A prospective double-blind randomized Phase III study of 300 mg vs. 150 mg erlotinib in current smokers with locally advanced or metastatic NSCLC in second-line setting after failure on chemotherapy

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To compare the efficacy of two dose levels of erlotinib (150 mg and 300 mg) on progression-free survival (PFS) in current smokers with stage IIIB/IV NSCLC after failure of first-line platinum-based chemotherapy.

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

Summary

ID

NL-OMON36738

Source
ToetsingOnline

Brief title
CURRENTS

Condition

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

Synonym
locally advanced or metastatic (stage IV) non-small cell lung cancer, lung cancer

Research involving
Human

Sponsors and support

Primary sponsor: Hoffmann-La Roche
Source(s) of monetary or material Support: Hoffman-La Roche

Intervention

Keyword: CURRENTS, erlotinib, NSCLC, smokers

Outcome measures

Primary outcome

PFS, defined as the time from randomization to the date of first occurrence of

disease progression or death.

Secondary outcome

Overall survival:

- Defined as the time from randomization to the date of death due to any cause.

- Response rate and disease control rate based on best response measured

according to RECIST criteria.

Study description

Background summary

Lung cancer is the most common cause of cancer death worldwide, accounting for up to 18% of cancer-related deaths (Parkin et al., 2005). Non-small cell lung cancers (NSCLC) comprise 80% of reported lung cancer cases (Cartman et al., 2002). Indeed, the majority of new cases of lung cancer are advanced NSCLC (Haura, 2001). Due to late diagnosis, only a small proportion of NSCLC cases are operable as over 60% of patients present with advanced stages of the disease (Makitaro et al., 2002). In comparison with other solid tumors, the objective response and overall survival (OS) rates in patients with advanced NSCLC are low: five-year survival rates for stage IIIB inoperable disease are less than 10%, decreasing to less than 2% in disease stage IV (Ginsberg et al.,

2001). For this population of patients in whom treatment is mainly palliative, the main goal is to achieve symptom control and prolong overall survival (Vansteenkiste, 2007). Standard of care for patients with locally advanced or metastatic NSCLC is platinum-based doublet chemotherapy (Pfister et al., 2004). Doublet chemotherapy has been found to be superior to single-agent chemotherapy (Delbaldo et al., 2004), with cisplatin-based therapy the current reference treatment for patients with advanced NSCLC. However, no doublet combination has been proven to be clinically superior to the others (Greco et al., 2002; Scagliotti et al., 2002; Schiller et al., 2002; Smit et al., 2003). Current data suggest that chemotherapy has reached a therapeutic plateau, conferring no improvements in survival despite the availability of new combinations of cytotoxic agents (Helbekkmo et al., 2007; Schiller et al., 2002). In addition, there are only limited treatment options for those who fail first-line chemotherapy. Overall, the survival outcomes for NSCLC patients remain poor, with a one-year survival rate of only 35% (Ettinger, 2002). Recent trials have shown that patients with advanced NSCLC can benefit from secondline therapy (Vansteenkiste, 2007). However, treatment options in this setting are fairly limited. Currently, docetaxel and pemetrexed are the only chemotherapy agents approved for use as second-line therapy (Reck and Crino, 2008). Further compounding the problem, there remains a large population of patients who do not benefit from these agents (Vansteenkiste, 2007). Targeting the epidermal growth factor receptor (EGFR) has played an important role in advancing NSCLC therapy and improving patient outcomes (Gridelli et al., 2007). Erlotinib has been approved in the US and Europe for second-line treatment of NSCLC (Gridelli et al., 2007). Results from a pivotal Phase III trial (BR.21) in patients with stage IIIB/IV NSCLC who had previously received chemotherapy showed that the use of erlotinib resulted in a 42.5% improvement in mean OS compared to placebo (Shepherd et al., 2005). Erlotinib acts via a different mechanism of action than chemotherapy agents, providing an important treatment alternative for those patients who do not benefit from standard chemotherapy.

Study objective

To compare the efficacy of two dose levels of erlotinib (150 mg and 300 mg) on progression-free survival (PFS) in current smokers with stage IIIB/IV NSCLC after failure of first-line platinum-based chemotherapy.

Study design

This is a randomized, double-blind, prospective, multi-center Phase III study of two dose levels of erlotinib in current smokers with stage IIIB/IV NSCLC who have failed one platinum-based chemotherapy regimen for metastatic disease. The study will consist of a screening period of maximum 14 days. Hereafter eligible subjects will be randomized and will visit the site every 6 weeks, until PD, death, or unacceptable toxicity occurs. For all patients who have discontinued study drug treatment and are alive, information on further therapy for NSCLC

and survival will be collected. A End of Study-visit will be performed PD, death, or unacceptable toxicity is achieved. After the End of Study-visit, further therapy and survival follow-up will be performed every 12 weeks (or as appropriate).

Intervention

Tarceva.

Study burden and risks

Erlotinib is an approved treatment for NSCLC after failure of one cycle of previous chemotherapy and for treatment of metastatic pancreatic cancer in combination with gemcitabine. Your medical condition may improve from taking erlotinib. However, we cannot and do not guarantee or promise that you will receive any benefits from this study. Your participation in the study may be helping patients in the future by giving important information about erlotinib and the treatment of NSCLC.

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

Disease Specific Inclusion Criteria:;1. Histologically or cytologically documented inoperable, locally advanced (stage IIIB with supraclavicular lymph node metastases or malignant pleural or pericardial effusion) or metastatic (stage IV) NSCLC disease.;2. Measurable disease must be characterized according to the Response Evaluation Criteria in Solid Tumors (RECIST) criteria (Eisenhauer et al., 2009).;3. Must have received one prior platinum-based chemotherapy regimen for advanced NSCLC and now exhibit PD, and must have recovered from any treatment-related toxicity.;4. Eastern Cooperative Oncology Group (ECOG) performance status 0-2.;5. Life expectancy * 12 weeks.;6. Current cigarette smoker (having smoked > 100 cigarettes in entire lifetime and currently smoking on average * 1 cigarette per day), not intending to stop smoking during the study.;7. Adequate hematological function:;* Absolute neutrophil count (ANC) * 1.5 x 109/L, and;* Platelet count * 100 x 109/L, and;* Hemoglobin * 9 g/dL (may be transfused to maintain or exceed this level).;8. Adequate liver function:;* Total bilirubin < 1.5 x upper limit of normal (ULN), and;* AST, ALT < 2.5 x ULN in patients without liver metastases; < 5 x ULN in patients with liver metastases.;9. Adequate renal function:;* Serum creatinine * 1.25 x ULN,;* Creatinine clearance * 60 ml/min.;10.Female patients must be either: a) postmenopausal (24 months of amenorrhea), b) surgically sterile or c) not pregnant (negative urine or serum pregnancy test within 3 days of randomization).;Male patients must be surgically sterile or agree to use a barrier method of contraception.;Female and male patients must be willing to use an effective method of contraception during the trial and for 60 days after last administration of erlotinib. cceptable methods of contraception include an established hormonal therapy or intrauterine device for females, or the use of a barrier contraceptive (i.e. diaphragm or condoms) with spermicide.;General Inclusion Criteria:;11.Patients able and willing to give written informed consent. The consent must be obtained before the first screening procedure.;12.Males or females aged * 18 years.;13.Able to comply with the required protocol and follow-up procedures, and able to receive oral medications.;14.Patients able to read, and understand the local language(s) for which the Functional Assessment of Cancer Therapy * Lung (FACT-L) questionnaires are available.

Exclusion criteria

Cancer Treatment Related Exclusion Criteria:;1. Received prior therapy against EGFR, either with antibody or small molecule (tyrosine kinase inhibitor).;2. Received radiotherapy within 28 days prior to enrolment.;3. Received treatment with any other investigational agent, or participated in another clinical trial, with the following exceptions:;* Chemotherapy-only trials are permitted including where chemotherapy in combination with bevacizumab has been

used (if study drug completed * 28 days prior to receiving the first dose of erlotinib).;* Previous adjuvant or neo-adjuvant treatment for non-metastatic disease is permitted if completed * 6 months before receiving the first dose of study drug. ;* Prior surgery is permitted if performed * 4 weeks before receiving the first dose of study drug and the patient is fully recovered.;* Prior localized radiotherapy is permitted if it was not administered to target lesions selected for this study, unless progression of the selected target lesions within the radiation portal is documented, and provided it has been completed * 4 weeks before receiving the first dose of study drug.;* Participation in a methodological or observational study in which no investigational agent was given.;4. Received more than one line of chemotherapy (first-line maintenance chemotherapy after first-line platinum-based chemotherapy is allowed) for locally advanced/metastatic NSCLC.;Cancer Related Exclusion Criteria:;5. History of breast cancer or melanoma at any time, or history of another malignancy in the last 5 years with the exception of the following:;* Other malignancies cured by surgery alone and having a continuous disease-free;interval of * 5 years.;* Cured basal cell carcinoma of the skin and cured in situ carcinoma of the uterine cervix.;6. History and symptomatic evidence of brain metastases.;Other Study Drug Related Exclusion Criteria;7. Known hypersensitivity to erlotinib or any of its excipients.;8. Any significant ophthalmologic abnormality, especially severe dry eye syndrome, keratoconjunctivitis sicca, Sjögren syndrome, severe exposure keratitis or any other disorder likely to increase the risk of corneal epithelial lesions. The use of contact lenses is not recommended during the study. The decision to continue to wear contact lenses should be discussed with the patient*s treating oncologist and the;ophthalmologist.;9. Coumarins (CoumadinTM; warfarin) use. If the patient requires anti-coagulation therapy, then the use of low molecular weight heparin instead of coumarins is recommended where clinically possible.;General Exclusion Criteria;10.Unstable systemic disease (including active infection, uncontrolled hypertension, unstable angina, congestive heart failure, myocardial infarction within the previous year, serious cardiac arrhythmia requiring medication, hepatic, renal, or metabolic disease).;11.Evidence of any other disease, neurological or metabolic dysfunction, physical examination or laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or puts the patient at high risk for treatment-related complications.;12.Female patients of childbearing potential who are: a) pregnant according to urine or serum pregnancy test within 3 days of randomization, b) breast-feeding. Female and male patients of reproductive potential not willing to use an effective method of;contraception during the trial and for 60 days after last administration of erlotinib.;13.Patients with pre-existing parenchymal lung disease such as pulmonary fibrosis, lymphangiosis carcinomatosis.;14.Patients with known infection with HIV, HBV, HCV. Testing is not required in the absence of clinical signs and symptoms suggestive of these conditions.;15.Patients assessed by the investigator to be unable or unwilling to comply with the;requirements of the protocol.

Study design

Design

Study phase:	3
Study type:	Interventional
Masking:	Double blinded (masking used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	26-10-2010
Enrollment:	20
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	erlotinib
Generic name:	Tarceva
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	21-06-2010
Application type:	First submission
Review commission:	METC Amsterdam UMC

Approved WMO

Date:	29-09-2010
Application type:	First submission
Review commission:	METC Amsterdam UMC

Approved WMO

Date:	27-10-2010
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Approved WMO

Date:	01-12-2010
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-03-2011
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	19-07-2011
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	07-09-2011
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	EUCTR2010-018476-24-NL
CCMO	NL31007.029.10