



## Clinical trial results:

### Phase II, Open-Label Study of Erlotinib (Tarceva®) Treatment in Patients With Locally Advanced or Metastatic Non-Small Cell Lung Cancer Who Present Activating Mutations in the Tyrosine Kinase Domain of the Epidermal Growth Factor Receptor

#### Summary

EudraCT number	2010-022509-17
Trial protocol	PT
Global end of trial date	29 September 2017

#### Results information

Result version number	v1 (current)
This version publication date	12 October 2018
First version publication date	12 October 2018

#### Trial information

##### Trial identification

Sponsor protocol code	ML25434
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01260181
WHO universal trial number (UTN)	-

Notes:

#### Sponsors

Sponsor organisation name	Hoffmann-La Roche
Sponsor organisation address	Grenzacherstrasse 124, Basel, Switzerland, CH-4070
Public contact	F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.com
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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:

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**Results analysis stage**

Analysis stage	Final
Date of interim/final analysis	29 September 2017
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	29 September 2017
Was the trial ended prematurely?	No

Notes:

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**General information about the trial**

Main objective of the trial:

This single arm, open-label study evaluated the efficacy and safety of erlotinib (Tarceva) in subjects with locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) mutations.

Protection of trial subjects:

All study subjects were required to read and sign an informed consent form.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	31 March 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

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**Population of trial subjects****Subjects enrolled per country**

Country: Number of subjects enrolled	Portugal: 30
Worldwide total number of subjects	30
EEA total number of subjects	30

Notes:

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**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)	13
From 65 to 84 years	17
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

A total of 30 subjects were included in the study.

### Pre-assignment

Screening details:

A total of 216 subjects were screened for this study in Portugal. From those, 186 were screening failures due to not complying with inclusion/exclusion criteria or at subjects decision. Thirty subjects were enrolled to 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
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Arm description:

Subjects received erlotinib 150 milligrams (mg) orally daily until disease progression.

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 tablet was taken orally daily.

Number of subjects in period 1	Erlotinib
Started	30
Completed	29
Not completed	1
Decision of Investigator	1

## Baseline characteristics

### Reporting groups

Reporting group title	Erlotinib
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Reporting group description:

Subjects received erlotinib 150 milligrams (mg) orally daily until disease progression.

Reporting group values	Erlotinib	Total	
Number of subjects	30	30	
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)	13	13	
From 65-84 years	17	17	
85 years and over	0	0	
Age Continuous			
Units: years			
arithmetic mean	66.33		
standard deviation	± 9.21	-	
Sex: Female, Male			
Units: Subjects			
Female	24	24	
Male	6	6	
Race (NIH/OMB)			
Units: Subjects			
American Indian or Alaska Native	0	0	
Asian	0	0	
Native Hawaiian or Other Pacific Islander	0	0	
Black or African American	0	0	
White	0	0	
More than one race	0	0	
Unknown or Not Reported	30	30	

## End points

### End points reporting groups

Reporting group title	Erlotinib
Reporting group description:	
Subjects received erlotinib 150 milligrams (mg) orally daily until disease progression.	

### Primary: Percentage of Subjects with Objective Response (Complete Response [CR]/Partial Response [PR]) Based on Computer Tomography (CT) or Magnetic Resonance Imaging (MRI) According to Response Evaluation Criteria in Solid Tumors (RECIST) Version (v) 1.1

End point title	Percentage of Subjects with Objective Response (Complete Response [CR]/Partial Response [PR]) Based on Computer Tomography (CT) or Magnetic Resonance Imaging (MRI) According to Response Evaluation Criteria in Solid Tumors (RECIST) Version (v) 1.1 <sup>[1]</sup>
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#### End point description:

Objective response (OR) was based on criteria related to changes in size of target lesions according to modified RECIST. Target lesions were selected on the basis of their size (lesions with the longest diameter) as well as the feasibility of reproducible repeated measurements. OR was the sum of complete response (CR) and partial response (PR) four at least 4 weeks during treatment. CR: disappearance of all target lesions. PR: at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters.

End point type	Primary
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#### End point timeframe:

Baseline up to 5 years (assessed at Baseline, every 8 weeks until disease progression or death or end of treatment period [up to 5 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: This was a one-armed study so no statistical analyses were done.

End point values	Erlotinib			
Subject group type	Reporting group			
Number of subjects analysed	30			
Units: percentage of subjects				
number (confidence interval 95%)	63.3 (46.1 to 80.6)			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Progression Free Survival (PFS) Based on CT or MRI According to RECIST v 1.1

End point title	Progression Free Survival (PFS) Based on CT or MRI According to RECIST v 1.1
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#### End point description:

Kaplan Meier estimate of the median PFS was defined as the time at which half of the participants have progressed (progressive disease [PD]) based on RECIST tumor response criteria or died from any cause, whichever occurred first. PD: At least a 20% increase in the sum of diameters of target lesions, taking

as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. Patients who had not died or progressed at the time of the final analysis were censored at the date of last contact.

End point type	Secondary
End point timeframe:	
Baseline up to 5 years (assessed at Baseline, every 8 weeks until disease progression or death or end of treatment period [up to 5 years])	

<b>End point values</b>	Erlotinib			
Subject group type	Reporting group			
Number of subjects analysed	30			
Units: weeks				
median (confidence interval 95%)	40 (31 to 63)			

## Statistical analyses

No statistical analyses for this end point

## Secondary: Overall Survival

End point title	Overall Survival
End point description:	
Overall Survival (OS) was defined as the time between the date of randomization and the date of death due to any cause.	
End point type	Secondary
End point timeframe:	
Baseline up to 5 years	

<b>End point values</b>	Erlotinib			
Subject group type	Reporting group			
Number of subjects analysed	30			
Units: weeks				
median (confidence interval 95%)	83 (56 to 125)			

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Subjects with Adverse Events

End point title	Percentage of Subjects with Adverse Events
End point description:	
An adverse event is any untoward medical occurrence in a participant administered a pharmaceutical	

product and which does not necessarily have to have a causal relationship with the treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a pharmaceutical product, whether or not considered related to the pharmaceutical product. Preexisting conditions which worsen during a study are also considered as adverse events.

End point type	Secondary
End point timeframe:	
Baseline up to 5 years	

<b>End point values</b>	Erlotinib			
Subject group type	Reporting group			
Number of subjects analysed	30			
Units: percentage of subjects	29			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Subjects with Epidermal Growth Factor Receptor (EGFR) Mutation in Study Population

End point title	Percentage of Subjects with Epidermal Growth Factor Receptor (EGFR) Mutation in Study Population	
End point description:		
Mutations in the EGFR included exon 19 deletion mutations and the single-point substitution mutation L858R in exon 21.		
End point type	Secondary	
End point timeframe:		
Screening (21 days prior to Day 1)		

<b>End point values</b>	Erlotinib			
Subject group type	Reporting group			
Number of subjects analysed	30			
Units: percentage of subjects				
Exon 19 mutation	40			
Exon 21 mutation	60			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Median Time Taken From the First Response Until Disease Progression Based on RECIST v 1.1 as Determined by the Investigator

End point title	Median Time Taken From the First Response Until Disease Progression Based on RECIST v 1.1 as Determined by the Investigator
End point description:	
The response duration was defined as the time of initial response (complete response (CR) /partial response (PR) whichever is first recorded) until documented disease progression. CR was defined as disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm. Partial response was defined as at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters. Disease progression was defined as At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study).	
End point type	Secondary
End point timeframe:	
Baseline up to 5 years (assessed at Baseline, every 8 weeks until disease progression or death or end of treatment period [up to 5 years])	

<b>End point values</b>	Erlotinib			
Subject group type	Reporting group			
Number of subjects analysed	30			
Units: weeks				
median (confidence interval 95%)	41.5 (32 to 63)			

### Statistical analyses

No statistical analyses for this end point



## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

5 years

Adverse event reporting additional description:

The safety population was identical to the ITT population, which included all subjects enrolled in the study.

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	21.0
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### Reporting groups

Reporting group title	Erlotinib
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Reporting group description:

Subjects received erlotinib 150 milligrams (mg) orally daily until disease progression.

Serious adverse events	Erlotinib		
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 30 (26.67%)		
number of deaths (all causes)	4		
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Fracture			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Death			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Intestinal Perforation			

subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Respiratory, thoracic and mediastinal disorders			
Pulmonary Embolism			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Rhabdomyolysis			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Pelvic Infection			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

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

<b>Non-serious adverse events</b>	Erlotinib		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	29 / 30 (96.67%)		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	7 / 30 (23.33%)		
occurrences (all)	8		
Oedema Peripheral			
subjects affected / exposed	5 / 30 (16.67%)		
occurrences (all)	6		
Influenza Like Illness			
subjects affected / exposed	4 / 30 (13.33%)		
occurrences (all)	4		
Asthenia			
subjects affected / exposed	3 / 30 (10.00%)		
occurrences (all)	3		
Pain			
subjects affected / exposed	3 / 30 (10.00%)		
occurrences (all)	4		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	4 / 30 (13.33%)		
occurrences (all)	4		
Dyspnoea			
subjects affected / exposed	3 / 30 (10.00%)		
occurrences (all)	7		
Haemoptysis			
subjects affected / exposed	3 / 30 (10.00%)		
occurrences (all)	3		
Nasal Congestion			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		
Productive Cough			

subjects affected / exposed occurrences (all)	2 / 30 (6.67%) 2		
Psychiatric disorders Anxiety subjects affected / exposed occurrences (all)	4 / 30 (13.33%) 4		
Depression subjects affected / exposed occurrences (all)	3 / 30 (10.00%) 3		
Insomnia subjects affected / exposed occurrences (all)	3 / 30 (10.00%) 3		
Investigations Blood Bilirubin Increased subjects affected / exposed occurrences (all)	2 / 30 (6.67%) 5		
Neutrophil Count Increased subjects affected / exposed occurrences (all)	2 / 30 (6.67%) 2		
Weight Decreased subjects affected / exposed occurrences (all)	2 / 30 (6.67%) 2		
Nervous system disorders Headache subjects affected / exposed occurrences (all)	4 / 30 (13.33%) 4		
Dizziness subjects affected / exposed occurrences (all)	3 / 30 (10.00%) 3		
Blood and lymphatic system disorders Leukocytosis subjects affected / exposed occurrences (all)	2 / 30 (6.67%) 2		
Eye disorders Dry Eye subjects affected / exposed occurrences (all)	5 / 30 (16.67%) 6		

Blepharitis			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		
Cataract			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	15 / 30 (50.00%)		
occurrences (all)	19		
Constipation			
subjects affected / exposed	6 / 30 (20.00%)		
occurrences (all)	6		
Nausea			
subjects affected / exposed	5 / 30 (16.67%)		
occurrences (all)	6		
Stomatitis			
subjects affected / exposed	5 / 30 (16.67%)		
occurrences (all)	6		
Dyspepsia			
subjects affected / exposed	3 / 30 (10.00%)		
occurrences (all)	3		
Abdominal Pain			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		
Odynophagia			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		
Vomiting			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		
Skin and subcutaneous tissue disorders			
Dermatitis Acneiform			
subjects affected / exposed	19 / 30 (63.33%)		
occurrences (all)	30		
Rash Maculo-Papular			

subjects affected / exposed	8 / 30 (26.67%)		
occurrences (all)	11		
Alopecia			
subjects affected / exposed	5 / 30 (16.67%)		
occurrences (all)	5		
Acne			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	3		
Erythema			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		
Pruritus			
subjects affected / exposed	5 / 30 (16.67%)		
occurrences (all)	5		
Renal and urinary disorders			
Pollakiuria			
subjects affected / exposed	3 / 30 (10.00%)		
occurrences (all)	3		
Musculoskeletal and connective tissue disorders			
Back Pain			
subjects affected / exposed	5 / 30 (16.67%)		
occurrences (all)	7		
Pain in Extremity			
subjects affected / exposed	3 / 30 (10.00%)		
occurrences (all)	4		
Arthralgia			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	3		
Bone Pain			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		
Musculoskeletal Chest Pain			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		
Neck Pain			

subjects affected / exposed occurrences (all)	2 / 30 (6.67%) 2		
Infections and infestations			
Paronychia			
subjects affected / exposed	7 / 30 (23.33%)		
occurrences (all)	13		
Upper Respiratory Tract Infection			
subjects affected / exposed	7 / 30 (23.33%)		
occurrences (all)	7		
Eye Infection			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		
Conjunctivitis			
subjects affected / exposed	6 / 30 (20.00%)		
occurrences (all)	8		
Metabolism and nutrition disorders			
Decreased Appetite			
subjects affected / exposed	8 / 30 (26.67%)		
occurrences (all)	12		
Hyperglycaemia			
subjects affected / exposed	3 / 30 (10.00%)		
occurrences (all)	5		
Hypomagnesaemia			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 October 2011	Protocol was amended to extend the recruitment period and study duration so that the sample size aimed for the study (30) would be achieved.
12 February 2014	Protocol was amended to include an interim analysis. This interim analysis allowed a preliminary understanding about the clinical benefits of erlotinib in this population and compared it with published studies that were conducted in the Caucasian international population. Also to allow the basal characterization of this population, specially the rate of EGFR mutation and the histological type.

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported