A randomized, double-blind, placebo-controlled Phase III study of first-line maintenance Tarceva vs Tarceva at the time of disease progression in patients with advanced non-small cell lung cancer (NSCLC) who have not progressed following 4 cycles of platinum-based chemotherapy.

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

Summary

ID

NL-OMON35789

Source
ToetsingOnline

Brief title
Roche BO25460 NSCLC Tarceva

Condition

- Respiratory and mediastinal neoplasms malignant and unspecified

Synonym
non-small-cell lung carcinoma (NSCLC)

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Chemotherapy, Non-small cell lung cancer, Tarceva

Outcome measures

Primary outcome

ASSESSMENTS OF:

- EFFICACY (Primary) Overall Survival

- EFFICACY (Secondary) Progression Free Survival (RECIST) and Response (RECIST)

- SAFETY Safety of the treatment will be evaluated by: adverse events,

laboratory tests, vital signs, electrocardiogram and performance status.

All subjects who received at least one dose of treatment will be included in

the safety evaluation.

Secondary outcome

- MOLECULAR MARKER ANALYSIS: EGFR mutational analysis.

Exploratory analyses of both tumour tissue and blood for other biomarkers

relevant to EGFR signal transduction and erlotinib clinical benefit (such as,

but not limited to, markers of Epithelial-Mesenchymal Transition (EMT)).

- OPTIONAL BIOMARKER SAMPLE (non-DNA): Roche Clinical Repository (RCR) non-DNA

specimen(s) will be taken from consenting subjects

as described in the Schedule of Assessment tableThe RCR sampling is optionalRCR samples will be collected to promote, facilitate and improve individualized healthcare by better understanding/predicting erlotinib efficacy, dose responses, safety, mode of action, progression of NSCLC and associated diseases. These specimen(s) may be stored for up to 15 years after the end of study BO25460.

- OPTIONAL BIOMARKERS SAMPLES (DNA): All subjects who have been enrolled in the study will be asked to donate an optional DNA specimen for pharmacogenetic and genetic research. RCR DNA sampling will involve taking a blood sample at baseline. The study protocol BO25460 which includes RCR sampling is submitted to the concerned Ethic Committee and is available for Competent Authority review upon request. These specimen(s) will be stored for up to 15 yearsafter the end of study BO25460.

- MANDATORY BIOMARKER SAMPLES (MBS): A tumour sample will be provided within 3 weeks of the patient starting the scheduled noninvestigational) platinum-based chemotherapy. This sample will be used to assess the EGFR mutation status to confirm eligibility of the patient in the Blinded phase of the study. In addition, a mandatory plasma and serum sample will be taken.

Study description

Background summary

The use of the single-agent EGFR tyrosine kinase inhibitor erlotinib in NSCLC after chemotherapy is supported by the results of the BR.21 Phase III study. In 2004, the FDA approved erlotinib for the treatment of patients with locally advanced or metastatic NSCLC after failure of at least one prior chemotherapy regimen, based on the results of BR.21 that showed an overall survival benefit for patients treated with erlotinib. This was followed by the approval in this setting in the EU and other countries.

The collective information derived from the BR.21 and SATURN trials indicates that erlotinib provides a PFS and OS benefit for patients with advanced NSCLC either in the first-line maintenance setting or at the time of disease relapse. In particular, the data from the SATURN trial showed that erlotinib in the maintenance setting provided a PFS and OS benefit compared to patients that were randomized to placebo and waited until progression before receiving a second-line of treatment. However, because the secondline treatment was at the investigator*s discretion, the trial was not able to address the specific question of the relative benefit of *early* erlotinib maintenance therapy versus *late* erlotinib administration at the time of disease progression. This present study is designed to prospectively determine the relative survival benefit of *early* versus *late* erlotinib therapy in patients with advanced (Stage IIIB and not amenable for combined modality treatment) or metastatic (Stage IV) NSCLC.

Study objective

The primary objective of this study is to compare the Overall Survival (OS) of first-line maintenance therapy with erlotinib versus erlotinib administered at the time of disease progression in patients with histologically documented, advanced or recurrent (Stage IIIB and not amenable for combined modality treatment) or metastatic (Stage IV) NSCLC

(according to the ISC updated Lung cancer staging criteria [44]), whose tumours do not
harbour an EGFR activating mutation (exon 19 deletion or exon 21 L858R mutation), and
who have not experienced disease progression or unacceptable toxicity during 4 cycles of
platinum-based chemotherapy.

Secondary objectives are:
* To compare the PFS between the treatment arms during the Blinded (first-line maintenance) phase;
* To compare overall response rate (ORR) and disease control rate (DCR) between treatment arms during the Blinded (first-line maintenance) phase;
* To evaluate the safety and tolerability profile of erlotinib in this patient population.

Study design

This is a multi-centre, randomized, placebo-controlled, Phase III study. The study will
consist of three components: (1) Screening phase, (2) Blinded phase, and (3) Open-label
phase.

The screening phase will consist of screening patients into the chemotherapy run-in
period with a (non-investigational) platinum based chemotherapy. In order to reflect current
practices in the management of advanced NSCLC, bevacizumab
can be added to the first-line chemotherapy regimen in countries where it has been
approved in this setting, and continued until disease progression in the Blinded phase of
the study in combination with erlotinib or placebo (depending on randomization).

Patients with already known EGFR mutated tumours (exon 19 deletion or exon 21 L858R
mutation) determined by local test will not be allowed into the Screening phase. Patients
with unknown EGFR mutation status or wild-type status determined by local test will be
allowed into the Screening phase, and their tumour will be tested in a central laboratory
to determine their EGFR mutational status (or confirm it as wild-type if locally assessed).
Patients whose sample is found to harbor an EGFR activating mutation by central laboratory test will not be randomized into the Blinded phase. In the event of

discordant
results, the central laboratory test result will overrule the local test result.
Patients whose tumours do not harbour an EGFR activating mutation (exon 19 deletion or
exon 21 L858R mutation) or have an indeterminate EGFR mutation status following central testing, and who do not progress following 4 cycles of platinum based chemotherapy (i.e. with documented complete response, partial response or stable disease
according to RECIST v1.1), will be randomized into the Blinded phase of the study (with
stratification).

The Blinded phase of the study will consist of patients being randomized to 150 mg/day
erlotinib (*early erlotinib* arm) or placebo (*late erlotinib* arm) in the maintenance
setting until the occurrence of disease progression, death or unacceptable toxicities.
Following randomization, patients who demonstrate disease progression (according to
RECIST v1.1 or because of symptomatic deterioration attributed to suspected tumour
progression), will be unblinded and will enter the Open-label phase of the study. If the
patient was randomized to the *early erlotinib* arm, the investigator will have the option
of providing the patient with best supportive care or an approved second line therapy
(such as pemetrexed or docetaxel, but not EGFR-directed therapies). This decision will
be guided by the patient*s preference and the investigator*s medical judgment. If the
patient was randomized to the *late erlotinib* arm (first-line maintenance with placebo),
the patient will receive second-line erlotinib provided by the sponsor until the occurrence
of further disease progression (confirmed by the treating physician; determined on the
basis of radiological evidence or symptomatic deterioration, according to local practices),
death, or unacceptable toxicities.During the Blinded phase of the study, data will be captured.

In the Open-label phase of the study, only SAEs will be captured in addition to survival and
subsequent treatment data until PD, death or unacceptable toxicity. Only survival and

subsequent treatment data will be collected thereafter.

Intervention

Take one tablet of Tarceva or placebo oraaly every day.

Study burden and risks

Erlotinib has been shown to improve survival in patients with advanced NSCLC without concomitant bone marrow toxicity. In NSCLC, erlotinib monotherapy has shown a clinically relevant and statistically significant survival benefit in the first-line maintenance, second-line and third-line settings Collectively, data from the SATURN and BR.21 studies support the benefit of Tarceva in both the first-line maintenance and second-line setting in NSCLC patients. The purpose of the present study is to prospectively determine the relative survival benefit of *early* versus *late* erlotinib therapy in patients with advanced (Stage IIIB and not amenable for combined modality treatment) or metastatic (Stage IV) NSCLC.
Given the demonstrated efficacy of erlotinib when administered in the first-line maintenance and second-line setting, and its the well established safety profile in NSCLC patients, the potential benefits to patients enrolling in study BO25460 outweigh the potential risks.

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

- Adult patients, >/<= 18 years of age (or >/<= legal age of consent if greater than 18)
- Advanced or recurrent (Stage IIIb) or metastatic (Stage IV) non-small cell lung cancer (NSCLC)
- Completion of 4 cycles of platinum-based chemotherapy without progression (end of last cycle - ECOG performance status 0-1
(for complete inclusion criteria see protocol p34-35)

Exclusion criteria

- Prior exposure to agents directed at HER axis (e.g. erlotinib, gafitinib, cetuximab)
- Patients whose tumours harbour EGFR activating mutation
- Prior chemotherapy or therapy with systemic anti-neoplastic therapy for advanced disease before screening (platinum-based chemotherapy)
- Use of pemetrexed in maintenance setting (pemetrexed is allowed during the chemotherapy run-in)
- Patients who have undergone complete tumour resection after responding to platinum-based chemotherapy during the screening phase
- Any other malignancies within 5 years, except for curatively resected carcinoma in situ of the cervix, basal or squamous cell skin cancer, ductal carcinoma in situ or organ confined prostate cancer
- CNS metastases or spinal cord compression that has not been definitely treated with surgery and/or radiation, or treated CNS metastases or spinal cord compression without stable disease for >/=2 months
- HIV, hepatitis B or hepatitis C infection
- Any inflammatory changes of the surface of the eye
(for complete exclusion criteria see protocol p35-36)

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	26-04-2012
Enrollment:	32
Type:	Actual

Medical products/devices used

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

Ethics review

Approved WMO Date:	20-06-2011
Application type:	First submission
Review commission:	METC Z: Zuyderland-Zuyd (Heerlen)
Approved WMO Date:	12-09-2011
Application type:	First submission
Review commission:	METC Z: Zuyderland-Zuyd (Heerlen)

Approved WMO Date:	20-10-2011
Application type:	Amendment
Review commission:	METC Z: Zuyderland-Zuyd (Heerlen)
Approved WMO Date:	10-11-2011
Application type:	Amendment
Review commission:	METC Z: Zuyderland-Zuyd (Heerlen)
Approved WMO Date:	13-12-2011
Application type:	Amendment
Review commission:	METC Z: Zuyderland-Zuyd (Heerlen)
Approved WMO Date:	12-04-2012
Application type:	Amendment
Review commission:	METC Z: Zuyderland-Zuyd (Heerlen)
Approved WMO Date:	25-07-2012
Application type:	Amendment
Review commission:	METC Z: Zuyderland-Zuyd (Heerlen)
Approved WMO Date:	18-04-2013
Application type:	Amendment
Review commission:	METC Z: Zuyderland-Zuyd (Heerlen)

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	EUCTR2010-024468-16-NL
CCMO	NL36882.096.11