A single arm phase II trial evaluating the activity of alectinib for the treatment of pretreated RET-rearranged advanced NSCLC

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The primary objective is to assess the efficacy of alectinib in terms of best overall response (OR) assessed by RECIST v1.1. The secondary objectives are to evaluate secondary measures of clinical efficacy including disease control, progression-free...

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

Summary

ID

NL-OMON46669

Source
ToetsingOnline

Brief title
ALERT-lung

Condition

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

Synonym
RET-rearranged 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: ETOP;het Europese platform voor thoraxoncologie,Hoffmann-La Roche

Intervention

Keyword: advanced stage disease, alectinib, non-small cell lung cancer, RET-rearrangement

Outcome measures

Primary outcome

The primary endpoint of this study is the best overall response (OR = complete response or partial response), per investigator assessment, according to RECIST 1.1., from the start of trial treatment across all time points until the end of trial treatment.

Secondary outcome

Secondary endpoints:

- Best overall response per independent review

- Disease control at 24-weeks: best overall response of complete response or partial response, or stable disease (or non-complete response/non-progressive disease in the case of non-measurable disease only)

- Progression-free survival defined as the time from the date of enrolment until documented progression or death, if progression is not documented

- Overall survival defined as time from the date of enrolment until death from any cause

- Safety and tolerability

Study description

Background summary

Despite advances in the treatment of non-small cell lung cancer (NSCLC) over the past several decades, only small incremental overall survival benefits have been demonstrated and treatments beyond first-line remain limited in unselected NSCLC.

In 2004 the discovery of the Epidermal Growth Factor Receptor (EGFR) mutations in NSCLC and their predictive value for therapy with EGFR tyrosine kinase inhibitors (TKIs) opened the way to an intense program of research on lung cancer, aiming at identifying other genomic or protein alterations that could be used as target for treatment. Subsequently, genetic rearrangements of the anaplastic lymphoma kinase (ALK) gene in lung cancer and its oncogenic features were discovered in 2007. The impressive clinical results obtained with the inhibition of ALK and EGFR kinases compared to classical chemotherapy further supported the hypothesis that targeting signaling pathways aberrantly active in cancer cells, might lead to a better outcome of therapy for molecularly selected lung cancer patients. However, EGFR mutations and ALK translocations cover only 15-20% of NSCLC in Western populations, calling for discovery and development of novel targets. Studies on molecular alterations of lung tumours highlighted specific differences of biomarkers expression and role in the several histotypes of lung cancer. Adenocarcinoma (ADC) is the most prevalent histologic subtype among lung tumours and certainly the most characterized for its molecular features. To date, a targetable alteration may be recognized in 20-30% of adenocarcinomas in Caucasian patients.

After the discovery of ALK fusions, other genes have been to be found genetically rearranged in lung cancer. The RET gene is located on chromosome 10 and encodes for a transmembrane receptor with tyrosine kinase activity. Mutations of RET are known to be involved in the multiple endocrine neoplasia type 2 (MEN2) syndrome, sporadic medullary thyroid cancer and sporadic and radiation induced papillary thyroid carcinoma. RET fusions are transforming in vitro and in vivo, and inhibition of RET in RET-rearranged lung cancer cells leads to suppressed viability.

RET rearrangements have been identified in lung ADC as well, with a prevalence of 1-2%. RET-positive lung carcinomas are more common in poorly differentiated tumours and in never-smokers. Therapeutically, several multiple kinases inhibitors, such as vandetanib (Astrazeneca, London, England), cabozantinib (Exelis Inc. USA), ponatinib (Ariad, USA), axitinib (Pfizer, USA), sunitinib (Pfizer, USA), sorafenib (Bayer Healthcare, Germany), and alectinib (Roche, Switzerland) are potentially able to inhibit RET kinase function. Phase III trials data in biologically unselected NSCLC are available for some of these agents both as monotherapy and in combination. However, all the results from

these studies were negative and none of the drugs was approved for lung cancer treatment, probably due to the absence of genotypic selection. On the other hand, some case reports describe anecdotal responses to treatment with vandetanib and cabozantinib in RET-positive lung cancer patients.

Preclinical studies have recently shown that alectinib has potent anti-tumour activity in RET rearranged NSCLC. To date, a unique small clinical report of alectinib activity in RET-rearranged NSCLC is available. Recently, in the Journal of Thoracic Oncology, the Massachusetts General Lung Group reported on four RET-rearranged advanced NSCLC patients who were treated with alectinib (600 mg twice daily, N=3; 900 mg twice daily, N=1) as part of single-patient, compassionate use protocols or off-label use of the commercially available drug. Three of the four had received prior RET TKIs including cabozantinib and experimental RET inhibitors. In total, they describe two (50%) objective radiographic responses following treatment with alectinib (one confirmed and one unconfirmed), with durations of therapy of 6 months and 5+ months (treatment ongoing), respectively. Notably, one of these two patients was dose escalated to alectinib 900 mg twice daily and had clinical improvement in central nervous system metastases. In addition, one patient (25%) experienced a best response of stable disease lasting ~6 weeks (drug discontinued for toxicity). A fourth patient who was RET TKI-naïve had primary progression on alectinib. Therefore, alectinib demonstrated preliminary antitumour activity in advanced RET-rearranged NSCLC patients.

Study objective

The primary objective is to assess the efficacy of alectinib in terms of best overall response (OR) assessed by RECIST v1.1.

The secondary objectives are to evaluate secondary measures of clinical efficacy including disease control, progression-free survival (PFS), and overall survival (OS) as well as to assess safety and tolerability of the treatment and to describe the association of primary and secondary outcomes with tumour characteristics.

Study design

This is a single arm, multicentre phase II trial evaluating the activity of alectinib as second-line treatment of pretreated RET-rearranged advanced non-small cell lung cancer (NSCLC).

Patients must have histologically or cytologically documented advanced NSCLC (recurrent stage IV) with locally tested RET rearrangement after at least one previous line of platinum-based systemic therapy. RET rearrangement will later be centrally confirmed.

If the subject meets the criteria to take part in the study, he/she will receive alectinib 600 mg orally, twice per day (1200 mg per day in total) until progression, refusal or unacceptable toxicity. Trial treatment may also continue beyond progression, with physician and patient agreement, for as long as the patient may still derive clinical benefit as per investigator decision.

Treatment has to start as soon as possible after enrolment, ideally within 7 days. Treatment visits are planned at treatment start (week 0) and then every 2 weeks (±3 days) for the first 12 weeks and every 4 weeks (±3 days) thereafter. Radiological tumor assessments by CT scans of thorax/upper abdomen will be done at baseline and repeated every 8 weeks (±4 days) after first dose of alectinib until disease progression. At the end of trial treatment and irrespective of the reason for stopping treatment, an end of treatment visit should be performed within 30 days following the decision to stop trial treatment.

Patients who discontinue trial treatment before progression will perform follow-up visits every 8 weeks (±4 days). Patients with progression that ends trial treatment will be followed up every 12 weeks (±2 weeks) starting from date of progression until trial end.

Intervention

All patients in this study will be treated in the same way. If the subject meets the criteria to take part in the study, he/she will receive alectinib 600 mg (4 x 150 mg capsules) orally, twice per day (total 1200 mg, 8 capsules daily)until progression, refusal or unacceptable toxicity. The capsules must be swallowed whole at the same time each day with food. Trial treatment may also continue beyond progression, with physician and patient agreement, for as long as the patient may still derive clinical benefit as per investigator decision. Treatment has to start as soon as possible after enrolment, ideally within 7 days. Treatment visits are planned at treatment start (week 0) and then every 2 weeks (±3 days) for the first 12 weeks and every 4 weeks (±3 days) thereafter.

Study burden and risks

Distinct subtypes of non-small cell lung cancer are driven by a specific genetic alteration and are known to be sensitive to inhibition of the corresponding activated oncogenic pathway. RET rearrangements have been identified in lung adenocarcinoma with an incidence of 1-2% and several multiple kinases inhibitors (such as alectinib) are potentially able to inhibit RET kinase function. Recently, alectinib demonstrated preliminary antitumour activity in advanced RET-rearranged NSCLC patients. Alectinib has been administered in several clinical trials and it has been shown that it was generally well tolerated and had an acceptable safety profile.

At study entry, subjects will have a physical examination, radiological

examination (MRI or CT of the brain and CT of thorax and upper abdomen within 6 weeks prior to enrolment), electrocardiogram (ECG), blood and urine tests. A pregnancy test will be done in women of childbearing potential. The subjects will also be asked questions about their medical history and medication they take. During the treatment with alectinib, the subject should visit the study doctor every 2 weeks for the first 12 weeks and every 4 weeks thereafter for a physical examination and blood and urine analyses. The subject will also be asked questions about side effects, medications, treatments and hospital stays. The doctor will assess the performance status by asking questions about his/her general wellbeing. Radiological examinations (CT thorax and upper abdomen) will be done every 8 weeks until disease progression.

Patients will receive alectinib 600 mg (4 capsules of 150mg) orally, twice per day (total 1200 mg) until disease progression, refusal or unacceptable toxicity. Trial treatment may also continue beyond progression, with physician and patient agreement, for as long as the patient may still derive clinical benefit as per investigator decision. Patients will be given a diary to fill in the day and time they take alectinib capsules and to note any side effects they experience. The completed diary should be brought to each clinic visit, together with all empty, full and partly used bottles of alectinib.

At the end of trial treatment and irrespective of the reason for stopping treatment, an end of treatment visit should be performed within 30 days following the decision to stop trial treatment. During this visit, a physical examination, ECG, blood and urine tests will be performed. A CT of thorax and upper abdomen needs to be performed if not done within 6 weeks prior to the end of treatment visit. Patients who discontinue trial treatment before progression will perform follow-up visits every 8 weeks. Patients with progression that ends trial treatment will be followed up every 12 weeks starting from date of progression until trial end.

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-documented non-small cell lung carcinoma
- Advanced disease defined as recurrent stage IV (according to 8th TNM classification) or recurrent or progressive disease following multimodal therapy (radiation therapy, surgical resection, or definitive chemo-radiation therapy for locally advanced disease)
- RET rearrangement detected by FISH, Nanostring or by parallel-sequencing on FFPE tumour tissue (biopsy, resection or cytoblock) assessed locally.
- Availability of FFPE tumour material for central confirmation of RET-rearrangement
- At least one prior platinum-based systemic regimen: Adjuvant or neoadjuvant or definitive platinum-based chemo-radiotherapy treatments are considered as a line of treatment only if completed less than 6 months before enrolment. Maintenance therapy following platinum doublet-based chemotherapy is not considered a separate regimen of therapy.
- Measurable or non-measurable, but radiologically evaluable (except for skin lesions) disease according to RECIST v1.1 criteria
- Adequate haematological, renal and liver function
- ECOG Performance Status 0-2

Exclusion criteria

- Untreated, active CNS metastases
- Carcinomatous meningitis
- Baseline symptomatic bradycardia
- Prior treatment with any RET TKI or RET targeted therapy
- Known EGFR, ALK, ROS, and BRAF mutation (in addition to RET rearrangement)
- Any GI disorder that may affect absorption of oral medications, such as malabsorption syndrome or status post-major bowel resection

- History of hypersensitivity to any of the additives in the alectinib drug formulation
- Pregnant or lactating women
- Known HIV positivity or AIDS-related illness
- Any concurrent systemic anticancer therapy

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):	17-05-2019
Enrollment:	4
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Alecensa
Generic name:	Alectinib
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	16-08-2018
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

Approved WMO Date:	11-01-2019
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	15-03-2019
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	16-10-2020
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	25-11-2020
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	EUCTR2017-002063-17-NL
ClinicalTrials.gov	NCT03445000

Register	ID
CCMO	NL64609.031.18