An open-label phase II trial of erlotinib and bevacizumab in patients with advanced non-small cell lung cancer and activating EGFR mutations

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To determine long-term outcome of patients with advanced non-squamous NSCLC harbouring at diagnosis EGFR mutations with and without T790M mutation and treated with the combination of erlotinib and bevacizumab.

Ethical review	Not approved
Status	Will not start
Health condition type	Respiratory and mediastinal neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON37461

Source
ToetsingOnline

Brief title
Bevacizumab and Erlotinib in EGFR mutated NSCLC

Condition

- Respiratory and mediastinal neoplasms malignant and unspecified

Synonym
Lungcancer

Research involving
Human

Sponsors and support

Primary sponsor: European Thoracic Oncology Platform

Source(s) of monetary or material Support: ETOP

Intervention

Keyword: Bevacizumab, EGFR mutation, Erlotinib, NSCLC

Outcome measures

Primary outcome

Progression-free survival.

Secondary outcome

Time to treatment failure, overall survival, objective respons rate, disease

control rate, duration of response, toxicity.

Study description

Background summary

Advanced non-small-cell lung cancer (NSCLC) patients harbouring epidermal growth factor receptor (EGFR) mutations (del19 or L858R) show an impressive progression-free survival between 9 and 14 months when treated with erlotinib. However, the presence of EGFR mutations can only imperfectly predict outcome. We hypothesize that progression-free survival could be influenced both by the pretreatment EGFR T790M mutation and by components of DNA repair pathways. We propose a model of treatment whereby patients with EGFR mutations (single or with T790M) can attain a benefit with longer overall PFS when treated with erlotinib plus bevacizumab. When the patients are grouped by BRCA1 mRNA levels and T790M the hypothesis is that the combination of erlotinib plus bevacizumab can improve the PFS in all subgroups.

Study objective

To determine long-term outcome of patients with advanced non-squamous NSCLC harbouring at diagnosis EGFR mutations with and without T790M mutation and treated with the combination of erlotinib and bevacizumab.

Study design

This is a multinational, multi-center phase II trial of erlotinib plus bevacizumab in patients with advanced non-squamous NSCLC harbouring EGFR

mutations confirmed by central re-assessment. Patients will be stratified into two subgroups, with and without EGFR T790M mutation. The stratification will be done after teh inclusion of patients.

Intervention

Patients will be treated with Bevacizumab and Erlotinib
Bevacizumab: 15 mg/kg i.v. on day 1 of each 3-week cycle
Erlotinib: 150 mg p.o., daily
Treatment will be given until disease progression.

Study burden and risks

Risks: side effects of bevacizumab and erlotinib.
Burden: the extent of burden for the patient is less. A lot of tests which the patient should have undergone are common practise. Extra burden associated with participation are the extra serum samples for translational research. Samples (3) should be taken at baseline, at the time of first documentation of response, and at the time of progression.
Possibly (optional) there would be an additional tumor biopsy taken at the time of progression .

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

-Age * 18 years
-ECOG performance status 0-2
-Adequate haematological function: haemoglobin > 9 g/dL, neutrophils count > 1.5 x 109/L, platelet count > 100 x 109/L
-Adequate coagulation: INR * 1.5
-Adequate liver function: Total bilirubin < 1.5 x ULN, ALT and/or AST < 2.5 x ULN, alkaline phosphatase < 5 ULN, except in the presence of exclusive bone metastases and in the absence of any liver disorder
-Adequate renal function: Calculated creatinine clearance * 50 mL/min (Cockroft-Gault) and proteinuria < 2+ (dipstick)
-Oral swallowing capability, patient capable of proper therapeutic compliance, and accessible for correct follow-up
-Life expectancy of at least 2 months
-Women of childbearing age, including women who had their last menstrual period in the last 2 years, must have a negative serum or urine pregnancy test within 7 days before beginning treatment. Not eligible: Women who are pregnant or in the period of lactation
-All sexually active men and women of childbearing age must use an effective contraceptive method during the study treatment and for a period of at least 12 months following the last administration of trial drugs. Not eligible: sexually active men and women of childbearing age who are not willing to use an effective contraceptive method during the study
-Written informed consent must be signed and dated by the patient and the investigator prior to any trial-related intervention for a) trial treatment and b) tissue submission for central review and central EGFR testing
-Pathological diagnosis of predominantly non-squamous, non-small-cell lung cancer (NSCLC). Not eligible: patients with any other lung cancer sybtype, patients with mixed NSCLC with predominantly squamous cell cancer, or with any small cell lung cancer (SCLC) component
-TNM version 7 stage IV disease including M1a (malignant effusion) or M1b (distant metastasis), or locally advanced disease not amenable to curative treatment (including patients progressing after radio-chemotherapy for stage III disease). Not eligible: patients who are candidates for radical surgery and/or radio(chemo)therapy with curative intention
-Measurable or evaluable disease (according to RECIST 1.1 criteria). Not eligible: patients with only one measurable or evaluable tumor lesion which was resected or irradiated prior to enrolment
-Centrally confirmed EGFR exon 19 deletion (del19) or exon 21 mutation (L858R). Not eligible:patients with local test result not confirmed by central laboratory
-Patients with asymptomatic and stable cerebral metastases will be eligible for the study. Not eligible: patients with symptomatic or instable cerebral metastases requiring medical

treatment

Exclusion criteria

-Not eligible: patients with increased risk of bleeding, defined by:
a. major surgery or significant traumatic injury within 28 days prior to inclusion
b. minor surgery (including permanent catheter insertion) within 24 hours prior to first treatment with bevacizumab
c. history or evidence of bleeding diathesis or hereditary coagulopathy
d. history of haemoptysis (defined as at least half a teaspoon's emission or red blood) in the 3 months prior to inclusion
e. evidence by CT of tumor cavitations, or tumours invading or abutting major blood vessels
f. uncontrolled hypertension (systolic blood pressure > 150 mm Hg and/or diastolic > 100 mm Hg)
-Not eligible: patients with clinically significant cardiovascular diseases, including
a. cerebral vascular accident (<6 months before inclusion)
b. acute myocardial infarction (< 6 months before inclusion)
c. unstable angina
d. congestive heart failure class > NYHA II
e. serious cardiac arrhythmia requiring medication during the study and which could interfere with regularity of study treatment or is not controlled with medication
-Not eligible: patients with a history of thrombosis or thromboembolism in the 6 months prior to treatment
-Not eligible: patients with gastrointestional problems including
a. intestinal transit problems (such as malabsorption syndrome, chronic intestinal inflammatory disease, or other pathologies that can alter absorption of the medication
b. history of abdominal fistula, intestinal perforation or intra-abdominal abscess within 6 months prior to inclusion
c. uncontrolled active peptic ulcer
d. presence of trachea-oesophageal fistula
-Not eligible: patients with neurologic problems, including
a. evidence of spinal cord compression
b. significant neurological or psychiatric disorders (including dementia and epileptic seizures)
-Not eligible: 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 breast carcinoma
-Not eligible: patients with known significant ophthalmologic anomaly of the ocular surface. The use of contact lenses is not recommended
-Not eligible: patients with 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 study
-Not eligible: Known hypersensitivity to bevacizumab or erlotinib or any of its excipients
-Not eligible: patients who received prior chemotherapy for metastatic disease. Patients with prior neoadjuvant or adjuvant chemotherapy or definitive radiochemotherapy for localised disease are eligible if chemotherapy has stopped at least 6 months before entering the study

-Not eligible: patients who received previous treatment for lung cancer with drugs targeting EGFR or VEGF. Patients with previous intraocular treatment with VEGF-targeting drugs are eligible
-Not eligible: patients who received treatment with an investigational drug agent during the 3 weeks before enrolment in the study
-Not eligible: patients with current or recent use (within the last 10 days) of full doses of anticoagulants or thrombolytics, either orally or parenterally. Use of anticoagulant prophylaxis is permitted (low dose heparin or aspirin * 325 mg, prophylactic FXa inhibitors)
-Not eligible: patients with concurrent use of CYP3A4 inducers/inhibitors (such as, but not limited to, atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefzodone, nelfinavir, ritonavir, saquinavir, telithromycin, troleandomycin (TAO), voriconazole, or grapefruit or grapefruit juice)

Study design

Design

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

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	6
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Avastin
Generic name:	Bevacizumab
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Tarceva
Generic name:	Erlotinib

Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	21-02-2012
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Not approved Date:	19-06-2012
Application type:	First submission
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	EUCTR2011-004481-15-NL
CCMO	NL39652.031.12