



## Clinical trial results:

### A 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	2010-023869-21
Trial protocol	FI
Global end of trial date	20 November 2013

#### Results information

Result version number	v1 (current)
This version publication date	14 July 2016
First version publication date	06 August 2015

#### Trial information

##### Trial identification

Sponsor protocol code	ML25575
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01287754
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, <a href="mailto:global.trial_information@roche.com">global.trial_information@roche.com</a>
Scientific contact	Roche Trial Information Hotline, F. Hoffmann-La Roche AG, 41 616878333, <a href="mailto:global.trial_information@roche.com">global.trial_information@roche.com</a>

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	03 November 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	20 November 2013
Global end of trial reached?	Yes
Global end of trial date	20 November 2013
Was the trial ended prematurely?	Yes

Notes:

## General information about the trial

Main objective of the trial:

The study was designed to assess the efficacy of erlotinib (Tarceva[™]; 150 milligrams [mg]) on progression-free survival (PFS) in patients with non-small cell lung cancer (NSCLC) in locally advanced or metastatic stages (stage IIIB and stage IV) 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:

This study was done in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	22 March 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	Finland: 24
Worldwide total number of subjects	24
EEA total number of subjects	24

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)	11
From 65 to 84 years	12
85 years and over	1

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

All participants underwent EGFR mutation testing at Screening. Those positive for the EGFR mutation and who met eligibility criteria (number of participants [n] = 3) received treatment with erlotinib. The remaining participants (n = 21) were followed for overall survival but did not receive treatment.

### 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

Are arms mutually exclusive?	No
<b>Arm title</b>	Erlotinib

Arm description:

Participants positive for the EGFR mutation and who met eligibility criteria received treatment with erlotinib, 150 mg orally once daily until disease progression or unacceptable toxicity.

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

Dosage and administration details:

Participants received treatment with erlotinib, 150 mg orally once daily until disease progression or unacceptable toxicity.

<b>Arm title</b>	Untreated
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Arm description:

Participants without the EGFR mutation were followed for overall survival but did not receive treatment. Additionally, participants positive for the EGFR mutation who were excluded from treatment were followed for overall survival.

Arm type	No intervention
No investigational medicinal product assigned in this arm	
<b>Arm title</b>	Total Population

Arm description:

All participants underwent EGFR mutation testing at Screening. Those positive for the EGFR mutation and who met eligibility criteria (n = 3) received treatment with erlotinib, 150 mg orally once daily until disease progression or unacceptable toxicity. The remaining participants (n = 21) were followed for overall survival but did not receive treatment.

Arm type	Experimental or no intervention
Investigational medicinal product name	Erlotinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Eligible participants (n = 3) received treatment with erlotinib, 150 mg orally once daily until disease progression or unacceptable toxicity.

<b>Number of subjects in period 1</b>	Erlotinib	Untreated	Total Population
Started	3	21	24
Completed	0	0	0
Not completed	3	21	24
Death	2	12	14
Lost to follow-up	1	6	7
Protocol deviation	-	3	3

## Baseline characteristics

### Reporting groups

Reporting group title	Erlotinib
Reporting group description: Participants positive for the EGFR mutation and who met eligibility criteria received treatment with erlotinib, 150 mg orally once daily until disease progression or unacceptable toxicity.	
Reporting group title	Untreated
Reporting group description: Participants without the EGFR mutation were followed for overall survival but did not receive treatment. Additionally, participants positive for the EGFR mutation who were excluded from treatment were followed for overall survival.	
Reporting group title	Total Population
Reporting group description: All participants underwent EGFR mutation testing at Screening. Those positive for the EGFR mutation and who met eligibility criteria (n = 3) received treatment with erlotinib, 150 mg orally once daily until disease progression or unacceptable toxicity. The remaining participants (n = 21) were followed for overall survival but did not receive treatment.	

Reporting group values	Erlotinib	Untreated	Total Population
Number of subjects	3	21	24
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years			
arithmetic mean	75	67	68
standard deviation	± 7.6	± 8.4	± 8.5
Gender categorical Units: Subjects			
Female	2	13	15
Male	1	8	9

Reporting group values	Total		
Number of subjects	24		
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days)			

Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years arithmetic mean standard deviation	-		
Gender categorical Units: Subjects			
Female	15		
Male	9		

## End points

### End points reporting groups

Reporting group title	Erlotinib
Reporting group description: Participants positive for the EGFR mutation and who met eligibility criteria received treatment with erlotinib, 150 mg orally once daily until disease progression or unacceptable toxicity.	
Reporting group title	Untreated
Reporting group description: Participants without the EGFR mutation were followed for overall survival but did not receive treatment. Additionally, participants positive for the EGFR mutation who were excluded from treatment were followed for overall survival.	
Reporting group title	Total Population
Reporting group description: All participants underwent EGFR mutation testing at Screening. Those positive for the EGFR mutation and who met eligibility criteria (n = 3) received treatment with erlotinib, 150 mg orally once daily until disease progression or unacceptable toxicity. The remaining participants (n = 21) were followed for overall survival but did not receive treatment.	

### Primary: Progression-Free Survival (PFS) among Erlotinib-Treated Participants with the EGFR Mutation

End point title	Progression-Free Survival (PFS) among Erlotinib-Treated Participants with the EGFR Mutation <sup>[1][2]</sup>
End point description: PFS was defined as the time from the first dose of erlotinib to the first documentation of disease progression or death, whichever occurred first. Tumor progression was determined using Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1), which defines progression as a 20 percent (%) or greater increase in the sum of diameters of target lesions with an absolute increase of at least 5 millimeters (mm), or the appearance of one or more new lesions. PFS was calculated in months as [first event date minus first dose date plus 1] divided by 30.44. All participants who received at least one dose of erlotinib were included in the analysis. (99999 = not estimable because data for 1 of 3 participants were censored, and thus a confidence interval upper limit was not reached.)	
End point type	Primary
End point timeframe: Per standard of care (every 3 months) until discontinuation for up to approximately 2 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: Statistical analysis was not performed and/or reported because there were no statistical assumptions. Only descriptive statistics were planned.

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Erlotinib-treated participants were analyzed for all reported outcome measures; untreated participants were only followed for overall survival and are thus only included in the survival outcome measures. Except for the percentage of participants with EGFR mutation at Screening, outcome measures were not analyzed for the total collective population.

End point values	Erlotinib			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: months				
median (confidence interval 95%)	13.7 (2 to 99999)			

## Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Erlotinib-Treated Participants with the EGFR Mutation with an Objective Response per RECIST v1.1

End point title	Number of Erlotinib-Treated Participants with the EGFR Mutation with an Objective Response per RECIST v1.1 <sup>[3]</sup>
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End point description:

Objective tumor response was assessed by the investigator using RECIST v1.1 and recorded as complete response (CR), partial response (PR), or unmeasurable. RECIST v1.1 defines CR as disappearance of all target lesions, with short-axis reduction to less than (<) 10 mm for any pathological lymph nodes, and PR as a 30% or greater reduction from baseline in the sum of diameters of target lesions. All participants who received at least one dose of erlotinib were included in the analysis.

End point type	Secondary
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End point timeframe:

Per standard of care (every 3 months) until discontinuation for up to approximately 2 years

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Erlotinib-treated participants were analyzed for all reported outcome measures; untreated participants were only followed for overall survival and are thus only included in the survival outcome measures. Except for the percentage of participants with EGFR mutation at Screening, outcome measures were not analyzed for the total collective population.

End point values	Erlotinib			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: participants				
Partial response	2			
Unmeasurable	1			

## Statistical analyses

No statistical analyses for this end point

### Secondary: Overall Survival (OS) among Erlotinib-Treated and Untreated Participants

End point title	Overall Survival (OS) among Erlotinib-Treated and Untreated Participants <sup>[4]</sup>
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End point description:

OS was defined as the time from recorded diagnosis to death from any cause or last patient last visit. OS was calculated in months as [death date or last-known alive date minus diagnosis date plus 1] divided by 30.44. All erlotinib-treated participants who received at least one dose of erlotinib, in addition to all enrolled untreated participants, were included in the analysis. (99999 = not estimable because data for 1 of 3 participants were censored, and thus a confidence interval upper limit was not reached.)

End point type	Secondary
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End point timeframe:

Per standard of care (every 3 months) until discontinuation for up to approximately 2 years

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Erlotinib-treated participants were analyzed for all reported outcome measures; untreated participants were only followed for overall survival and are thus only included in the survival outcome measures. Except for the percentage of participants with EGFR mutation at Screening, outcome measures were not analyzed for the total collective population.

End point values	Erlotinib	Untreated		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	21		
Units: months				
median (confidence interval 95%)	17.8 (17.6 to 99999)	11.3 (8.4 to 11.4)		

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Participants Alive at 6 and 12 Months

End point title	Percentage of Participants Alive at 6 and 12 Months <sup>[5]</sup>
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End point description:

Death from any cause was documented at 6 and 12 months from recorded diagnosis. The percentage of participants alive at each timepoint was calculated as [number of participants alive divided by number enrolled] multiplied by 100. All erlotinib-treated participants who received at least one dose of erlotinib, in addition to all enrolled untreated participants, were included in the analysis.

End point type	Secondary
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End point timeframe:

At 6 and 12 months

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Erlotinib-treated participants were analyzed for all reported outcome measures; untreated participants were only followed for overall survival and are thus only included in the survival outcome measures. Except for the percentage of participants with EGFR mutation at Screening, outcome measures were not analyzed for the total collective population.

End point values	Erlotinib	Untreated		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	21		
Units: percentage of participants				
At 6 months	100	67		
At 12 months	100	24		

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Participants with EGFR Mutation at Screening

End point title	Percentage of Participants with EGFR Mutation at Screening <sup>[6]</sup>
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End point description:

Participants were tested at Screening for the presence of activating mutations in the tyrosine kinase domain of EGFR. The percentage of participants with mutation was calculated as [number of mutation-positive participants divided by number tested] multiplied by 100. All erlotinib-treated participants who received at least one dose of erlotinib, in addition to all enrolled untreated patients, were included in the analysis.

End point type	Secondary
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End point timeframe:

Screening

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Erlotinib-treated participants were analyzed for all reported outcome measures; untreated participants were only followed for overall survival and are thus only included in the survival outcome measures. The percentage of participants with EGFR mutation at Screening was reported for the total collective population.

End point values	Total Population			
Subject group type	Reporting group			
Number of subjects analysed	24			
Units: percentage of participants	17			

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Up to 2 years

Adverse event reporting additional description:

Only participants treated with erlotinib were assessed for adverse events.

Assessment type	Non-systematic
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### Dictionary used

Dictionary name	NCI CTC-AE
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Dictionary version	4.0
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### Reporting groups

Reporting group title	Erlotinib
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Reporting group description:

Participants positive for the EGFR mutation and who met eligibility criteria received treatment with erlotinib, 150 mg orally once daily until disease progression or unacceptable toxicity.

Serious adverse events	Erlotinib		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 3 (33.33%)		
number of deaths (all causes)	2		
number of deaths resulting from adverse events	0		
Infections and infestations			
Epidural catheter infection			
subjects affected / exposed	1 / 3 (33.33%)		
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 %

Non-serious adverse events	Erlotinib		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 3 (66.67%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lipoma			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Periosteal reaction			

subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 1		
Nervous system disorders Paraparesis subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 1		
Gastrointestinal disorders Bleeding from mouth subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 1		
Skin and subcutaneous tissue disorders Alopecia subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 1		
Infections and infestations Eye infection subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 1		

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 September 2011	The study design was modified to collect follow-up information on survival in each study arm.

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported