Clinical trial results:
Phase II, open-label study of erlotinib (Tarceva®) treatment in patients with locally advanced, metastatic or recurrent non-small cell lung cancer who present activating mutations in the tyrosine kinase domain of the epidermal growth factor receptor

Summary

EudraCT number	2010-024061-48
Trial protocol	BG
Global end of trial date	10 January 2014

Results information

Result version number	v1 (current)
This version publication date	12 March 2016
First version publication date	12 March 2016

Trial information

Trial identification

Sponsor protocol code	ML25423

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01372384
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	F. Hoffmann-La Roche AG
Sponsor organisation address	Grenzacherstrasse 124, Basel,, Switzerland, CH-4070
Public contact	Roche Trial Information Hotline, F. Hoffmann-La Roche AG, +41 61 6878333, global.trial_information@roche.com
Scientific contact	Roche Trial Information Hotline, F. Hoffmann-La Roche AG, +41 61 6878333, global.trial_information@roche.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	10 January 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	10 January 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Evaluate efficacy of erlotinib (Tarceva TM; 150 mg) on progression free survival (PFS) in participants with non-small cell lung cancer (NSCLC) in locally advanced or metastatic stages (Stage IIIB and Stage IV) or recurrent NSCLC who have not received previous chemotherapy for their disease and who present activating mutations in the tyrosine kinase (TK) domain of the epidermal growth factor receptor (EGFR).

Protection of trial subjects:

The conduct of this clinical study met all local legal and regulatory requirements. The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and the International Conference on Harmonization guideline E6: Good Clinical Practice. Before entering the study, the informed consent form was read by and explained to all participants and/or their legally authorized representative. Participants signed informed consent form and could withdraw from the study at any time without any disadvantage and without having to provide a reason for this decision. Only investigators qualified by training and experience were selected as appropriate experts to investigate the study drug.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	06 January 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Bulgaria: 6
Worldwide total number of subjects	6
EEA total number of subjects	6

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0

Adults (18-64 years)	2
From 65 to 84 years	4
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

In all, 145 patients were screened. Of these, 6 participants were randomized; major reason for screen failure was negative mutation status.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	Erlotinib

Arm description:

Participants received recommended dose of erlotinib (150 mg/day). No dose escalation of erlotinib was permitted. Participants were treated until disease progression, unacceptable toxicity, death or participant request for discontinuation.

Arm type	Experimental
Investigational medicinal product name	Erlotinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Erlotinib was administered as a single daily oral dose as a Tablet of 150 mg, with up to 200 ml of water, preferably in the morning. No dose escalation of erlotinib was permitted. The study drug was taken at least 1 hour before or 2 hours after ingestion of food or any other medication.

Number of subjects in period 1	Erlotinib
Started	6
Completed	3
Not completed	3
Progression of disease	3

Baseline characteristics

Reporting groups	
Reporting group title	Erlotinib
Reporting group description:	
Participants received recommended dose of erlotinib (150 mg/day). No dose escalation of erlotinib was permitted. Participants were treated until disease progression, unacceptable toxicity, death or participant request for discontinuation.	

Reporting group values	Erlotinib	Total	
Number of subjects	6	6	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	2	2	
From 65-84 years	4	4	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	66.5		
standard deviation	± 6.19	-	
Gender categorical Units: Subjects			
Female	3	3	
Male	3	3	

End points

End points reporting groups

Reporting group title	Erlotinib

Reporting group description:

Participants received recommended dose of erlotinib (150 mg/day). No dose escalation of erlotinib was permitted. Participants were treated until disease progression, unacceptable toxicity, death or participant request for discontinuation.

Subject analysis set title	Intent-to-treat population
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The Intent-to-treat (ITT) population included all participants with at least one valid post-baseline assessment.

Subject analysis set title	Per-Protocol population
Subject analysis set type	Per protocol

Subject analysis set description:

The per-protocol (PP) population included all participants from the ITT population who did not violate the inclusion criteria: Histologically documented inoperable, locally advanced (Stage IIIB with supraclavicular lymph node metastases or malignant pleural or pericardial effusion [if clinically significant – after treatment]) or metastatic (Stage IV) NSCLC or recurrent NSCLC disease who presented with activating mutations (exon 19 deletions or exon 21 substitution L858R) in the tyrosine kinase domain of EGFR.

Subject analysis set title	Safety population
Subject analysis set type	Safety analysis

Subject analysis set description:

All participants who received at least one dose of study drug and had a safety assessment performed post baseline were included in the safety population. Participants were analyzed according to the first dose received during the study.

Primary: Progression Free Survival

End point title	Progression Free Survival[1]

End point description:

Progression free survival is (PFS) defined as the time from the first dose of erlotinib to the date of first occurrence of disease progression or death. The ITT population was used for the analysis.

End point type	Primary

End point timeframe:

Until participants had disease progression, unacceptable toxicity or died (approximately 24 months).

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Primary end point was described using descriptive statistics; no statistical analyses were carried out.

End point values	Erlotinib			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: Days				
median (inter-quartile range (Q1-Q3))	223 (137 to 297)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival

End point title	Overall survival

End point description:

The overall survival (OS) is defined as the time from the first dose of erlotinib to the date of death due to any cause. The ITT population was used for the analysis.

End point type	Secondary

End point timeframe:

Until participants had disease progression, unacceptable toxicity, or died (approximately 24 months).

End point values	Erlotinib			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: Days				
median (inter-quartile range (Q1-Q3))	401 (160 to 670)			

Statistical analyses

No statistical analyses for this end point

Secondary: Objective Response Rate (Investigator Assessed)

End point title	Objective Response Rate (Investigator Assessed)

End point description:

Objective response rate (ORR) was defined by Response evaluation criteria in solid tumors (RECIST) criteria 1.1 : Partial response (PR) was defined as >= 30% decrease in the sum of longest diameter of all target lesions, from the baseline sum. Complete response (CR) was defined as disappearance of all target and non-target lesions. For CR or PR, tumor measurements must be confirmed by 2nd assessments within 4 weeks. Progression of disease (PD) was defined as 20% increase in the sum of longest diameter of all target lesions, from smallest sum of longest diameter of all target lesions recorded at or after baseline; or a new lesion; or progression of non-target lesions. Stable Disease (SD) was defined as neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on the study. The ITT population was used for the analysis.

End point type	Secondary

End point timeframe:

Visit 4, Visit 6, Visit 10 and Visit 22 (approximately 24 months)

End point values	Erlotinib			
Subject group type	Reporting group			
Number of subjects analysed	6[2]			
Units: Percentage				
number (confidence interval 95%)				
Visit 4, SD, n = 5	83.3 (35.87 to 99.58)			

Visit 4, PR, n = 1	16.7 (0.42 to 64.13)			
Visit 6, SD, n = 2	33.3 (4.32 to 77.73)			
Visit 6, PR, n = 2	33.3 (4.32 to 77.73)			
Visit 6, PD, n = 2	33.3 (4.32 to 77.73)			
Visit 10, PR, n = 2	33.3 (4.32 to 77.73)			
Visit 10, PD, n = 4	66.7 (22.27 to 95.68)			
Visit 22, PD, n = 6	100 (0 to 100)			

Notes:

[2] - Only those participants available at the specified time points were analyzed (represented by n=X)

Attachments (see zip file)	Statistical Analysis for between proportions of Re/Statistical

Statistical analyses

No statistical analyses for this end point

Secondary: Safety: Incidence of Adverse Events

End point title	Safety: Incidence of Adverse Events

End point description:

An AE is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product. An SAE is any experience that suggests a significant hazard, contraindication, side effect, or precaution. The safety population was used for the analysis.

End point type	Secondary

End point timeframe:

Until participants had disease progression, unacceptable toxicity, or died (approximately 24 months).

End point values	Erlotinib			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: Participants				
Any AE	6			
Any SAE	1			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 24 months

Adverse event reporting additional description:

Serious adverse events and non-serious adverse events are reported in Safety Analysis Set, consists of all participants who received at least one dose of study drug and had a safety assessment performed post baseline.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	Erlotinib

Reporting group description:

Participants received recommended dose of erlotinib (150 mg/day). No dose escalation of erlotinib was permitted. Participants were treated until disease progression, unacceptable toxicity, death or participant request for discontinuation.

Serious adverse events	Erlotinib		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 6 (16.67%)		
number of deaths (all causes)	3		
number of deaths resulting from adverse events	0		
Respiratory, thoracic and mediastinal disorders			
Bronchopneumonia			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Erlotinib		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 6 (100.00%)		
Investigations			
Blood bilirubin increased			
subjects affected / exposed	2 / 6 (33.33%)		
occurrences (all)	2		

Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	 1 / 6 (16.67%) 1		
Eye disorders Keratitis subjects affected / exposed occurrences (all)	 1 / 6 (16.67%) 1		
Reproductive system and breast disorders Orchitis subjects affected / exposed occurrences (all) Candidiasis subjects affected / exposed occurrences (all)	 1 / 6 (16.67%) 1 1 / 6 (16.67%) 1		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) Dyspnoea subjects affected / exposed occurrences (all) Pleural effusion subjects affected / exposed occurrences (all)	 1 / 6 (16.67%) 1 1 / 6 (16.67%) 1 1 / 6 (16.67%) 1		
Skin and subcutaneous tissue disorders Rash maculo-papular subjects affected / exposed occurrences (all) Alopecia subjects affected / exposed occurrences (all)	 5 / 6 (83.33%) 7 1 / 6 (16.67%) 1		
Musculoskeletal and connective tissue disorders Parasternal pain subjects affected / exposed occurrences (all)	 1 / 6 (16.67%) 1		

Infections and infestations Forunculosis subjects affected / exposed occurrences (all)	 1 / 6 (16.67%) 1		
Metabolism and nutrition disorders Abnormal loss of weight subjects affected / exposed occurrences (all) Abnormal weight gain subjects affected / exposed occurrences (all)	 2 / 6 (33.33%) 2 1 / 6 (16.67%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

None reported

Notes: