symptoms and quality of life using the mesothelioma adaptation of the Lung Cancer Symptom Scale (LCSS-Meso)

Study design

Study Design:
This is an open label, randomized, Phase 3 study in adult (therapy for diagnosed unresectable malignant pleural mesothelioma
Subjects in each arm will be stratified by
* histology: Epithelioid vs non-epithelioid
* gender: male or female

Subjects will be randomized in 1:1 and treated with one of the following open-label treatments;
* Arm A: nivolumab administered IV over 30 minutes at 3 mg/kg every 2 weeks combined with ipilimumab administered IV over 30 minutes at 1mg/kg every 6weeks until progression, unacceptable toxicity, or other reasons specified in the protocol and for a maximum treatment duration of 2 years. Treatment beyond initial investigator-assessed and BICR confirmed progression according to adapted modified RECIST (m-RECIST) and /or RECIST 1.1 defined progression is permitted if the subject has investigator assessed clinical benefit and is tolerating nivolumab.
* Arm B: pemetrexed plus cisplatin or carboplatin chemotherapy administered on day 1 of every 21 days for up to 6 cycles. Chemotherapy treatment will continue until disease progression, unacceptable toxicity or completion of 6 cycles, whichever comes first.

On-study tumor assessments will begin at Week 6 post randomisation (+/-7 days) and be performed every 6 weeks

(+/-7 days) for the first 12 months and every 12 weeks (+/- 7 days) thereafter or until disease progression, whichever occurs later.
Enrollment will end after approximately 600 subjects have been randomised.

Intervention

The medicinal interventions include nivolumab/ipilimumab combination therapy (Arm A) and pemetrexed plus cisplatin or carboplatin chemotherapy (Arm B).

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. In addition patients will undergo radiographic assessment of their tumours (by CT). CT scan of Chest and upper abdomen, and all other known sites of disease within 28 days prior to first dose. Response will be assessed at 6 weeks (+/- 7 days) from first dose date, then every 6 weeks (+/- 7days) for the first 12 months (until week 48) and every 12 weeks (+/- 7 days) thereafter, or until disease progression is confirmed, whichever occurs first.
Subjects will have pre-treatment and optional on-treatment biopsies performed. Blood will also be collected at certain visits for research purposes (immunogenicity and biomarker studies). The frequency of visits and number of procedures carried out during this trial would typically be considered over and above standard of care. These procedures are conducted by medically trained 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. Patients will be instructed when to contact their treating physicians if side effects occur and are given a patient card with detailed information

Contacts

Public
Bristol-Myers Squibb

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Bristol-Myers Squibb

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

-Male and female subjects (18 years of age and over).
-Histologically proven diagnosis of (MPM), thoracoscopy is highly recommended.
-Advanced unresectable disease that is not amenable to therapy with curative intent (surgery with or without chemotherapy). Subjects that refuse potentially curative surgery are ineligible.
-Available (archival and/or fresh) pathological samples for centralized PD-L1 IHC testing during the screening period. Subjects cannot be randomized until the tumor tissue for PD-L1 testing has been received at the Central Lab, however, the result of the testing is not required prior to randomization. Subjects can initiate therapy before the result of PD-L1 testing is available.
-Prior palliative radiotherapy is acceptable, but at least 14 days must have passed since the administration of the radiotherapy and all signs of toxicity must have remitted.
-ECOG Performance Status of 0-1
-Weight loss < 10% during last 3 months
-Measurable disease, defined as at least 1 lesion measured in up to two positions at three separate levels on transverse cuts of CT scan that is suitable for repeated assessment using adapted modified Response Evaluation Criteria in Solid Tumors [m-RECIST] for pleural mesothelioma
-Adequate hematological, renal and hepatic functions

Exclusion criteria

-Primitive peritoneal, pericardial and tunica vaginalis testis mesotheliomas
-Brain metastasis, except if surgically resected or treated with stereotaxic radiotherapy with

no evolution within the 3 months before inclusion, and asymptomatic. In addition, subjects must be either off corticosteroids, or on a stable or decreasing dose of <=10 mg daily prednisone (or equivalent) for at least 2 weeks prior to randomization
-Prior treatment with adjuvant or neoadjuvant chemotherapy, radical pleuropneumonectomy with or without intensity modulated radiotherapy or non-palliative RT
-Prior intraoperative or intracavity chemotherapy for pleural mesothelioma
-Prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways.
-History of chronic inflammatory or autoimmune disease,
-Concurrent or prior malignancy requiring or anticipated to require concurrent intervention
-Subjects with interstitial lung disease that is symptomatic or may interfere with the detection or management of suspected drug-related pulmonary toxicity.

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):	04-08-2017
Enrollment:	18
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Alimta (Pemetrexed)
Generic name:	PEMETREXED
Registration:	Yes - NL intended use

Product type:	Medicine
Brand name:	CISPLATIN Neocorp
Generic name:	CISPLATIN
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Opdivo
Generic name:	Nivolumab
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Paraplatin
Generic name:	CARBOPLATIN
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Yervoy
Generic name:	Ipilimumab
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	03-11-2016
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	22-05-2017
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	29-06-2017
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	21-07-2017
Application type:	Amendment
Review commission:	METC NedMec

Approved WMO Date:	03-11-2017
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	09-11-2017
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	22-01-2018
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	08-11-2018
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	29-11-2018
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	08-03-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	26-07-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	29-07-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	24-10-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO	

Date:	18-11-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	01-05-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	14-05-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	11-02-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	14-06-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	24-06-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	11-12-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	23-12-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	08-04-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO	

Date:	08-06-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	28-06-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	12-08-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	15-08-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	21-02-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	09-03-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	26-05-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	05-06-2023
Application type:	Amendment
Review commission:	METC NedMec

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	EUCTR2016-001859-43-NL
CCMO	NL58915.031.16

Study results

Date completed: 26-04-2023

Results posted: 25-04-2024

First publication
01-01-1900