A randomised open-label phase II trial of consolidation with nivolumab and ipilimumab in limited-stage SCLC after chemo-radiotherapy

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The primary objective is to evaluate if patients treated with chemo-radiotherapy and prophylactic cranial irradiation followed by consolidation treatment (nivolumab plus ipilimumab) have a better outcome in terms of progression-free survival (time...

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

Summary

ID

NL-OMON45134

Source
ToetsingOnline

Brief title
Phase II trial of nivolumab and ipilimumab in limited-stage SCLC

Condition

- Respiratory and mediastinal neoplasms malignant and unspecified
- Respiratory tract neoplasms

Synonym
limited stage small cell lung carcinoma

Research involving
Human

Sponsors and support

Primary sponsor: European Thoracic Oncology Platform (ETOP)
Source(s) of monetary or material Support: Bristol-Myers Squibb,ETOP;het Europees platform voor thoraxoncologie

Intervention

Keyword: ipilimumab, limited-stage disease, nivolumab, small cell lung cancer

Outcome measures

Primary outcome

The primary endpoints of this study are the progression-free survival as assessed by RECIST 1.1(time from date of randomisation until documented progression of death, if progression is not documented) and the overall survival (time from date of randomisation until death from any cause) of the patients.

Secondary outcome

Secondary endpoints are:

* Objective response (best overall response across all assessment time-points from randomisation to termination of trial treatment) determined by RECIST 1.1

* Time to treatment failure (time from date of randomisation to discontinuation of treatment for any reason)

* Adverse events graded according to CTCAE v 4.0.

Study description

Background summary

Lung cancer accounts for 12% of all incident cases of cancer, of which 13% are small cell lung cancer (SCLC). Over 90% of SCLC patients are current or past

smokers. The median age at diagnosis exceeds 70 years and most patients have at least one cardiovascular, respiratory, or metabolic co-morbidity. At the time of diagnosis, 30% of patients with SCLC will have limited stage disease, now called stage I-IIIB (IASLC). The outcome of limited disease SCLC is still poor, with a median survival (i.e. 50% of patients are still alive) of 16 to 24 months with current forms of treatment and only 15-25% long term survivors.

Because SCLC is a systemic disease, chemotherapy is and remains the backbone of the treatment. Adequate local therapy, such as resection, chest radiography and prophylactic cranial irradiation, nevertheless improves long-term survival significantly when delivered together with systemic treatment. However, both distant metastases and local recurrences remain problematic even after concurrent chemo-radiotherapy and profylactic cranial irradiation. Many targeted therapies have been evaluated in the treatment of SCLC, but, in contrast to advanced-stage NSCLC (non-SCLC), none of these have been successful.

Several studies in patients with NSCLC suggested an association of increased immune cell infiltration into tumours with improved survival. In recent years, a continuously improved identification of antigenic targets, the addition of immunoadjuvants, and the production of more efficient delivery systems have resulted in more efficient vaccines. These are able to elicit a potent immune response, leading to the development of immunotherapy as a fundamentally new treatment of NSCLC.

The adaptive immune response is triggered via effector T-cells, antigen-presenting cells (APCs) and co-stimulatory signals mediated by T cell receptors such as CD28. The interplay of these signals results in the activation and clonal proliferation of T cells.
T-cell proliferation is tightly regulated in order to avoid autoimmunity. The balance between co-stimulatory signals mediated by CD28 and co-inhibitory signals via so called immune checkpoint receptors is crucial for the maintenance of self-tolerance and to protect tissues from damage during normal immune response. After activation, T-cells express the immune checkpoint receptors cytotoxic T-lymphocyte antigen-4 (CTLA-4) and programmed cell death protein 1 (PD-1).

CTLA-4- and PD-1 expressing T-cells play a critical role in maintaining self-tolerance but are also responsible for non-responsiveness to tumour antigens. Cancer cells escape from immune surveillance by expressing immune checkpoint receptors. The goal of immune checkpoint inhibitor therapies is not to activate the immune system to attack particular tar-gets on tumour cells, but rather to remove inhibitory pathways that block effective anti-tumour T cell responses.

Ipilimumab is a monoclonal antibody that binds to CTLA-4 and inhibits the interactions with the ligands B7.1 and B7.2,

Nivolumab is a monoclonal antibody that targets PD-1. Engagement of PD-1 by its natural ligands, PD-L1 and PD-L2, results in an inhibition of T cell proliferation, survival and cyto-kine secretion. Nivolumab abrogates this interaction between PD-1 and its ligands.

The two antibodies, nivolumab and ipilimumab, do not only target different immune cell receptors, they also regulate distinct inhibitory pathways and have therefore non-overlapping mechanisms of action. A combination treatment with anti-CTLA-4 (e.g. ipilimumab) plus anti PD-1 (e.g. nivolumab) or anti-PD-L1 antibodies should enable the creation of an immunogenic tumour microenvironment with subsequent clinical benefit for patients.

Nivolumab plus ipilimumab will be administered as a consolidation treatment after completion of a standard treatment including chemo-radiotherapy and prophylactic cranial irradiation (PCI).

Study objective

The primary objective is to evaluate if patients treated with chemo-radiotherapy and prophylactic cranial irradiation followed by consolidation treatment (nivolumab plus ipilimumab) have a better outcome in terms of progression-free survival (time from date of randomisation until documented progression of death, if progression is not documented) and overall survival (time from date of randomisation until death from any cause), compared to patients treated with chemo-radiotherapy and prophylactic cranial irradiation without consolidation treatment.

Secondary objectives are:
* to evaluate secondary measures of clinical efficacy including objective response rate (best overall response across all assessment time-points from randomisation to termination of trial treatment) and time to treatment failure (time from date of randomisation to discontinuation of treatment for any reason)
* to assess the safety and the tolerability of the treatment in both arms.

Study design

This is an open-label, randomised, two-arm, phase II international multi-centre clinical trial with interim analysis for safety in patients with radically treated limited-stage small cell lung carcinoma following completion of thoracic radiotherapy concomitant to chemotherapy and prophylactic cranial irradiation.

The trial consists of the following phases:
* Screening: baseline evaluations must be done within 28 days prior to enrolment
* Chemotherapy: will be started in the week following enrolment and consist of 4 cycles of cisplatin or carboplatin and etoposide, repeated every 3 weeks ;

Thoracic radiotherapy: twice-daily over 3 weeks or once-daily over 6 weeks, with start on day 1 of the first or second chemotherapy cycle ; Prophylactic cranial irradiation: start between day 8 and day 15 of cycle 4 of chemotherapy and finished no later than day 29 from start of cycle 4.
* Randomisation: should take place 5-6 weeks after day 1 of cycle 4 of chemotherapy. Only patients without disease progression can be randomised into one of two treatment arms:
° Arm 1: Nivolumab + Ipilimumab consolidation, consisting of induction phase (nivolumab + ipilimumab once every 3 weeks x 4 cycles - started 1-2 weeks after randomisation) and maintenance phase (nivolumab once every 2 weeks for a maximum of 12 weeks - first dose 3 weeks after last dose of induction phase)
° Arm 2: Observation (no further study treatment)
* End of treatment: Arm 1: within 30 days following the last administered dose of trial treatment
Arm 2: within 30 days of tumour progression or
15 months after randomisation
Non-randomised subjects: within 30 days
following tumour progression or within 30 days following the last chemotherapy cycle.
* Follow-up period: Before tumour progression: in first 18 months after randomisation: together with CT scans, then every 12 (+/- 1) weeks until

tumour progression for a maximum of 4,5 years after the enrolment of the last patient.
After tumour progression: every 12 weeks in the
1st year after randomisation starting from the date of progression,
then
every 6 months up to 4.5 years after enrolment of the last patient. This applies to all patients
who
have been enrolled but not randomised.

Intervention

After enrolment, the patient will receive standard of care treatment for limited-stage small cell lung cancer, consisting of:
* Chemotherapy: will be started in the week following enrolment (alternatively, maximum 1 cycle of chemotherapy may be administered before enrolment), and consists of a total of 4 cycles of cisplatin (25 mg/m2 i.v. days 1 * 3 or 75 mg/ m2 on day 1) or carboplatin (AUC 5-6 i.v. on day 1), plus etoposide (100 mg/ m2 i.v. days 1 * 3), repeated every 3 weeks (+/- 3 days without cycle delay)
* Concomitant thoracic radiotherapy: accelerated twice-daily administration of 1.5 Gy × 30 over three weeks (preferred) or once-daily administration of 2 Gy over six weeks. Two options are allowed: thoracic radiotherapy MUST start either from day 1 of cycle 1 or day 1 of cycle 2. Start on day 1 of cycle 3 is allowed if patient is enrolled after the first cycle only but should be exceptional.

* Prophylactic cranial irradiation: 25 Gy in 10 fractions started between day 8 and day 15 of cycle 4 and finished no later then day 29 from start of cycle 4.

After randomisation (should take place 5-6 weeks after Day 1 of cycle 4):
* Arm 1 (Experimental arm):
° Induction phase: nivolumab (at a dose of 1 mg/kg) + ipililumab (at a dose of 3mg/kg) every 3 weeks × 4 cycli, start 1-2 weeks after randomisation
° Maintenance phase: nivolumab (240 mg) every 2 weeks for a maximum of 12 months from the start of the maintenance. The first dose will be administered 3 weeks after the last doses of the induction phase
* Arm 2 (Observational arm): Observation

Study burden and risks

Physical, radiological and lab examinations will be performed at the time of study entry. In women who could become pregnant, a pregnancy test will be done on blood serum or urine within 7 days prior to the start of the chemotherapy. The test needs to be repeated within 7 days before randomisation, thereafter each 6 weeks during the consolidation phase. A pregnancy test needs to be repeated around 30 days and around 70 days after the end of the consolidation phase. During the first phase of the study treatment (chemoradiotherapy) and during the induction phase (first part of the consolidation phase), patients will visit the study doctor every 3 weeks. During the maintenance phase (second part of the consolidation phase) the patients will visit the study doctor every 2 weeks.
Also blood samples (1 teaspoon (5ml)) will be collected prior or during enrolment in the study, at randomisation, at 9 weeks after randomisation, at 18 weeks after randomisation and at the time of tumour growth for the determination of the serum concentration of biomarkers and circulating antibodies. Additional, blood samples (0,5 - 10 teaspoons (2.5-50 ml)) for future research will be requested to collect prior or during enrolment in the study, at randomisation, at 9 weeks after randomisation and at 18 weeks after randomisation.

Radiological examinations will be performed to determine the status of the disease and the treatment effect. FDG-PET-CT may be performed at study entry, which is not a routine assessment. The patient will have to be fasting for at least 6 hours (drinking of water is allowed). Following injection of a radioactive substance in a vein, the patient will have to wait for about one hour. Then the scanning session will start and it may take up to 30 minutes. A CT of thorax and upper abdomen will be performed at the end of the standard treatment prior to randomisation and thereafter every 9 weeks (until 18 months), every 12 weeks (until year 2), every 6 months (year 3 and 4) and at week 260 (at 5 years). The doctor may also suggest other tests, such as CT of the brain, whole body PET-CT, bone scans and MRI (as appropriate). In the event

that the tumour starts to grow again, a biopsy might be taken if the patient agrees to this at that time.

Previous clinical trials suggest that a combination of nivolumab and ipilimumab could lead to a higher efficacy in a broad range of cancers, including small cell lung carcinoma (SCLC). Ipilimumab is approved by the Health Authorities in Europe, United States and Switzerland for the treatment of malignant melanoma (a type of skin cancer), but at this moment not for small cell lung carcinoma. Nivolumab has been approved for the treatment of malignant melanoma by the Health Authorities in Europe, United States and Japan, but not in Switzerland. Recently it was also approved for treatment of small cell lung carcinoma in the Unites States (since March 2015) and in Europe (since July 2015). Consolidation therapy (combination of nivolumab and ipilimumab) following the standard treatment might increase overall survival in patients with small cell lung carcinoma.

The most common side effects of nivolumab and ipilimumab are immune-related and generally medically manageable with topical and/or systemic immunosuppressants. Special attention will be given to a possible enhancement of pulmonary toxicity due to ipilimumab. A safety evaluation will take place 12 weeks after the first 30 patients have been randomised into the experimental arm (total of 60 patients, 30 in the nivolumab plus ipilimumab combination and 30 in the observation arm).

In summary, the combination of ipilimumab and nivolumab offers a significant survival benefit to patients with advanced melanoma and evidence of clinical activity in randomised studies in other tumour types, including small cell lung carcinoma. These findings, together with evidence of a safety profile that is manageable with careful monitoring and appropriate intervention for treatment of immune-mediated toxicities, suggest a favourable benefit to risk ratio.

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

At enrolment:
* histologically or cytologically confirmed small cell lung carcinoma
* untreated limited stage disease (with the exception of one cycle of chemotherapy given prior enrolment) as defined by stage I-IIIB based on 7th TNM classification (IASLC classification for small cell lung cancer proposal). M0 proven by
a) whole body FDG-PET CT including a contrast-enhanced CT of thorax and upper abdomen (incl. liver, kidney, adrenals);
OR contrast-enhanced CT of thorax and upper abdomen (incl. liver, kidney, adrenals) and bone scan;
AND
b) brain MRI (or contrast enhanced CT of the brain).
* within 28 days before start of chemotherapy
* age * 18 years
* ECOG performance status 0-1
* adequate haematological, renal, hepatic and lung function
* pulmonary function FEV1 of 1.0 L or > 40% predicted value and DLco > 40% predicted value;At randomisation:
* chemo-radiotherapy completed per protocol: 4 cycles of chemotherapy, 85% of planning target volume of thoracic radiotherapy, as well as completed, mandatory prophylactic cranial irradiation (PCI)
* non-progressive disease after chemo-radiotherapy and PCI

Exclusion criteria

At enrolment:

* patient with mixed small-cell and non-small-cell histologic features
* patient with pleural or pericardial effusions proven to be malignant
* documented history of severe autoimmune or immune mediated symptomatic disease that required prolonged (more than 2 months) systemic immunosuppressive (e.g. steroids) treatment such as ulcerative colitis and Crohn*s disease, rheumathoid arthritis, systemic progressive sclerosis (scleroderma), systemic lupus erythematosus, or autoimmune vasculitis (eg, Wegener*s granulomatosis)
*Subjects with an autoimmune paraneoplastic syndrome requiring concurrent immunosuppressive treatment.
* interstitial lung disease or pulmonary fibrosis
* women who are pregnant or in the period of lactation
* patients with any concurrent anticancer systemic therapy (except for chemotherapy cycle 1).
* HIV, Hepatitis B or Hepatitis C infection
* patients who have had in the past 5 years any previous or concomitant malignancy EXCEPT adequately treated basal or squamous cell carcinoma of the skin, in situ carcinoma of the cervix or bladder, in situ ductal carcinoma of the breast (if no radiotherapy was involved).
* previous radiotherapy to the thorax (prior to inclusion), including radiotherapy for breast cancer
* planned mean lung dose > 20 Gy or V20 > 35 %

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)

Primary purpose: Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	27-11-2015
Enrollment:	24
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:	27-03-2015
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-07-2015
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	03-07-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-03-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-05-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-06-2016
Application type:	Amendment

Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-08-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-08-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	06-07-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	27-07-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-12-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	29-01-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-08-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-11-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-01-2019
Application type:	Amendment

Review commission:	METC Amsterdam UMC
Approved WMO Date:	19-02-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-07-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	03-09-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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	EUCTR2013-002609-78-NL
ClinicalTrials.gov	NCT02046733
CCMO	NL51751.029.15