A phase II trial evaluating the safety and efficacy of the addition of concurrent anti-PD-1 nivolumab to standard first-line chemotherapy and radiotherapy in locally advanced stage IIIA/B Non-Small Cell Lung Carcinoma

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Primary objective: To assess the feasibility of the addition of nivolumab consolidation to standard first-line chemotherapy and radiotherapy in locally advanced stage IIIA/B NSCLC, as defined by the rate of grade *3 pneumonitis (CTCAE V4.0) 6 months...

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

Summary

ID

NL-OMON44704

Source
ToetsingOnline

Brief title
Phase II trial evaluating nivolumab in stage IIIA/B NSCLC

Condition

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

Synonym
locally advanced non-small cell lung cancer

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: anti-PD1, nivolumab, non-small cell lung cancer, stage IIIA/B

Outcome measures

Primary outcome

Primary endpoint:

Grade *3 pneumonitis (CTCAE V4.0) observed any time during 6 months from end of

radiotherapy; for definition, see section 14.1.

Secondary outcome

* Progression-free survival by RECIST v1.1

* Time to first grade *3 pneumonitis

* Objective response determined by RECIST v1.1

* Time to treatment failure

* Overall survival

* Adverse events graded according to CTCAE V4.0

Study description

Background summary

Over the past decade, concomitant chemotherapy and radiotherapy has become the first choice treatment for most patients with stage III non-small-cell lung carcinoma (NSCLC). Currently, approximately 30% of patients are alive 5 years

after concomitant therapy. This figure remains approximately the same with the addition of surgery. After chemo-radiotherapy, at least 30-40% of the patients show local tumour progression on CT scans as first site of relapse.
Also after surgery, about 30% of patients fail locally as a first site of recurrence. In addition, more than half of the patients eventually develop distant metastases that may have been present but undetected at the time of staging or that may have come from persistent or recurring local disease. It is thus obvious that new approaches that preferentially tackle both local and distant disease sites are needed to improve long-term survival and cure rates.
Dose-limiting toxicity of thoracic radiotherapy includes radiation pneumonitis (RP). Starting from two months after the end of radiotherapy, about 15% of the patients develop increasing dyspnoea and cough, provoked by a mixed T-lymphocyte infiltrate in lung areas that have been irradiated. RP may happen up to 6 months post-treatment, however about three quarters of RP cases occur 3 months after radiotherapy. Besides dose and volume parameters of the radiotherapy, such as the mean lung dose (MLD) or the V20 (that is the percentage of the lungs that received more than 20 Gy), the most important risk factor for developing RP is the inflammatory status of the lungs before therapy. The more baseline inflammation, the higher is the risk of RP. Inflammation in the lungs can be visualized and quantified by measuring the 18F-fluoro-D-deoxyglucose (FDG) in the lung parenchyma by standard FDG-PET-CT scans obtained at the time of staging. As the relative FDG uptake in the lung vs. the aorta is used,
no specific calibration of the PET-scanner is required. Attempts to improve the long-term survival include radiotherapy dose escalation/acceleration, new chemotherapy combinations, and adding biological agents and cancer vaccines to standard regimens. At present, none of these have demonstrated an improved outcome. Improved understanding of the immune profile of NSCLC has led to immunotherapeutic strategies, including inhibitory molecules responsible for abrogating an anti-cancer immune response such as PD-1 and CTLA-4. Bristol-Myers Squibb*s nivolumab, an investigational monoclonal antibody that inhibits the immune checkpoint receptor PD-1 expressed on activated T cells, has demonstrated positive results in several trials of previously treated patients with advanced NSCLC. However, rare cases of severe or fatal pneumonitis have been
reported throughout clinical trials using anti-PD-1 or anti-PD-L1 compounds. Pre-clinical data show a clear beneficial effect by combining local radiotherapy and anti-PD-1. Not only was the local tumour control increased, but an *abscopal* effect on distant metastases could be observed. Radiotherapy clearly acted as an *in situ* tumour vaccination resulting in the induction of specific anti-tumour immunity in all sites of the body that could result in a clinical anti-tumour effect because of the combination with anti-PD-1. The initial dose and schedule of nivolumab will be 360 mg i.v. The rational for flat dosing is based on the expected similarity of safety and efficacy to the approved 3 mg/kg dose. Based on a wide therapeutic window of nivolumab monotherapy, the range of exposures with flat dosing are not expected to affect the efficacy because the exposures predicted for the 360 mg Q3W is on the flat

part of the exposure response curve. For safety, doses up to 10 mg/kg nivolumab Q2W have been well tolerated across multiple tumours and an increase in exposure is not associated with a probability of increasing adverse events. Therefore, flat dose of 360 mg Q3W for nivolumab monotherapy is recommended for further investigation in this trial. From cycle five on, nivolumab will be administered at 480 mg Q4W for up to 1 year from commencement of nivolumab treatment. Based on pharmacokinetic modelling, the 480 mg Q4W will provide similar steady-state average concentrations as 3 mg/kg. The 4-weekly schedule will be more convenient for patients. While the role of immunotherapy is currently being evaluated as monotherapy or in combination with chemotherapy or tyrosine kinase inhibitors in all lines of treatment of advanced NSCLC, as monotherapy in early NSCLC adjuvant setting as well as monotherapy in consolidation after completion of definitive chemo-radiotherapy, it has not yet been assessed in combination with radiotherapy. Historical data of concurrent treatment in the palliative setting suggest acceptable safety and a good tolerability of such combination. Initially the NICOLAS trial was set up as prospective evaluation of the safety of the checkpoint inhibition concurrent with chemoradiotherapy.
In summary, there is a definite unmet need in the multidisciplinary care to improve the prognosis of patients diagnosed with stage III NSCLC, with a strong rationale supporting the combination of chemo-radiotherapy with anti-PD-1. A major theoretical concern is the development of pneumonitis, a rare toxicity of both radiotherapy and checkpoint inhibitors. The main aim of the current trial proposal is therefore to evaluate the pneumonitis rate in patients being treated with chemotherapy and radiotherapy in combination with concomitant or sequential nivolumab treatment.
Rational for protocol amendment 2:
Since the NICOLAS trial was initiated, the landscape of combining chemo-radiotherapy with immune-checkpoint inhibition, such as anti-PD-1 antibodies, has changed rapidly, opening a new window of opportunity.
There is a very strong interest of the multidisciplinary lung cancer community to investigate the optimal integration of anti-PD-1 treatment into chemo-radiotherapy. Currently, 11 sites from 5 countries are activated for the NICOLAS trial and recruiting strongly (ahead of schedule). Using this momentum will allow us to rapidly recruit additional patients in order to reach the power to not only determine the feasibility in terms of pneumonitis grade 2 and abouve, but also to evaluate the efficacy of the concurrent treatment.
So far, during the regular safety review, the ETOP IDMC did not observe any additional toxicity compared the chemo-radiotherapy alone.
Additionally, a first planned analysis of the PACIFIC trial (stage III NSCLC treated with concurrent chemotherapy and radiotherapy, followed by the anti-PD-L1 durvalumab or observation, NCT02125461) showed an increased progression-free survival (PFS), which was co-primary endpoint together with overall survival (OS). The full details are not known, yet, but it appears that the pre-clinical rationales of combined chemo-radiotherapy and anti-PD-1 treatment can be successfully transferred into clinical trials, without serious toxicities.

A recent secondary analysis of the Keynote 001 trial indicates synergistic affects of radiotherapy and immunotherapy. This international, multicentre phase I trial assessed the effect of pembrolizumab monotherapy in patients with progressive locally advanced or metastatic NSCLC. Patients were assigned to multiple expansion cohorts to allow for the inclusion of patients who were naïve to systemic therapy and those who had progression after one or two previous regimens.
The results from this study showed that the effect of pembrolizumab was significantly higher in patients who received previous radiotherapy than in patients without previous radiotherapy (median PFS: 4.4 months versus 2.1 months, hazard ratio 0.56, p=0.019; median OS: 10.7 months versus 5.3 months, hazard ratio 0.58, p=0.026).
These findings were well in line with pre-clinical studies that underlined the ability of radiotherapy to enhance antitumour immune response.
In the absence of of serious pulmonary toxicity, the apperant benefit of chemo-radiotherapy and anti-PD-1 and the high interest of the NICOLAS study group, we propose to amend the NICOLAS trial protocol to expand on the number of patients in order to reach sufficient power for an efficacy readout (progression-free survival).

Study objective

Primary objective: To assess the feasibility of the addition of nivolumab consolidation to standard first-line chemotherapy and radiotherapy in locally advanced stage IIIA/B NSCLC, as defined by the rate of grade *3 pneumonitis (CTCAE V4.0) 6 months post-radiotherapy (see section 17: Statistical Considerations).

Most important secondary objective:
* Progression free survival after 1 year

Other secondary objectives
* To evaluate secondary measures of clinical efficacy including time to first grade *3 pneumonitis (TFP3), progression-free survival (PFS), objective response rate (ORR), time to treatment failure (TTF) and overall survival (OS).
* To assess the safety and the tolerability of the treatment.

Study design

This is a multicenter phase II trial evaluating the addition of anti-PD1 nivolumab consolidation to standard first-line chemotherapy and radiotherapy in locally advanced stage IIIA/B non-small cell lung cancer.

The trial consists of the following phases:
* Screening: within 28 days prior to enrolment
* Standard chemo-radiotherapy. Radiotherapy is given concurrent with

chemotherapy. Chemotherapy will consist of cisplatin and vinorelbine or etoposide or pemetrexed given every 3 weeks for 3 cycles. If cisplatin cannot be used, it will be replaced by carboplatin. Radiotherapy (5 days per week) is delivered concurrent with cycle 2 and 3 of chemotherapy.
* Trial treatment with nivolumab, which should start together with radiotherapy. Nivolumab is to be administered as a 30-minute infusion. The first 4 doses (360mg) are administered every 3 weeks. As from dosis 5, nivolumab (480mg) will be administered every 4 weeks. The treatment duration with nivolumab is 1 year from start of nivolumab treatment, unless treatment stops earlier due to unacceptable toxicity, disease progression or withdrawal of consent.
* Follow-up visits after trial treatment stop but before progression will take place every 9 weeks (first year after completion of chemo-radiotherapy), 12 weeks (year 2) or 6 months from year 3. Follow-up visits after progression will take place every 6 months (starting from date of progression). Follow-up will continue until 2 years from start of nivolumab treatment of the last recruited patient in the trial.

Intervention

* Chemotherapy:
Cisplatin 80 mg/m2 as an infusion on day 1 and vinorelbine 30 mg/m2 (20 mg/m2 during cycle 2 and 3) as an infusion days 1 and 8 , given every 3 weeks for 3 cycles
OR
Cisplatin 80 mg/m2 as an infusion on day 1 and etoposide 100 mg/m2 as an infusion days 1 * 3 given every 3 weeks for 3 cycles
OR
Cisplatin 75 mg/m2 as an infusion on day 1 and pemetrexed 500 mg/m2 as an infusion on day 1, given every 3 weeks for 3 cycles
Please note, if for some reason cisplatin cannot be used, it will be replaced by carboplatin as an infusion on day 1 given every 3 weeks for 3 cycles.
* Radiotherapy will consist of a physical dose of at least 60 Gy i delivered concurrent with chemotherapy cycles two and three.
* Nivolumab (experimental treatment) will start concurrently with chemotherapy cycles two and three.
The first 4 doses of nivolumab will be administered at 360 mg in 30-minute intravenous infusions every 3 weeks. From dose 5 on, nivolumab will be administered at 480 mg every 4 weeks for up to 1 year from the start of nivolumab treatment.
Treatment with nivolumab will continue for up to 1 year unless unacceptable side effects, disease progression, or withdrawal of consent.

Study burden and risks

At the time of study entry, physical, radiological and lab examinations will be

performed. In addition, an electrocardiogram will be taken and pulmonary function will be measured. In women who could become pregnant, a pregnancy test will be done (on serum or urine) prior to receiving study treatment. During the study treatment, patients must visit the study doctor every 3 weeks during the chemotherapy phase and every 4 weeks during the treatment with nivolumab for a physical examination and routine blood analyses. Inpatient admission into a hospital is not envisaged, but can potentially become necessary.
Nivolumab will start concurrently with chemotherapy cycles two and three. The first 4 doses of nivolumab will be administered at 360 mg in 30-minute intravenous infusions every 3 weeks. From dose 5 on, nivolumab will be administered at 480 mg every 4 weeks for up to 1 year from the start of nivolumab treatment. Treatment with nivolumab will continue for up to 1 year unless unacceptable side effects, disease progression, or withdrawal of consent. Follow-up visits after trial treatment stop but before progression will take place every 9 weeks (first year after completion of chemo-radiotherapy), 12 weeks (year 2) or 6 months from year 3. Follow-up visits after progression will take place every 6 months (starting from date of progression). Follow-up will continue until 2 years from start of nivolumab treatment of the last recruited patient in the trial.

FDG-PET-CT must be performed at study entry. The FDG-PET exam is part of the standard practice. The patient will have to be fasting for at least 6 hours (drinking of water is allowed). After injection of a radioactive substance into a vein, the patient will have to wait for about one hour. Then the scanning session will start which may take up to 30 minutes.

After completion of the chemotherapy and radiotherapy, a CT of the thorax and upper abdomen will be performed. This will be repeated every 9 weeks in the first year after chemotherapy and radiotherapy, every 12 weeks in the second year, and later every 6 months.These examinations can be carried out more frequently, if the doctor considers this appropriate. The study doctor may also suggest other tests, such as CT of the brain.

Although many attempts were made to improve the long-term survival of patients with locally advanced non-small cell lung cancer, none of these have demonstrated improved outcome. Improved understanding of the immune profile of non-small cell lung cancer has led to immunotherapeutic strategies, including inhibitory molecules responsible for abrogating an anti-cancer immune response such as PD-1. Nivolumab is a monoclonal antibody that inhibits the immune checkpoint receptor PD-1 and it has demonstrated positive results in several trials of previously treated patients with advanced non-small cell lung cancer. Nivolumab was never tested in the context of definitive radio-chemotherapy for stage III disease. It was not specifically described to date to interact with palliative radiotherapy in the stage IV setting. The unmet need in this curative context presents a favourable risk/benefit ratio with as major concern the cumulative risk of radiotherapy induced pneumonitis and nivolumab-related pneumonitis. Since 2014 nivolumab has been approved in US and Japan for the

treatment of malignant melanoma, in Europe since June 2015. For the treatment of non-small cell lung cancer nivolumab has recently gained approval in US and Europe and is now available for compassionate use for 2nd line treatment of non-small cell lung cancer.

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

* Histologically or cytologically confirmed locally advanced stage IIIA or III B (T0-3, N2-3 or T4 N0-3 M0) non-small cell lung carcinoma (NSCLC), according to 7th TNM classification.
* Nodal status N2 or N3 need to be proven (by biopsy, EBUS, mediastinoscopy or thoracoscopy) except for overt cT4 disease.
* Measurable disease according to RECIST v1.1.
* Previous delivery of a maximum of one 3-weekly cycle of platinum-based chemotherapy.

* ECOG performance status 0-1.
* Adequate hepatic, haematological and renal function.
* All AEs from previous therapies (including the first chemotherapy cycle in the context of this trial) resolved to grade <2 (except fatigue, alopecia, nausea lack of appetite or peripheral neuropathy)

Exclusion criteria

* Metastatic disease (as determined by PET-CT and brain MRI (preferred) or highquality brain CT with intravenous contrast at the time of staging, performed within 28 days before the beginning of first chemotherapy cycle).
* Previous radiotherapy to the chest, including radiotherapy for breast cancer.
* Prior chemotherapy, radiotherapy or molecular targeted therapy for NSCLC (with the exception of one cycle of chemotherapy given prior to enrolment into this trial).
* Active, known or suspected autoimmune disease

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	29-06-2016
Enrollment:	18
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Opdivo

Generic name:	Nivolumab
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	12-10-2015
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-04-2016
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	03-10-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	13-10-2016
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:	18-07-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	19-10-2017
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:	11-01-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	29-01-2019
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	EUCTR2014-005097-11-NL
ClinicalTrials.gov	NCT02434081
CCMO	NL54245.029.15