An Open-Label, Randomized, Phase 3 Trial of Nivolumab versus Investigator*s Choice Chemotherapy as First-Line Therapy for Stage IV or Recurrent PD-L1+ Non-Small Cell Lung Cancer

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The study will look at patients with advanced Non-Small Cell Lung Cancer (NSCLC) whose tumours express a certain type of protein called PD-L1. The research aims to compare a new drug called nivolumab against Investigator's choice of...

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

Summary

ID

NL-OMON44891

Source
ToetsingOnline

Brief title
CA209-026 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: Pharmaceutical Industry

Intervention

Keyword: Nivolumab, Non-small cell lung cancer (NSCLC), PD-L1

Outcome measures

Primary outcome

The primary objective is to compare the Progression Free Survival, based on Independent Radiographic Review, of nivolumab monotherapy versus investigator choice chemotherapy in subjects with stage IV or recurrent NSCLC with strongly positive PD-L1 tumour expression.

Secondary outcome

• To compare the objective response rate (ORR), based on IRRC assessment, of nivolumab monotherapy and investigator*s choice chemotherapy in subjects with stage IV or recurrent NSCLC with strongly PD-L1+ tumor expression.

• To compare the PFS, based on IRRC assessment, of nivolumab monotherapy with investigator*s choice chemotherapy in subjects with stage IV or recurrent NSCLC with any PD-L1+ tumor expression.

• To compare overall survival (OS) associated with nivolumab monotherapy and investigator*s choice chemotherapy in subjects with stage IV or recurrent NSCLC with strongly PD-L1+ tumor expression.

• To evaluate the proportion of randomized subjects exhibiting disease-related symptom improvement by 12 weeks as measured by the Lung Cancer Symptom Score (LCSS) in the nivolumab monotherapy arm and the investigator*s choice

chemotherapy arm.

Study description

Background summary

Subjects with advanced NSCLC represent a great unmet medical need. Current platinum based chemotherapy (standard of care for first line therapy) provide patients with approximately 10 month median survival, and a 5 year survival rate of less than 5%.
Nivolumab has shown substantial activity in previously treated NSCLC patients. However, the potential benefit of nivolumab monotherapy over standard of care first-line chemotherapy is not yet known. The current platinum-based first line chemotherapy regimens have similar clinical activity and well characterized safety profiles. Nivolumab has a different safety profile, characterized by liver toxicity, pneumonitis, diarrhea, and endocrinopathies, which are mostly low grade and manageable with the use of corticosteroids.
In order to assess the potential benefit of nivolumab monotherapy over current first-line chemotherapy, a randomized trial comparing nivolumab monotherapy to investigator*s choice chemotherapy in subjects with stage IV or recurrent NSCLC is needed.
Preliminary data suggest that PD-L1+ tumor expression may be associated with response to nivolumab. Therefore, to increase the potential benefit to risk ratio, this study will select only those subjects with PD-L1 tumor expression.

Study objective

The study will look at patients with advanced Non-Small Cell Lung Cancer (NSCLC) whose tumours express a certain type of protein called PD-L1. The research aims to compare a new drug called nivolumab against Investigator's choice of chemotherapy to see which treatment helps patients, who are strongly PD-L1 positive, live longer without their disease getting worse, this is known as progression free survival (PFS).

Study design

This is an open-label, 2-arm, randomized, Phase 3 study in adult male and female subjects with chemotherapy-naive stage IV or recurrent non-small cell lung cancer with PD L1+ tumor expression. PD-L1 status will be determined by immunohistochemical (IHC) staining of PD-L1 protein. This will be performed on the submitted tumor sample prior to randomization.
Subjects will be randomized 1:1 into one of the two treatment arms. They will be stratified by PD-L1 expression level (< 5% versus greater than or equal to 5%) and histology (squamous vs non-squamous).

Subjects will receive open-label treatment with one of the following:
• Arm A: Nivolumab 3 mg/kg IV every 2 weeks until disease progression or unacceptable toxicity. Nivolumab treatment beyond initial investigator-assessed RECIST 1.1 defined progression is permitted if the subject has investigator assessed clinical benefit and is tolerating nivolumab
• Arm B: Investigator*s Choice Chemotherapy is administered in 3-week cycles for up to a maximum of 6 cycles of IV chemotherapy. Chemotherapy treatment will continue until disease progression, unacceptable toxicity or completion of the 6 cycles, whichever comes first. Choice of chemotherapy regimens is dependent on NSCLC histology.
* Squamous: gemcitabine (1250 mg/m2) with cisplatin (75 mg/m2) (gemcitabine administered Day 1 and Day 8 of each cycle); or gemcitabine (1000 mg/m2) with carboplatin (AUC 5) (gemcitabine administered Day 1 and Day 8 of each cycle); or paclitaxel (200 mg/m2) with carboplatin (AUC 6).
* Non-Squamous: pemetrexed (500 mg/m2) with either cisplatin (75 mg/m2) or carboplatin (AUC 6). Non squamous subjects who have stable disease or response after Cycle 4 are permitted to continue pemetrexed alone as maintenance therapy until disease progression or unacceptable toxicity.
Subjects who progress on or after chemotherapy may be eligible to receive optional crossover nivolumab, as long as they meet certain protocol specific criteria. There is a separate ICF Addendum for consenting patients onto the crossover nivolumab.
After treatment in either Arm A or B subjects will enter the follow-up phase of the study. Subjects will have 2 visits within the first 3 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 PFS endpoint is expected to be 33 months. The study will end once additional survival follow-up has concluded.

Intervention

The medicinal interventions include nivolumab or Investigator's choice of: gemcitabine, cisplatin, carboplatin, pemetrexed and paclitaxel. All of these compounds will be supplied by the sponsor.

Nivolumab is given intravenously every 2 weeks continuing will depend on the subject*s response to the medicine. The other investigator choice chemotherapies will be given intravenously every 3 weeks for up to a maximum of 6 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 (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
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Scientific
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

- ECOG Performance Status of less than or equal to 1.
- Subjects with histologically confirmed Stage IV or recurrent NSCLC, squamous or nonsquamous histology, with no prior systemic anticancer therapy (including EGFR and ALK inhibitors) given as primary therapy for advanced or metastatic disease. Prior adjuvant or neoadjuvant chemotherapy is permitted as long as the last administration of the prior regimen occurred at least 6 months prior to enrollment.
- Measurable disease by CT or MRI per RECIST 1.1 criteria.
- Subjects must be PD-L1+ on IHC testing performed by the central lab during the Screening period.
- Men and women, ages 18 years of age and above.

Exclusion criteria

- Subjects with known EGFR mutations which are sensitive to available targeted inhibitor therapy (including, but not limited to, deletions in exon 19 and exon 21 [L858R] substitution mutations) are excluded. All subjects with non-squamous histology must have been tested for EGFR mutation status; use of an FDA-approved test is strongly encouraged. Non-squamous subjects with unknown or indeterminate EGFR status are excluded.
- Subjects with known ALK translocations which are sensitive to available targeted inhibitor therapy are excluded. If tested, use of an FDA-approved test is strongly encouraged. Subjects with unknown or indeterminate ALK status may be enrolled.
- Subjects with untreated CNS metastases are excluded. Subjects are eligible if CNS metastases are adequately treated and subjects are neurologically returned to baseline (except for residual signs or symptoms related to the CNS treatment) for at least 2 weeks prior to enrollment. In addition, subjects must be either off corticosteroids, or on a stable or decreasing dose of less than or equal to 10 mg daily prednisone (or equivalent).
- Subjects with previous malignancies (except non-melanoma skin cancers, and the following in situ cancers: bladder, gastric, colon, cervical/dysplasia, melanoma, or breast) are excluded unless a complete remission was achieved at least 2 years prior to study entry and no additional therapy is required or anticipated to be required during the study period.
- Subjects with an active, known or suspected autoimmune disease. Subjects with type I diabetes mellitis, 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.

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:	Recruitment stopped
Start date (anticipated):	25-06-2014
Enrollment:	21
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:	Nivolumab
Generic name:	BMS-936558
Product type:	Medicine
Brand name:	Paraplatin
Generic name:	Carboplatin
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Taxol

Generic name:	Paclitaxel
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	29-04-2014
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	03-06-2014
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	31-07-2014
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	12-08-2014
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	14-11-2014
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	24-11-2014
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	27-01-2015

Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	13-02-2015
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	16-02-2015
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	23-04-2015
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	27-05-2015
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	08-06-2015
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	30-09-2015
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	02-10-2015
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

Approved WMO Date:	21-03-2016
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	15-04-2016
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	02-08-2016
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	06-09-2016
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	25-11-2016
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	22-12-2016
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	02-02-2017
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	23-02-2017
Application type:	Amendment

Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	11-05-2017
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	17-05-2017
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	16-01-2018
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	30-03-2018
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	24-11-2020
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	02-09-2021
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	09-09-2021
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

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	EUCTR2012-004502-93-NL
ClinicalTrials.gov	NCT02041533
CCMO	NL47867.031.14

Study results

Results posted: 06-02-2023

First publication
01-01-1900