An Open-Label, Randomized Phase 3 Trial of Nivolumab, or Nivolumab plus Ipilimumab, or Nivolumab plus platinum doublet chemotherapy versus platinum doublet chemotherapy in Subjects with Chemotherapy-Naïve Stage IV or Recurrent Non-Small Cell Lung Cancer (NSCLC)

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The study will look at patients with chemotherapy-naive Stage IV or recurrent Non-Small Cell Lung Cancer (NSCLC). The research aims to compare a new drug called nivolumab OR nivolumab with ipilimumab (another cancer drug) OR nivolumab combined with...

Ethical review	Approved WMO
Status	Completed
Health condition type	Respiratory and mediastinal neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON47766

Source
ToetsingOnline

Brief title
CA209-227: Nivolumab in advanced Non Small Cell Lung Cancer

Condition

- Respiratory and mediastinal neoplasms malignant and unspecified

Synonym
Non-small cell lung cancer (NSCLC)

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Ipilimumab, Nivolumab, Non-small cell lung cancer (NSCLC), Stage IV/Recurrent

Outcome measures

Primary outcome

Subjects with PD-L1 expressing tumors:

• To compare *overall survival (OS)* of nivolumab in combination with

ipilimumab (Arm B) to platinum-doublet chemotherapy (Arm C) in subjects whose

tumors have greater than/equal to 1% PD-L1 expression

(The 'overall survival rate' is the percentage of people in a clinical trial

who are still alive for a certain period of time after they were diagnosed with

or started treatment for a disease, such as cancer.)

Subjects with high baseline tumor mutation burden:

• To compare OS progression-free survival (PFS based on Blinded Independent

Central Review (BICR) assessment), of nivolumab in combination with ipilimumab

(Arms B plus D) to platinum-doublet chemotherapy (Arms C plus F) in subjects

with high baseline tumor mutation burden regardless PD-L1 expression level

(Progression-free survival (PFS) is "the length of time during and after the treatment of a disease, such as cancer, that a patient lives with the disease but it does not get worse").

Secondary outcome

In subjects with previously untreated stage IV or recurrent NSCLC:

* Subjects depending on tumoral PD-L1 expression (these objectives will be hierarchically tested if the co-primary objective of OS in subjects with PD-L1 expressing tumors is positive):

•*To compare PFS, based on BICR assessment, of nivolumab in combination with platinum-doublet chemotherapy (Arm G), to platinum-doublet chemotherapy (Arm F) in subjects whose tumors do not express PD-L1 (<1%)

•*To compare OS of nivolumab in combination with platinum-doublet chemotherapy (Arm G), to platinum-doublet chemotherapy (Arm F) in subjects whose tumors do not express PD-L1 (<1%)To compare OS of nivolumab monotherapy (Arm A) to platinum-doublet chemotherapy (Arm C) in subjects whose tumors have greater than/equal to 50% PD-L1 expression

*

- Subjects with high baseline tumor mutation burden (these objectives will be hierarchically tested if the co-primary objective of PFS in subjects with high TMB tumors is positive):

•*To compare PFS (based on BICR assessment) of nivolumab monotherapy (Arm A) to platinum doublet chemotherapy (Arm C) in subjects whose tumors have >= 1% PD-L1 expression and with high baseline tumor mutation burden

•*To compare OS of nivolumab in combination with ipilimumab (Arms B plus D) to

platinum-doublet chemotherapy (Arms C plus F) in subjects with high baseline

tumor mutation burden regardless PDL1 expression level

•*To compare OS of nivolumab (Arm A) to platinum-doublet chemotherapy (Arm C)

in subjects whose tumors have greater than/equal to PD-L1 expression and with

high baseline tumor mutation burden

Study description

Background summary

This is a clinical trial of nivolumab OR nivolumab with ipilimumab OR nivolumab with platinum doublet chemotherapy, versus standard of care chemotherapy in patients with chemotherapy-naive Stage IV or recurrent Non-Small Cell Lung Cancer (NSCLC). Lung cancer is the second most common cancer in the UK and the most common cause of cancer related deaths in men and women. A significant number of patients have advanced lung cancer at diagnosis. Unfortunately with current standard of care chemotherapy, the survival rate remains poor, with less than 5% of advanced lung cancer patients alive five years on from diagnosis. There is a clear unmet medical need for patients with advanced NSCLC. Nivolumab, is a new type of immunotherapy drug which stimulates the body*s own immune system to help attack cancer cells. It works by blocking a protein on the body*s immune cells, called PD1, so that tumours can be recognised as foreign and attacked by the immune system. Ipilimumab is already on the market in the UK for the treatment of melanoma, a type of skin cancer. Following a screening period, eligible patients will be randomised to 1 of 6 treatment arms depending on their PD-L1 status and their type of NSCLC. Patients will receive either nivolumab; nivolumab and ipilimumab in combination; nivolumab and chemotherapy in combination OR chemotherapy alone. Patients will receive study drugs until their cancer progresses or their doctor decides they should come out of the study (except for the chemotherapy arm). Patients will undergo the following procedures during the study: tumour tissue biopsy (possible), CT/MRI scans, physical exams, vital signs and blood sampling for routine safety testing and study specific testing. 1980 patients will be treated in the study with approximately 30 being treated in the Netherlands.

Study objective

The study will look at patients with chemotherapy-naive Stage IV or recurrent Non-Small Cell Lung Cancer (NSCLC). The research aims to compare a new drug called nivolumab OR nivolumab with ipilimumab (another cancer drug) OR

nivolumab combined with chemotherapy against standard of care chemotherapy to see which treatment helps patients live longer without their cancer getting worse, which is known as Progression Free Survival (PFS). The study will also measure Overall Survival (OS) i.e. the length of time from the start of treatment that patients are still alive.

Study design

This is a randomised, open label six-arm study in patients with chemotherapy-naive stage IV or recurrent Non-Small Cell Lung Cancer (NSCLC). All patients will be randomly assigned to active treatment, either nivolumab alone OR nivolumab combined with Ipilimumab OR nivolumab combined with chemotherapy OR standard of care chemotherapy.
Nivolumab and ipilimumab are both immunotherapy drugs - but nivolumab works in a different way to ipilimumab. Nivolumab works by blocking a body substance called PD-L1. PD-L1 (programmed death) is a type of protein found on the surface of some cancer cells. However, as not all patients produce this protein, their PD-L1 status will be determined by immunohistochemical (IHC) staining of PD-L1 protein. This will be performed on the submitted tumour sample prior to randomisation. Subjects will be randomised into equal ratios into one of the six treatment arms. Subjects will be stratified by PD-L1 expression level and histology (squamous vs non-squamous).
Subjects will receive open-label treatment with nivolumab (Arm A); a specific regimen of nivolumab & ipilimumab in combination (Arms B and D); a regimen of nivolumab combined with chemotherapy (Arm G) or standard of care chemotherapy (Arms C and F).
Chemotherapy (Arms C and F) is administered in 3-week cycles for up to a maximum of 4 cycles of IV chemotherapy. Chemotherapy treatment will continue until disease progression, unacceptable toxicity or completion of the 4 cycles, whichever comes first. Subjects with squamous histology may receive either gemcitabine (1250 mg/m2) with cisplatin (75 mg/m2) or gemcitabine (1000 mg/m2) with carboplatin (AUC 5); subjects with non-squamous histology may receive pemetrexed (500 mg/m2) with either cisplatin (75 mg/m2) or carboplatin (AUC 6); subjects with non-squamous histology may also receive optional continuation maintenance therapy with pemetrexed alone until disease progression or unacceptable toxicity.
Nivolumab in combination with chemotherapy (arms G) is administered in 3-week cycles for up to a maximum of 4 cycles of IV chemotherapy, followed by nivolumab monotherapy or nivolumab in combination with maintenance chemotherapy every 3 weeks until disease progression or unacceptable toxicity.
Treatment with nivolumab +/-ipilimumab will be for a maximum of 24 months
After treatment, all subjects will enter the follow-up phase of the study.
Subjects will have 2 visits within the first 4 months after stopping treatment.
The remaining follow-up visits can be conducted over the phone and will occur every 3 months. The duration of the study from start of enrolment to analysis of the primary OS and PFS endpoint is expected to be 47 months. The study will

end once additional survival follow-up has concluded.

Intervention

Subjects will receive open-label treatment with nivolumab (Arm A); a specific regimen of nivolumab & ipilimumab in combination (Arms B and D); a regimen of nivolumab combined with chemotherapy (Arm G) or standard of care chemotherapy (Arms C and F).
All of these compounds 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 (including oxygen saturation levels), blood tests for safety assessment, pregnancy testing (for females of child bearing potential), and monitoring for adverse events. In addition, every 6 weeks (from week 6 until week 48) and then every 12 weeks, patients will undergo radiographic assessment of their tumours (by CT or MRI) until disease progression or treatment discontinuation whichever occurs later. Blood will also be collected at certain visits for research purposes (PK, 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. An independent Data Monitoring Committee will be utilised in this trial.

Contacts

Public
Bristol-Myers Squibb

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Ballycoolin, Dublin D15 T867
IE
Scientific
Bristol-Myers Squibb

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IE

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

- Male and female subjects over the age of 18, with ECOG status of no greater than 1.- Patients with histologically confirmed Stage IV or recurrent NSCLC (per the 7th International Association for the Study of Lung Cancer classification squamous or nonsquamous histology, with no prior systemic anticancer therapy (including EGFR and ALK inhibitors) given as primary therapy for advanced or metastatic disease.-Measurable disease by CT or MRI per RECIST 1.1 criteria.ommons/l

Exclusion criteria

- Subjects with known EGFR mutations which are sensitive to available targeted inhibitor therapy
- Subjects with known ALK translocations which are sensitive to available targeted inhibitor therapy
- Subjects with untreated CNS metastases are excluded, even if asymptomatic
- Subjects with an active, known or suspected autoimmune disease.
Subjects 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 enroll
-Subjects with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of randomization. Inhaled or topical steroids, and adrenal replacement steroid > 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.

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):	03-03-2016
Enrollment:	30
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:	Carboplatin
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:	04-08-2015
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	02-11-2015
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	09-12-2015
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	24-12-2015
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	26-01-2016
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	29-01-2016
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	13-06-2016

Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	16-06-2016
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	08-02-2017
Application type:	Amendment
Review commission:	METC NedMec
Not approved Date:	08-05-2017
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	13-07-2017
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	21-07-2017
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	24-01-2018
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	15-02-2018
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	20-09-2018
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	17-10-2018

Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	01-03-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	28-03-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	13-06-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	24-06-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	29-07-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	30-08-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	23-12-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	09-01-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	23-04-2020

Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	28-04-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	10-12-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	24-12-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	23-05-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	27-05-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	07-10-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	28-10-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	08-04-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	11-06-2022

Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	02-09-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	21-09-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	21-02-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	07-03-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	26-05-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	05-06-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	23-06-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	11-07-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	04-09-2023

Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	19-09-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	14-05-2024
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	15-05-2024
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	06-08-2024
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	20-08-2024
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)

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	EUCTR2014-003630-23-NL
ClinicalTrials.gov	NCT02477826
CCMO	NL53918.031.15