Clinical trial results:
OPEN LABEL STUDY OF ERLOTINIB (TARCEVA®) AS SINGLE AGENT FIRST LINE TREATMENT OF PATIENTS WITH LOCALLY ADVANCED OR METASTATIC LUNG ADENOCARCINOMA WITH ACTIVATING EPIDERMAL GROWTH FACTOR RECEPTOR (EGFR) MUTATIONS

Summary

EudraCT number	2011-002168-26
Trial protocol	HU LV
Global end of trial date	30 January 2015

Results information

Result version number	v1 (current)
This version publication date	25 February 2016
First version publication date	25 February 2016

Trial information

Trial identification

Sponsor protocol code	ML27880

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01609543
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	F.Hoffmann-LaRoche AG, Roche Trial Information Hotline, 41 616878333, global.trial_information@roche.com
Scientific contact	F.Hoffmann-LaRoche AG, Roche Trial Information Hotline, 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	30 January 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	30 January 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This was a Phase IV, open label, multicenter study to evaluate the effectiveness of erlotinib hydrochloride (Tarceva) in participants with locally advanced or metastatic lung adenocarcinoma with activating Epidermal Growth Factor Receptor (EGFR).

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	28 March 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	Hungary: 35
Country: Number of subjects enrolled	Latvia: 12
Country: Number of subjects enrolled	Turkey: 15
Worldwide total number of subjects	62
EEA total number of subjects	47

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)	24
From 65 to 84 years	36

85 years and over	2

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 651 participants were screened and among them 62 participants were enrolled in the study.

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 Hydrochloride

Arm description:

Participants received a single 150 milligrams (mg) oral dose of erlotinib hydrochloride (Tarceva) tablet daily from Day 1 until disease progression, death, unacceptable toxicity or consent withdrawal, whichever occurred first up to 34 months.

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

Dosage and administration details:

Participants received single 150 mg oral dose of erlotinib hydrochloride tablet daily from Day 1 until disease progression, death, unacceptable toxicity or consent withdrawal, whichever occurred first up to 34 months.

Number of subjects in period 1	Erlotinib Hydrochloride
Started	62
Completed	20
Not completed	42
Consent withdrawn by subject	1
Adverse Event	5
Death	7
Disease Progression	28
Protocol deviation	1

Baseline characteristics

Reporting groups	
Reporting group title	Overall Study (overall period)
Reporting group description:	
Participants received a single 150 milligrams (mg) oral dose of erlotinib hydrochloride (Tarceva) tablet daily from Day 1 until disease progression, death, unacceptable toxicity or consent withdrawal, whichever occurred first up to 34 months.	

Reporting group values	Overall Study (overall period)	Total	
Number of subjects	62	62	
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	 67.69 ± 10.562	 -	
Gender categorical Units: Subjects			
Female	50	50	
Male	12	12	

End points

End points reporting groups

Reporting group title	Erlotinib Hydrochloride

Reporting group description:

Participants received a single 150 milligrams (mg) oral dose of erlotinib hydrochloride (Tarceva) tablet daily from Day 1 until disease progression, death, unacceptable toxicity or consent withdrawal, whichever occurred first up to 34 months.

Primary: Progression-Free Survival (PFS)

End point title	Progression-Free Survival (PFS)[1]

End point description:

PFS was defined as median time from the first dose of study treatment to the first documentation of objective tumor progression (according to Response Evaluation Criteria in Solid Tumours [RECIST] version 1.1) or to death due to any cause, whichever occurred first. Progressive Disease (PD) was defined as at least a 20 percent (%) increase in the sum of diameters of target lesions, taking as reference the smallest sum on study. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. Unequivocal progression of existing non-target lesions. The appearance of one or more new lesions is also considered progression. Median and the 95% confidence interval were estimated using Kaplan-Meier survival methodology. Intent-to-treat (ITT) population included all enrolled participants.

End point type	Primary

End point timeframe:

Baseline to progressive disease or death (up to 34 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: As the study was non-comparative in nature, no statistical analysis was performed.

End point values	Erlotinib Hydrochloride			
Subject group type	Reporting group			
Number of subjects analysed	62			
Units: months				
median (confidence interval 95%)	12.846 (9.901 to 15.791)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Best Overall Response (BOR)

End point title	Percentage of Participants With Best Overall Response (BOR)

End point description:

BOR was defined as best tumor response (as per RECIST version 1.1) recorded for a participant during study. Complete Response (CR): disappearance of all target and non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (less than [<] 10 millimeters [mm] short axis). Partial Response (PR): at least a 30% decrease in sum of diameters of target lesions, taking as reference the baseline sum diameters. PD: at least a 20% increase in sum of diameters of target lesions, taking as reference the smallest sum on study. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. Unequivocal progression of

existing non-target lesions. Appearance of one or more new lesions is also considered progression. Stable Disease (SD): neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study. ITT population.

End point type	Secondary

End point timeframe:

Baseline to progressive disease or death (up to 34 months)

End point values	Erlotinib Hydrochloride			
Subject group type	Reporting group			
Number of subjects analysed	62			
Units: percentage of participants				
number (not applicable)				
CR	1.8			
PR	64.3			
SD	32.1			
PD	1.8			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Who Were Alive at 1 Year

End point title	Percentage of Participants Who Were Alive at 1 Year

End point description:

ITT population. Here, number of participants analyzed signifies those participants who were evaluable for this outcome.

End point type	Secondary

End point timeframe:

1 Year (12 months)

End point values	Erlotinib Hydrochloride			
Subject group type	Reporting group			
Number of subjects analysed	40			
Units: percentage of participants				
number (not applicable)	82.5			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Baseline up to 28 days after the last dose of study medication (up to 34 months)	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups	
Reporting group title	Erlotinib Hydrochloride
Reporting group description:	
Participants received a single 150 mg oral dose of erlotinib hydrochloride tablet daily from Day 1 until disease progression, death, unacceptable toxicity or consent withdrawal, whichever occurred first up to 34 months.	

Serious adverse events	Erlotinib Hydrochloride		
Total subjects affected by serious adverse events			
subjects affected / exposed	26 / 62 (41.94%)		
number of deaths (all causes)	13		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Infected neoplasm			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Chest pain			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pain			

subjects affected / exposed	1 / 62 (1.61%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pyrexia				
subjects affected / exposed	1 / 62 (1.61%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Sudden cardiac death				
subjects affected / exposed	1 / 62 (1.61%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Respiratory, thoracic and mediastinal disorders				
Cough				
subjects affected / exposed	1 / 62 (1.61%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Dyspnoea				
subjects affected / exposed	2 / 62 (3.23%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Haemoptysis				
subjects affected / exposed	1 / 62 (1.61%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Haemothorax				
subjects affected / exposed	1 / 62 (1.61%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pleural effusion				
subjects affected / exposed	2 / 62 (3.23%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Pneumothorax				

subjects affected / exposed	1 / 62 (1.61%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pulmonary embolism				
subjects affected / exposed	1 / 62 (1.61%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Pulmonary haemorrhage				
subjects affected / exposed	1 / 62 (1.61%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Investigations				
Alanine aminotransferase increased				
subjects affected / exposed	1 / 62 (1.61%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Aspartate aminotransferase increased				
subjects affected / exposed	1 / 62 (1.61%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Liver function test abnormal				
subjects affected / exposed	1 / 62 (1.61%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Atrial fibrillation				
subjects affected / exposed	1 / 62 (1.61%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pericardial effusion				
subjects affected / exposed	1 / 62 (1.61%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Nervous system disorders			
Balance disorder			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Headache			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			
subjects affected / exposed	5 / 62 (8.06%)		
occurrences causally related to treatment / all	4 / 5		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ileus paralytic			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Nausea			

subjects affected / exposed	1 / 62 (1.61%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	3 / 62 (4.84%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Hepatic function abnormal			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Liver injury			
subjects affected / exposed	2 / 62 (3.23%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	5 / 62 (8.06%)		
occurrences causally related to treatment / all	6 / 6		
deaths causally related to treatment / all	0 / 0		
Rash generalised			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Rash maculo-papular			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	2 / 62 (3.23%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		

Renal failure			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Musculoskeletal chest pain			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	2 / 62 (3.23%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
Hyponatraemia			
subjects affected / exposed	2 / 62 (3.23%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Hypovolaemia			
subjects affected / exposed	1 / 62 (1.61%)		
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 Hydrochloride		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	49 / 62 (79.03%)		
Investigations			

Blood alkaline phosphatase increased subjects affected / exposed occurrences (all) Weight decreased subjects affected / exposed occurrences (all)	5 / 62 (8.06%) 5 4 / 62 (6.45%) 5		
Nervous system disorders Headache subjects affected / exposed occurrences (all)	5 / 62 (8.06%) 5		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	5 / 62 (8.06%) 6		
General disorders and administration site conditions Asthenia subjects affected / exposed occurrences (all)	5 / 62 (8.06%) 9		
Eye disorders Growth of eyelashes subjects affected / exposed occurrences (all)	5 / 62 (8.06%) 5		
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all)	17 / 62 (27.42%) 26 4 / 62 (6.45%) 5		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) Dyspnoea subjects affected / exposed occurrences (all)	8 / 62 (12.90%) 8 5 / 62 (8.06%) 5		
Skin and subcutaneous tissue disorders			

Alopecia subjects affected / exposed occurrences (all) Dry skin subjects affected / exposed occurrences (all) Pruritus subjects affected / exposed occurrences (all) Rash subjects affected / exposed occurrences (all)	7 / 62 (11.29%) 7 11 / 62 (17.74%) 15 9 / 62 (14.52%) 10 36 / 62 (58.06%) 43		
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all)	7 / 62 (11.29%) 8		
Infections and infestations Conjunctivitis subjects affected / exposed occurrences (all)	6 / 62 (9.68%) 8		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	4 / 62 (6.45%) 4		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
31 May 2013	The protocol was amended to modify the required number of enrolled participants, number of initiated sites, and expansion of the recruitment period; to include permission for uric acid test and rescreening, tumour measurement and reporting of survival status at the end of study visit were included; to allow further participation in study after erlotinib was widely reimbursed for the countries and exclusion of data of non-compliant participant from the statistical analysis; to include guided questionnaire for the predefined events to monitor, to revise AE/SAE reporting requirement. Additional administrative changes and clarification were also made.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported