Clinical trial results:
Biomarkers Impact on the Response to Treatment With Erlotinib in First Line Non-small Cell Lung Cancer With EGFR Activating Mutations - BIOTEC

Summary

EudraCT number	2009-017063-42
Trial protocol	RO
Global end of trial date	14 July 2015

Results information

Result version number	v1 (current)
This version publication date	24 March 2017
First version publication date	24 March 2017

Trial information

Trial identification

Sponsor protocol code	ML22606

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01153984
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 616878333, global.trial_information@roche.com
Scientific contact	Roche Trial Information Hotline, F. Hoffmann-La Roche AG, +41 616878333, 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	14 July 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	14 July 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This is a multi-center open-label, single arm, Phase II trial with erlotinib as first-line therapy in participants who are chemotherapy-naive with advanced and/or metastatic (Stage IIIB/ IV) non-small cell lung cancer (NSCLC) and endothelial growth factor receptor (EGFR) activating mutations to assess the progression free survival, time to progression, objective response rate, and 1-year survival rate.

Protection of trial subjects:

The study was conducted in accordance with the principles of the "Declaration of Helsinki" and Good Clinical Practice (GCP).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 June 2011
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	Romania: 23
Worldwide total number of subjects	23
EEA total number of subjects	23

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)	19
From 65 to 84 years	4
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Ninety participants were screened and 23 participants were enrolled.

Period 1

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

Arms

Arm title	Erlotinib

Arm description:

Participants received 150 milligrams (mg) erlotinib orally daily until disease progression, unacceptable toxicity, withdrawal due to any reason or death.

Arm type	Experimental
Investigational medicinal product name	Erlotinib
Investigational medicinal product code	
Other name	Tarceva
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Erlotinib 150 mg oral doses were administered daily.

Number of subjects in period 1	Erlotinib
Started	23
Completed	21
Not completed	2
Consent withdrawn by subject	1
Adverse event	1

Baseline characteristics

Reporting groups	
Reporting group title	Erlotinib
Reporting group description:	
Participants received 150 milligrams (mg) erlotinib orally daily until disease progression, unacceptable toxicity, withdrawal due to any reason or death.	

Reporting group values	Erlotinib	Total	
Number of subjects	23		
Age categorical Units: Subjects			

Age Continuous Units: years			
arithmetic mean	55.52		
standard deviation	± 11.59	-	
Gender, Male/Female Units:			

End points

End points reporting groups

Reporting group title	Erlotinib

Reporting group description:

Participants received 150 milligrams (mg) erlotinib orally daily until disease progression, unacceptable toxicity, withdrawal due to any reason or death.

Primary: Progression-Free Survival (PFS), as Assessed by Investigator Using Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1)

End point title	Progression-Free Survival (PFS), as Assessed by Investigator Using Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1)[1]

End point description:

PFS was the time from inclusion in the study to the date of first documented PD or death from any cause, whichever occurred first. Participants without event were censored at the date of the last tumor assessment where non-progression was documented. If a participant received a second anti-cancer therapy without prior documentation of disease progression, the participant was censored at the date of last tumor assessment before starting new chemotherapy. Analysis was performed using Kaplan-Meier method. PD was defined as at least a 20% increase in the sum of LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of 1 or more new lesions. All enrolled participants.

End point type	Primary

End point timeframe:

Baseline up to approximately 4 years

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: No statistical analysis was planned in this study.

End point values	Erlotinib			
Subject group type	Reporting group			
Number of subjects analysed	23			
Units: days				
median (confidence interval 95%)	387 (103.592 to 670.408)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Disease Progression, as Assessed by Investigator Using RECIST v1.1

End point title	Time to Disease Progression, as Assessed by Investigator Using RECIST v1.1

End point description:

Time to disease progression was defined as the time from baseline evaluation to the first date PD was recorded. Participants without progression were censored at the date of last tumor assessment where non-progression was documented. PD was defined as at least a 20% increase in the sum of LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of 1 or more new lesions. All enrolled participants.

End point type	Secondary

End point timeframe:

Baseline up to approximately 4 years

End point values	Erlotinib			
Subject group type	Reporting group			
Number of subjects analysed	23			
Units: days				
median (confidence interval 95%)	193 (57.137 to 328.863)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Complete Response (CR) And Partial Response (PR) as Assessed by the Investigator Using RECIST v1.1

End point title	Percentage of Participants with Complete Response (CR) And Partial Response (PR) as Assessed by the Investigator Using RECIST v1.1

End point description:

CR was defined as the disappearance of all target lesions, and PR was defined as at least a 30% decrease in the sum of the longest diameter compared to baseline. All enrolled participants.

End point type	Secondary

End point timeframe:

Baseline up to approximately 4 years

End point values	Erlotinib			
Subject group type	Reporting group			
Number of subjects analysed	23			
Units: percentage of participants				
number (not applicable)				
CR	0			
PR	8.7			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants who Were Alive One Year After Study Treatment Initiation

End point title	Percentage of Participants who Were Alive One Year After

	Study Treatment Initiation
End point description:	
All enrolled participants with available data for this end point.	
End point type	Secondary
End point timeframe:	
Year 1	

End point values	Erlotinib			
Subject group type	Reporting group			
Number of subjects analysed	21			
Units: percentage of participants				
number (not applicable)	85.7			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants by Localization of PD as Assessed by Investigator Using RECIST v1.1

End point title	Percentage of Participants by Localization of PD as Assessed by Investigator Using RECIST v1.1
End point description:	
PD was assessed using RECIST v1.1. PD was defined as at least a 20% increase in the sum of LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of 1 or more new lesions. Percentage of participants by localization of PD were reported. Localization included: Left lung inferior lobe; Para-aortic; Left lung upper lobe; Right lung inferior lobe; and Infracranial. All enrolled participants with available data for this end point.	
End point type	Secondary
End point timeframe:	
Baseline up to approximately 4 years	

End point values	Erlotinib			
Subject group type	Reporting group			
Number of subjects analysed	21			
Units: percentage of participants				
number (not applicable)				
Left lung inferior lobe	24			
Para-aortic	14			
Left lung upper lobe	10			
Right lung inferior lobe	14			
Infracranial	38			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of EGFR Positive Participants Classified Based on Smoking Status

End point title	Number of EGFR Positive Participants Classified Based on Smoking Status

End point description:

Participants were asked: "Have you smoked at least 100 cigarettes in your entire life?" and "Do you now smoke cigarettes every day, some days, or not at all?" Responses were grouped into three categories: Current Smoker, Former Smoker, and Non-Smoker. Participants who reported smoking at least 100 cigarettes in their lifetime and who, at the time of survey, smoked either every day or some days were defined as 'Current smoker'. Participants who reported smoking at least 100 cigarettes in their lifetime and who, at the time of the survey, did not smoke at all were defined as 'Former smoker'. Participants who reported never having smoked 100 cigarettes were defined as 'Non-smoker'. All enrolled participants.

End point type	Secondary

End point timeframe:

Day 1

End point values	Erlotinib			
Subject group type	Reporting group			
Number of subjects analysed	23			
Units: participants				
number (not applicable)				
Non-smoker	17			
Former smoker	3			
Current smoker	3			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of EGFR Positive Participants Classified Based on Type of EGFR Mutations

End point title	Number of EGFR Positive Participants Classified Based on Type of EGFR Mutations

End point description:

Participants with NSCLC have tumor associated with EGFR mutations. These mutations occur within EGFR Exons 18-21, which encodes a portion of the EGFR kinase domain. All enrolled participants.

End point type	Secondary

End point timeframe:

Day 1

End point values	Erlotinib			
Subject group type	Reporting group			
Number of subjects analysed	23			
Units: participants				
number (not applicable)				
Exon 19 deletions	20			
Exon 21 L858R	3			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Similar EGFR Mutations Between Matched Plasma and Tumor Tissue Samples

End point title	Percentage of Similar EGFR Mutations Between Matched Plasma and Tumor Tissue Samples

End point description:

End point type	Secondary

End point timeframe:

Baseline up to approximately 4 years

End point values	Erlotinib			
Subject group type	Reporting group			
Number of subjects analysed	0[2]			
Units: percentage of similar EGFR mutations				
number (not applicable)				

Notes:

[2] - No participants were analyzed for this outcome as no plasma samples during the study.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to approximately 5 years 4 months

Adverse event reporting additional description:

Safety analysis population included all participants who receive at least one dose of treatment and had at least one monthly assessment.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	Unspecific

Reporting groups

Reporting group title	Erlotinib

Reporting group description:

Participants received 150 mg erlotinib orally daily until disease progression, unacceptable toxicity, withdrawal due to any reason or death.

Serious adverse events	Erlotinib		
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 23 (21.74%)		
number of deaths (all causes)	11		
number of deaths resulting from adverse events			
Vascular disorders			
Ischemic stroke			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Pericardial effusion			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Nervous system disorders			
Hemiparesis			

subjects affected / exposed	1 / 23 (4.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Brain neoplasm malignant			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Respiratory, thoracic and mediastinal disorders			
Pleural effusion			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Infections and infestations			
Respiratory tract infection			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Erlotinib		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	15 / 23 (65.22%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences (all)	1		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 23 (4.35%)		
occurrences (all)	1		
Pyrexia			
subjects affected / exposed	8 / 23 (34.78%)		
occurrences (all)	8		

Chest pain subjects affected / exposed occurrences (all)	1 / 23 (4.35%) 1		
Reproductive system and breast disorders Vaginal hemorrhages subjects affected / exposed occurrences (all)	1 / 23 (4.35%) 2		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) Pharyngeal inflammation subjects affected / exposed occurrences (all) Dyspnea subjects affected / exposed occurrences (all) Pneumonitis subjects affected / exposed occurrences (all)	1 / 23 (4.35%) 2 1 / 23 (4.35%) 1 1 / 23 (4.35%) 1 1 / 23 (4.35%) 1		
Investigations Transaminases increased subjects affected / exposed occurrences (all)	1 / 23 (4.35%) 2		
Injury, poisoning and procedural complications Arthropod bite subjects affected / exposed occurrences (all)	1 / 23 (4.35%) 1		
Cardiac disorders Syncope subjects affected / exposed occurrences (all)	1 / 23 (4.35%) 1		
Nervous system disorders Headache subjects affected / exposed occurrences (all)	1 / 23 (4.35%) 1		

Eye disorders Conjunctivitis subjects affected / exposed occurrences (all)	 1 / 23 (4.35%) 3		
Gastrointestinal disorders Vomiting subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Abdominal pain subjects affected / exposed occurrences (all) Dyspepsia subjects affected / exposed occurrences (all)	 1 / 23 (4.35%) 1 3 / 23 (13.04%) 6 1 / 23 (4.35%) 2 1 / 23 (4.35%) 1 1 / 23 (4.35%) 1		
Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all)	 7 / 23 (30.43%) 15		
Endocrine disorders Menorrhagia subjects affected / exposed occurrences (all)	 1 / 23 (4.35%) 1		
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all) Musculoskeletal pain subjects affected / exposed occurrences (all)	 1 / 23 (4.35%) 1 1 / 23 (4.35%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 August 2013	Protocol was amended to reduce the number of the enrolled participants, study procedures, adverse events reporting and other modifications.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported