Afatinib in pretreated patients with advanced NSCLC harbouring HER2 exon 20 mutations

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The primary objective is to evaluate the ability of afatinib to control disease in pretreated patients with advanced non-small cell lung cancer harbouring HER2 exon 20 mutations.Secondary objectives are:* To evaluate secondary measures of clinical...

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

Summary

ID

NL-OMON42560

Source
ToetsingOnline

Brief title
ETOP 7-14 NICHE

Condition

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

Synonym
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: Boehringer Ingelheim,ETOP;het Europese

platform voor thoraxoncologie

Intervention

Keyword: advanced stage disease, afatinib, HER2, non-small cell lung cancer

Outcome measures

Primary outcome

Disease control defined as complete or partial response, or disease

stabilisation lasting at least 12 weeks.

Secondary outcome

Secondary endpoints:

- Progression-free survival (time from the date of enrolment until documented

progression or death, if progression is not documented) determined by RECIST 1.1

- Objective response (best overall response across all assessment time-points

from enrolment to termination of trial treatment) determined by RECIST 1.1

- Overall survival (time from the date of enrolment until death from any cause)

- Adverse events graded according to CTCAE V4.0.

Study description

Background summary

Primary lung cancer is the most common malignancy after non-melanocytic skin cancer, with the highest number of deaths worldwide. Lung cancer accounts for 12% of all incident cases of cancer. Non-small cell lung cancers (NSCLC) account for 80-85% of lung cancers.

Advanced stage NSCLC is traditionally treated by systemic palliative chemotherapy, with cisplatin as basis. Chemotherapy efficacy seems to have reached a plateau though. In unselected patients, response rates are only 15-30% and median survival (i.e. 50% of the patients are still alive) is 10-12 months, while the majority of patients suffer severe side effects with no

therapeutic benefit. The treatment of cancer patients is characterized by great inter-individual variability. Since 1994, molecular research has centered on the identification of predictive biomarkers that can be successfully used to tailor treatment in these patients.

Previous clinical studies of NSCLC have shown that patients with tumors harboring specific gene mutations (changes) showed better results after treatment with tyrosine kinase inhibitors (TKIs), compared with classical treatment with chemotherapy. The treatment with TKI has become a new standard-of-care for patients with advanced lung cancer and specific mutations, such as epithelial growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK).

HER2 (human epidermal growth factor 2), a protein of the so called ErbB receptor tyrosine kinase family, is a lung cancer biomarker which remains poorly described. HER2 overexpression or gene amplification is widely known to be associated with sensitivity to HER2-targeting drugs (trastuzumab, lapatinib, pertuzumab and T-DM1) in breast cancer. Involvement of HER2 in lung carcinogenesis has been known for many years, but clinical research was slowed down when the first clinical trials with trastuzumab were negative. Indeed, the addition of trastuzumab to gemcitabine-cisplatin or to docetaxel failed to show any survival benefit in HER2 Immuno-Histo-Chemistry-positive (IHC) lung cancer patients. However, HER2 mutations may be more relevant in lung carcinogenesis than HER2 amplification or overexpression. HER2 mutations are identified in about 2% of non-small-cell lung cancers.

Afatinib has a marketing authorization for a different use in non-small cell lung cancer. Afatinib, the study drug, is a TKI which is approved by the European and the Swiss Medicines Agencies for the treatment of adult patients with non-small cell lung cancer with a mutation in the gene for EGFR, either as first-line treatment or as second-line treatment if prior chemotherapy has been insufficient. This trial aims at confirming the role of afatinib in HER2 mutated advanced NSCLC patients previously treated with platinum based chemotherapy.

Study objective

The primary objective is to evaluate the ability of afatinib to control disease in pretreated patients with advanced non-small cell lung cancer harbouring HER2 exon 20 mutations.

Secondary objectives are:
* To evaluate secondary measures of clinical efficacy including progression free survival (time from the date of enrolment until documented progression or death, if progression is not documented), objective response rate (best overall response across all assessment time-points from enrolment to termination of trial treatment) and overall survival (time from the date of enrolment until

death from any cause)
* To assess the safety and the tolerability of the treatment.

Study design

This is a multicenter phase II single-arm trial in patients with advanced stage non-small cell lung cancer, harbouring HER2 exon 20 mutations.

Participating sites will screen patients for HER2 exon 20 mutations in their local laboratory. Tumor tissue will also be sent to a central laboratory at the Medical University of Gdansk (Poland) for later confirmation of the mutations. If this central analysis does not confirm the presence of HER2 mutation, and thus deviates from the local analysis, the subject can still take part in the study if the investigator agrees with it.

If the subject meets the criteria to take part in the study, he/she will receive afatinib 40 mg orally, daily. Week 0 is the week of trial treatment start and subsequent visits will take place at 3, 6, 9 and 12 weeks after first dose, then every 4 weeks until stop of treatment. At the end of trial treatment and irrespective of the reason for stopping treatment, an end of treatment visit should be done within 30 days following the last dose.

Follow-up visits after trial treatment stop but before progression will take place every 8 weeks until progression. Follow-up visits after progression will take place every 3 months until death, or until 6 months from enrolment of the last patient, whichever occurs first.

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 afatinib 40 mg orally, daily. Treatment with the study medication should start within 7 days after enrolment. Afatinib should be taken at a fixed time and at least 1 hour before and 3 hours after the ingestion of food. The tablets should be swallowed whole with water. If swallowing of whole tablets is not possible, these can be dispersed in approximately 100 ml of noncarbonated drinking water. No other liquids should be used.

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 serum or urine) within 7 days prior to receiving study treatment. During the study treatment, patients must visit the study doctor every 3 weeks for the first 12 weeks for a physical examination and routine blood analysis, thereafter every 4 weeks. Inpatient admission into a hospital is not envisaged,

but can potentially become necessary. Patients must take afatinib tablets ((study drug) at a fixed time each day (at least 1 hour before or 3 hours after the ingestion of food) and record the intake in the patient diary. All empty, full and partly used boxes of afatinib tablets must be returned at the next visit to the study center.

At the end of trial treatment and irrespective of the reason for stopping treatment, an end of treatment visit should be done within 30 days following the last dose. Follow-up visits after trial treatment stop but before progression will take place every 8 weeks until progression. Follow-up visits after progression will take place every 3 months until death, or until 6 months from enrolment of the last patient, whichever occurs first.

Radiological examinations (CT of the chest and upper abdomen) will be conducted every 6 weeks (week 6 and 12) and later every 8 weeks until tumour progression. These examinations are carried out as part of medical routine and can be performed more frequently, if the study doctor considers this appropriate. Before the start of the study treatment, a CT or MRI of the brain will be performed. Compared to the standard treatment, an additional radiological examination (CT of thorax and upper abdomen) will be performed 6 weeks after the first dose of afatinib and at the end of the study treatment, if the last CT was performed more than 6 weeks before.

Afatinib has a marketing authorization for a different use in non-small cell lung cancer. Afatinib is approved by the European and the Swiss Medicines Agencies for the treatment of adult patients with non-small cell lung cancer with a mutation in the gene for EGFR, either as first-line treatment or as second-line treatment if prior chemotherapy has been insufficient. HER2 mutations offer a new treatment strategy beyond the standard chemotherapy. Afatinib is relatively well tolerated and presents a manageable toxicity profile. In the small series available to date, afatinib looks like being the most promising anti-HER2 treatment. Based on available data, afatinib is comparable or superior to classical second line chemotherapy (docetaxel), with a significantly better toxicity profile. Afatinib potentially offers a significant activity in terms of disease control and long term outcome. Therefore this treatment option offers a good benefit to risk ratio in patients with HER2-mutated advanced 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, non-predominant squamous subtype, stage IIIB (non amenable to curative-intent multimodal treatment) or IV NSCLC, according to 7th TNM classification
• Tumour is platinum-refractory
• Measurable or evaluable disease (according to RECIST 1.1 criteria)
• Locally documented HER2 mutation
• Eastern Cooperative Oncology Group (ECOG) Performance Status 0-2
• Life expectancy >3 months
• Adequate haematological, renal and hepatic function
• Effective contraception, no pregnancy

Exclusion criteria

• Mixed small-cell and non-small-cell histologic features
• Uncontrolled lepto-meningeal metastatic disease
• Previous treatment with HER2 targeted antibody or tyrosine kinase inhibitor
• Any previous (in the past 3 years) 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
• History or presence of clinically relevant cardiovascular abnormalities
• Other serious diseases or clinical conditions, including but not limited to uncontrolled active infection and any other serious underlying medical processes that could affect the patient*s capacity to participate in the trial
• Interstitial lung disease or pulmonary fibrosis
• 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):	26-08-2015
Enrollment:	6
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Giotrif
Generic name:	Afatinib
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	19-06-2015

Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	14-10-2015
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	22-04-2016
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	29-12-2016
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	06-01-2017
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	10-01-2017
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	25-01-2017
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	EUCTR2014-005098-35-NL
ClinicalTrials.gov	NCT02369484
CCMO	NL52780.031.15