An Open-label, Randomized, Phase 3 Study of Nivolumab or Chemotherapy in subjects with Relapsed Small-cell Lung Cancer after Platinum-based First Line Chemotherapy

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Ethical review	Not approved
Status	Will not start
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON42328

Source
ToetsingOnline

Brief title
CA209-331

Condition

- Other condition

Synonym
Small-cell Lung Cancer

Health condition

neoplasms in the lung

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Chemotherapy, Nivolumab, Small-Cell Lung Cancer

Outcome measures

Primary outcome

To compare the overall survival of Nivolumab versus Topotecan in subjects with relapsed SCLC after platinum based, first-line chemotherapy.(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.)

Secondary outcome

The secondary objectives are as follows:

To compare progression free survival of Nivolumab versus Topotecan.

To compare the objective response rate of Nivolumab versus Topotecan.

(Objective Response Rate: The percentage of patients whose cancer shrinks or disappears after treatment.)

Study description

Background summary

CA209-331 is a multi-centre, phase 3 study involving adult patients with relapsed Small Cell Lung Cancer (SCLC) that have been treated with prior

platinum-based chemotherapy. The study will involve an investigational drug called Nivolumab given alone to patients or patients will be given Topotecan. Lung cancer is the second most common cancer in the UK and the most common cause of cancer related deaths in men and women. Once patients with Small Cell Lung Cancer have been treated with their platinum based first-line therapy about 80% of these patients will experience disease progression. Patients that have progressed are rechallenged with either platinum doublet therapy or Topotecan. However despite this treatment, the median overall survival rate is 10 months. Therefore for patients with relapsed Small Cell Lung Cancer there is a high unmet medical need for further treatment.
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. The hypothesis of this study is that due to the immune response seen in patients with Small Cell Lung Cancer patients may experience an increase in their overall survival due to Nivolumab. Approximately 480 patients will take part in this study. 16 of those will be from the Netherlands.

Study objective

In Small Cell Lung Cancer patients the purpose of this study is to compare the overall survival of patients on Nivolumab with patients on Topotecan after they have been treated with platinum -based first line chemotherapy.

Study design

This is a randomised, open label, two arm study in adult patients with relapsed Small Cell Lung Cancer treated with prior platinum-based, first-line chemotherapy.

Patients will undergo three phases of the study: Screening, Treatment and Follow up.

Screening:
Patients will undergo various procedures to determine if they are eligible for the trial. All patients that are eligible will be randomly assigned to active treatment, either with Nivolumab or with Topotecan. Patients will be allocated treatment based on their response to their first-line treatment and also if they have any brain tumours present.

Treatment:
Nivolumab is an immunotherapy drug. 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. .Topotecan is currently approved in the Netherlands to treat Small Cell Lung Cancer.

Subjects that receive Nivolumab (Arm A) will be administered Nivolumab on Day 1 of a 14 day cycle as an IV infusion over 30mins. These patients will receive a dose of 240mg.
Patients that receive Topotecan (Arm B) will be administered Topotecan daily on Days 1-5 of a 21 day cycle. These patients will receive a dose of 1.5mg/m2 per cycle.
Treatment will continue until disease progression, unacceptable toxicity, withdrawal of consent, the patient is lost to follow up or the study ends.

Follow Up:
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 is expected to be 22.5 months which includes a minimum follow up time of 11.5 months. The study will end when analysis of survival is complete

Intervention

The medical interventions for this trial include both Nivolumab and Topotecan. All compounds will be supplied by the Sponsor company.

Subjects will be treated with one of the following:
Arm A: Nivolumab: 240mg Intravenous infusion given on Day 1 of a 14-day cycle.
Arm B: Topotecan: 1.5mg/m2 given as a Intravenous infusion once daily on Days 1-5 of a 21-day cycle.

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 30) 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

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Signed Written Informed Consent
a) Subjects must have signed and dated an IRB/IEC approved written informed consent form in accordance with regulatory and institutional guidelines. This must be obtained before the performance of any protocol related procedures that are not part of normal subject care
b) Subjects must be willing and able to comply with scheduled visits, treatment schedule, laboratory testing, and other requirements of the study.;Target Population
a) Histologically or cytologically confirmed Small-cell Lung Cancer
b) Must have recurrence or progression after platinum-based, first line chemotherapy or chemoradiation therapy for the treatment of limited or extensive disease stage Small-cell Lung Cancer:
i)Subjects must have received at least 4 cycles of platinum-based, first-line chemotherapy for either limited or extensive stage disease or if they received less than 4 cycles, they must

have had a best overall response (BOR) of a partial or complete response after completion of chemotherapy.
ii) Subjects must have had only 1 prior regimen of platinum-based, first-line treatment.
d) Evaluable disease by CT/MRI per RECIST 1.1 criteria
e) Subject must have demonstrated disease progression based on at least one tumour assessment done after completion of chemotherapy and prior to randomization. The tumour assessments performed during screening will be used as a baseline for efficacy assessments.
f) A formalin-fixed, paraffin-embedded tumour tissue block or unstained slides of tumour sample (archival or recent) must be available for biomarker evaluation, as described in Section 5.6.1. Specimens must be received by the central laboratory prior to randomization. Biopsy should be excisional, incisional or core needle. Fine needle aspiration is insufficient.
g) Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1.
h) Subject Re-enrolment: This study permits the re-enrollment of a subject that has discontinued the study as a pre-treatment failure (ie, subject has not been randomized / has not been treated) after obtaining agreement from the medical monitor prior to re enrolling a subject. If re-enrolled, the subject must be re-consented. Only the screening procedures performed outside of the protocol specified timing (eg, > 28 days) must be repeated.
i) Prior Radiotherapy or radiosurgery to metastases of the brain or bone must have been completed at least 2 weeks prior to randomization.;3. Age and Reproductive Status
a) Men and women, less than or equal to 18 years of age
b) Women of childbearing potential (WOCBP) must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of beta-human chorionic gonadotrophin) within 24 hours prior to the start of study drug.
c) Women must not be breastfeeding
d) WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with plus 5 half-lives of nivolumab (half-life up to 25 days) plus 30 days (duration of ovulatory cycle) for a total of 23 weeks post-treatment completion (for subjects treated in Arm A).
WOCBP must also agree to follow instructions for method(s) of contraception for the duration of treatment plus 5-half lives of chemotherapy plus 30 days (duration of ovulatory cycle) for a total of 30 days post treatments completion or a duration specified by the local labels of the chemotherapy drugs received, whichever is longer (for Subjects treated with Arm B).;e) Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with nivolumab plus 5 half-lives of nivolumab plus 90 days (duration of sperm turnover) for a total of 31 weeks post treatment completion (for subjects treated in Arm A).
Males who are sexually active with WOCBP must also agree to follow instructions for method(s) of contraception for the duration of treatment with chemotherapy plus 5 half-lives of chemotherapy plus 90 days (duration of sperm turnover) for a total of 90 days post treatment completion or a duration specified by the local labels of the chemotherapy drugs received, whichever is longer or a duration specified by the local labels of the chemotherapy drugs received, whichever is longer (for subjects treated in Arm B).;f) Azoospermic males and WOCBP who are continuously not heterosexually active are exempt from contraceptive requirements. However they must still undergo pregnancy testing as described in this section.

Exclusion criteria

1. Target Disease Exceptions
a) Active symptomatic central nervous system (CNS) metastases. Subjects are eligible if CNS metastases have been treated and subjects have neurologically returned to baseline (except for residual signs or symptoms related to the CNS treatment) for at least 2 weeks prior to randomization. In addition, subjects must have been either off corticosteroids, or on a stable or decreasing dose of < or equal to 10mg daily prednisolone (or equivalent) for at least 2 weeks prior to enrolment. ;2. Medical History and Concurrent Diseases
a) Women who are childbearing potential or breastfeeding
b) Documented carcinomatous meningitis
c) Active known or suspected autoimmune disease. Subjects with an autoimmune paraneoplastic syndrome requiring concurrent immunosuppressive treatment are excluded. However, 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.
d) A condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisolone equivalent) or other immunosuppressive medications within 14 days of randomization. However, corticosteroids with minimal systemic absorption (inhaled or topical steroids or as specified in Section 3.4.3), and adrenal replacement steroid does > 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.
e) Prior therapy with anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody (including ipilimumab or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways).
f) Prior treatment with toptecan or amrubicin.
g) Interstitial lung disease that is symptomatic or may interfere with the detection or management of suspected drug-related pulmonary toxicity.
h) All toxicities attributed to prior anti-cancer therapy other than alopecia and fatigue must have been resolved to Grade 1 (National Cancer Institute Common Toxicity Criteria for Adverse Events {NCI CTCAE} version 4) or baseline before administration of study drug. Subjects with toxicities attributed to prior anti-cancer therapy that re not expected to resovle and resulted in long lasting sequelae, such as neuropathy after platinum based therapy, are permitted to enroll.
I) Other active malignancy requiring concurrent intervention
j) Previous malignancies (except non-melanoma skin cancers, and the following in situ cancers: bladder, gastric, colon, endometrial, cervical/dysplasia, melanoma, or breast) unless a complete remission was achieved at least 2 years prior to study entry AND no additional therapy is required during the study period.
k) Known medical condition that, in the investigator's opinion, would increase the risk associated with study participation or study drug administration or interfere with the interpretation of safety results.
l) Treatment with any chemotherapy, biologics for cancer, or investigational therapy within 28 days of first administration of study drug (subjects with prior cytotoxic or investigational products <4 weeks prior to treatment might be eligible after discussion between investigator and sponsor, if toxicities from the prior treatment have been resolved to CTC Grade 1 Level).

m) Major surgery or significant traumatic injury that is not recovered at least 4 days before the first dose of study drug.;3. Physical and Laboratory Test Findings
a) Positive test for hepatitis B virus surface antigen (HBV sAg) or hepatitis C virus ribonucleic acid (HCV antibody) indicating acute or chronic infection
b) Known history of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS).
c) Inadequate hematologic function defined by
i) White Blood cells <2000/mm3
ii) Absolute Neutrophil count <1000/mm3 or
iii) Platelet count <100,000mm3, or
iv) Hemoglobin level <9 g/dL.
d) Inadequate hepatic function as defined by either:
i) Total Bilirubin level * 2.5 times the UNL or
ii)Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels * 2.5 times the ULN or * 5 times the ULN if live metastates are present. ;4. Allergies and Adverse Drug Reaction
a) History of allergy or hypersensitivity to any of the study drugs or study drug components.;5. Other Exclusion Criteria
a) Prisoners or subjects who are involuntarily incarcerated
b) Subjects who are compulsorily detained for treatment of either a psychiatric or physical (eg, infectious disease) illness

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:	Will not start
Enrollment:	16
Type:	Anticipated

Medical products/devices used

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

Ethics review

Approved WMO Date:	11-08-2015
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Not approved Date:	21-12-2015
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

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	EUCTR2015-001097-18-NL
ClinicalTrials.gov	NCT02481830
CCMO	NL53917.042.15