

**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 (EGFR) - (TRIGGER)****Summary**

EudraCT number	2010-023892-24
Trial protocol	IT
Global end of trial date	31 January 2017

Results information

Result version number	v2 (current)
This version publication date	06 January 2018
First version publication date	31 July 2016
Version creation reason	

Trial information**Trial identification**

Sponsor protocol code	ML25514
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01378962
WHO universal trial number (UTN)	-
Other trial identifiers	Study Name: TRIGGER

Notes:

Sponsors

Sponsor organisation name	F. Hoffmann-La Roche AG
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
Scientific contact	F. Hoffmann-La Roche AG, 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	31 January 2017
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	31 January 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This single-arm, open-label study evaluated the efficacy and safety of Tarceva (erlotinib) in subjects with locally advanced or metastatic non-small cell lung cancer. Subjects received a daily oral doses of 150 mg Tarceva. The anticipated time on study treatment was 12 months.

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?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Italy: 50
Worldwide total number of subjects	50
EEA total number of subjects	50

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)	26
From 65 to 84 years	24
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Fifty-one subjects were screened among the 7 centers involved in this study, however one patient was considered a screening failure and was not included in the enrolled population.

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 150 mg
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Arm description:

Erlotinib 150 milligrams (mg) tablet orally once daily up to end of study (12 months) or until disease progression, unacceptable toxicity or consent withdrawal.

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 orally once daily up to end of study (12 months) or until disease progression, unacceptable toxicity or consent withdrawal.

Number of subjects in period 1	Erlotinib 150 mg
Started	50
Completed	33
Not completed	17
Adverse event, serious fatal	14
Unspecified	2
Lost to follow-up	1

Baseline characteristics

Reporting groups

Reporting group title	Erlotinib 150 mg
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Reporting group description:

Erlotinib 150 milligrams (mg) tablet orally once daily up to end of study (12 months) or until disease progression, unacceptable toxicity or consent withdrawal.

Reporting group values	Erlotinib 150 mg	Total	
Number of subjects	50	50	
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)	26	26	
From 65-84 years	24	24	
85 years and over	0	0	
Age Continuous			
Units: years			
arithmetic mean	62.86		
standard deviation	± 11.42	-	
Gender, Male/Female			
Units: Subjects			
Female	34	34	
Male	16	16	

End points

End points reporting groups

Reporting group title	Erlotinib 150 mg
Reporting group description: Erlotinib 150 milligrams (mg) tablet orally once daily up to end of study (12 months) or until disease progression, unacceptable toxicity or consent withdrawal.	

Primary: Percentage of Subjects with Disease Progression or Death at 12 Months After Baseline

End point title	Percentage of Subjects with Disease Progression or Death at 12 Months After Baseline ^[1]
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End point description:

According to Response Evaluation Criteria in Solid Tumours version 1.1 (RECIST v1.1), progressive disease (PD) was defined as at least a 20 percent (%) increase in the sum of the longest diameter of target lesions, taking as reference the smallest sum of the longest diameter recorded since treatment started or the appearance of 1 or more new lesions. For non-target lesions, PD was defined as the appearance of 1 or more new lesions and/or unequivocal progression of existing non-target lesions. Intent to treat (ITT) population included all subjects enrolled in the study who received at least one dose of treatment.

End point type	Primary
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End point timeframe:

12 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: No statistical analyses were performed as this study has only one arm.

End point values	Erlotinib 150 mg			
Subject group type	Reporting group			
Number of subjects analysed	50			
Units: percentage of subjects				
number (not applicable)	42			

Statistical analyses

No statistical analyses for this end point

Primary: Progression-Free Survival (PFS)

End point title	Progression-Free Survival (PFS) ^[2]
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End point description:

PFS was defined as the time from baseline to the date of first occurrence of disease progression or death. According to RECIST v1.1, PD was defined as at least a 20% increase in the sum of the longest diameter of target lesions, taking as reference the smallest sum of the longest diameter recorded since treatment started or the appearance of 1 or more new lesions. For non-target lesions, PD was defined as the appearance of 1 or more new lesions and/or unequivocal progression of existing non-target lesions. PFS was assessed using Kaplan-Meier method. ITT population included all subjects enrolled in the study who received at least one dose of treatment.

End point type	Primary
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End point timeframe:

Up to 1 year after enrollment of the last participant (maximum up to 27 months)

Notes:

[2] - 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 analyses were performed as this study has only one arm.

End point values	Erlotinib 150 mg			
Subject group type	Reporting group			
Number of subjects analysed	50			
Units: months				
median (confidence interval 90%)	12.58 (10.25 to 16.95)			

Statistical analyses

No statistical analyses for this end point

Primary: Probability of Being Progression Free 12 Months after Baseline

End point title	Probability of Being Progression Free 12 Months after
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End point description:

According to RECIST v1.1, PD was defined as at least a 20% increase in the sum of the longest diameter of target lesions, taking as reference the smallest sum of the longest diameter recorded since treatment started or the appearance of 1 or more new lesions. For non-target lesions, PD was defined as the appearance of 1 or more new lesions and/or unequivocal progression of existing non-target lesions. ITT population included all subjects enrolled in the study who received at least one dose of treatment.

End point type	Primary
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End point timeframe:

12 months

Notes:

[3] - 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 analyses were performed as this study has only one arm.

End point values	Erlotinib 150 mg			
Subject group type	Reporting group			
Number of subjects analysed	50			
Units: probability of being progression-free				
arithmetic mean (standard error)	0.51 (\pm 0.08)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects who Died

End point title	Percentage of Subjects who Died
End point description: ITT population included all subjects enrolled in the study who received at least one dose of treatment.	
End point type	Secondary
End point timeframe: Every 8 weeks during treatment, after discontinuation participants were followed for up to 1 year after enrollment of the last participant (maximum up to 27 months)	

End point values	Erlotinib 150 mg			
Subject group type	Reporting group			
Number of subjects analysed	50			
Units: percentage of subjects				
number (not applicable)	28			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)
End point description: OS was defined as the time from randomization to the date of death due to any cause. OS was assessed using Kaplan-Meier method. ITT population included all subjects enrolled in the study who received at least one dose of treatment.	
End point type	Secondary
End point timeframe: Every 8 weeks during treatment, after discontinuation participants were followed for up to 1 year after enrollment of the last participant (maximum up to 27 months)	

End point values	Erlotinib 150 mg			
Subject group type	Reporting group			
Number of subjects analysed	50			
Units: months				
arithmetic mean (standard error)	17.48 (± 1.09)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With a Response by Best Overall Response

End point title	Percentage of Subjects With a Response by Best Overall
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End point description:

Tumour response assessed to RECIST v1.1. Complete response(CR): complete disappearance of all target lesions & non-target disease, with exception of nodal disease. All nodes must decrease to normal (short axis<10 mm), and no new lesions. Partial response(PR): greater than or equal to (\geq) 30% decrease under baseline of sum of diameters of all target lesions. The short axis was used in sum for target nodes, while longest diameter was used in sum for all other target lesions. No unequivocal progression of non-target disease, and no new lesions. PD: \geq 20% increase in sum of longest diameter of target lesions, taking as reference smallest sum of longest diameter recorded since treatment started or appearance of 1 or more new lesions. For non-target lesions, appearance of 1 or more new lesions and/or unequivocal progression of existing non-target lesions. Stable disease(SD): not qualifying for CR, PR, or PD. ITT population: all subjects enrolled who took at least one dose of treatment.

End point type	Secondary
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End point timeframe:

Baseline up to disease progression or end of study (up to 12 Months)

End point values	Erlotinib 150 mg			
Subject group type	Reporting group			
Number of subjects analysed	50			
Units: percentage of subjects				
number (not applicable)				
CR	6			
PR	62			
SD	12			
PD	4			
Not estimated	16			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Objective Response

End point title	Percentage of Subjects With Objective Response
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End point description:

Objective response: percentage of subjects with CR or PR as best overall response by RECIST v1.1. Status of PR or CR was assigned if changes in tumour measurements were confirmed by repeated assessments no less than 4 weeks after criteria for response were first met. CR: complete disappearance of all target lesions and non-target disease, with exception of nodal disease. All nodes, both target and non-target, must decrease to normal (short axis less than 10 mm), with no new lesions. PR was defined as \geq 30% decrease under baseline of sum of diameters of all target lesions. Short axis was used in sum for target nodes, while longest diameter was used in sum for all other target lesions. No unequivocal progression of non-target disease, and no new lesions. Non-responders: subjects with no tumour assessment after start of treatment. Percentage of subjects with response is presented. ITT population: all subjects enrolled who received at least one dose of treatment.

End point type	Secondary
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End point timeframe:

Baseline up to disease progression or end of study (up to 12 Months)

End point values	Erlotinib 150 mg			
Subject group type	Reporting group			
Number of subjects analysed	50			
Units: percentage of subjects				
number (confidence interval 95%)	68 (53 to 80)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Achieving CR, PR, or SD as Best Overall Response

End point title	Percentage of Subjects Achieving CR, PR, or SD as Best Overall Response
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End point description:

The Disease Control Rate was defined as the percentage of subjects who had CR or PR or SD as Best Overall Response achieved within the time between the first drug administration and documented disease progression or end of study. According to RECIST v1.1, CR was defined as complete disappearance of all target lesions and non-target disease, with the exception of nodal disease. All nodes, both target and non-target, must decrease to normal (short axis less than 10 mm), with no new lesions. PR was defined as $\geq 30\%$ decrease under baseline of the sum of diameters of all target lesions. The short axis was used in the sum for target nodes, while the longest diameter was used in the sum for all other target lesions. No unequivocal progression of non-target disease, and no new lesions. SD was defined as not qualifying for CR, PR, or PD. ITT population included all subjects enrolled in the study who received at least one dose of treatment.

End point type	Secondary
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End point timeframe:

Baseline up to disease progression or end of study (up to 12 Months)

End point values	Erlotinib 150 mg			
Subject group type	Reporting group			
Number of subjects analysed	50			
Units: percentage of subjects				
number (confidence interval 95%)	80 (66 to 90)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with Primary and Secondary Resistance

End point title	Percentage of Subjects with Primary and Secondary Resistance
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End point description:

Primary resistance: subjects did not reach SD or PR or CR before going to PD. Secondary resistance: subjects had PD after reached SD or PR or CR at least once. CR: complete disappearance of all target lesions and non-target disease, with exception of nodal disease. All nodes must decrease to normal (short axis < 10 mm), with no new lesions. PR: $\geq 30\%$ decrease under baseline of sum of diameters of

all target lesions. Short axis was used in sum for target nodes, and longest diameter was used in sum for all other target lesions. No unequivocal progression of non-target disease, and no new lesions. PD: $\geq 20\%$ increase in sum of longest diameter of target lesions, taking as reference smallest sum of longest diameter recorded since treatment started or appearance of 1 or more (≥ 1) new lesions. For non-target lesions, appearance of ≥ 1 new lesions and/or unequivocal progression of existing non-target lesions. ITT population: all subjects enrolled who received at least one dose of treatment.

End point type	Secondary
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End point timeframe:

Baseline up to disease progression (up to 12 Months)

End point values	Erlotinib 150 mg			
Subject group type	Reporting group			
Number of subjects analysed	24			
Units: percentage of subjects				
number (not applicable)				
Primary resistance	8.33			
Secondary resistance	91.67			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Epidermal Growth Factor Receptor (EGFR) Mutation by Mutation Type

End point title	Percentage of Subjects With Epidermal Growth Factor Receptor (EGFR) Mutation by Mutation Type
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End point description:

EGFR is a gene in the tumour tissues and mutations in this gene have been linked to a variety of tumors. Presence or absence of EGFR mutation was determined in liquid biopsies by reverse transcriptase-polymerase chain reaction (RT-PCR /Cobas).

End point type	Secondary
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End point timeframe:

Baseline, At progression of disease (up to 12 Months)

End point values	Erlotinib 150 mg			
Subject group type	Reporting group			
Number of subjects analysed	45			
Units: percentage of subjects				
number (not applicable)				
Baseline: EGFR18 Mutation (n=45)	0.00			
Baseline: EGFR19 Codon Deletion Mutation (n=45)	51.11			
Baseline: EGFR20 Codon T790M Mutation (n=45)	2.22			
Baseline: EGFR21 Codon L585R Mutation (n=45)	15.56			

At PD: EGFR18 Mutation (n=18)	0.00			
At PD: EGFR19 Codon Deletion Mutation (n=18)	50.00			
At PD: EGFR20 Codon T790M Mutation (n=18)	27.78			
At PD: EGFR21 Codon L585R Mutation (n=18)	16.67			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 1 year after enrollment of the last participant (maximum up to 27 months)

Adverse event reporting additional description:

Safety population included all subjects enrolled in the study who received at least one dose of treatment and had at least one safety assessment.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	14.0
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Reporting groups

Reporting group title	Erlotinib 150 mg
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Reporting group description:

Erlotinib 150 mg tablet orally once daily up to end of study (12 months) or until disease progression, unacceptable toxicity or consent withdrawal.

Serious adverse events	Erlotinib 150 mg		
Total subjects affected by serious adverse events			
subjects affected / exposed	10 / 50 (20.00%)		
number of deaths (all causes)	14		
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Hip fracture			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Vascular disorders			
Jugular vein thrombosis			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Cardiac failure acute			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		

Nervous system disorders			
Convulsion			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hemiplegia			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Dysphagia			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	2 / 50 (4.00%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 2		
Pneumothorax			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Confusional state			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			

Pneumonia			
subjects affected / exposed	2 / 50 (4.00%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 50 (2.00%)		
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 150 mg		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	46 / 50 (92.00%)		
Investigations			
Blood bilirubin increased			
subjects affected / exposed	3 / 50 (6.00%)		
occurrences (all)	3		
Injury, poisoning and procedural complications			
Contrast media reaction			
subjects affected / exposed	3 / 50 (6.00%)		
occurrences (all)	3		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	9 / 50 (18.00%)		
occurrences (all)	12		
Chest pain			
subjects affected / exposed	7 / 50 (14.00%)		
occurrences (all)	8		
Fatigue			
subjects affected / exposed	5 / 50 (10.00%)		
occurrences (all)	8		
Pyrexia			

<p>subjects affected / exposed occurrences (all)</p> <p>Oedema peripheral subjects affected / exposed occurrences (all)</p>	<p>9 / 50 (18.00%) 11</p> <p>3 / 50 (6.00%) 3</p>		
<p>Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences (all)</p>	<p>4 / 50 (8.00%) 5</p>		
<p>Eye disorders Conjunctivitis subjects affected / exposed occurrences (all)</p>	<p>11 / 50 (22.00%) 15</p>		
<p>Gastrointestinal disorders Abdominal pain upper subjects affected / exposed occurrences (all)</p> <p>Diarrhoea subjects affected / exposed occurrences (all)</p> <p>Stomatitis subjects affected / exposed occurrences (all)</p> <p>Vomiting subjects affected / exposed occurrences (all)</p> <p>Nausea subjects affected / exposed occurrences (all)</p>	<p>4 / 50 (8.00%) 8</p> <p>27 / 50 (54.00%) 58</p> <p>4 / 50 (8.00%) 10</p> <p>4 / 50 (8.00%) 5</p> <p>3 / 50 (6.00%) 5</p>		
<p>Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)</p> <p>Epistaxis subjects affected / exposed occurrences (all)</p>	<p>10 / 50 (20.00%) 16</p> <p>4 / 50 (8.00%) 14</p>		

Haemoptysis subjects affected / exposed occurrences (all)	3 / 50 (6.00%) 4		
Skin and subcutaneous tissue disorders			
Dry skin subjects affected / exposed occurrences (all)	4 / 50 (8.00%) 7		
Dermatitis acneiform subjects affected / exposed occurrences (all)	5 / 50 (10.00%) 5		
Alopecia subjects affected / exposed occurrences (all)	7 / 50 (14.00%) 9		
Pruritus subjects affected / exposed occurrences (all)	10 / 50 (20.00%) 18		
Rash subjects affected / exposed occurrences (all)	36 / 50 (72.00%) 130		
Skin ulcer subjects affected / exposed occurrences (all)	4 / 50 (8.00%) 19		
Nail disorder subjects affected / exposed occurrences (all)	3 / 50 (6.00%) 3		
Musculoskeletal and connective tissue disorders			
Back pain subjects affected / exposed occurrences (all)	4 / 50 (8.00%) 9		
Musculoskeletal pain subjects affected / exposed occurrences (all)	3 / 50 (6.00%) 3		
Muscle spasms subjects affected / exposed occurrences (all)	4 / 50 (8.00%) 6		
Infections and infestations			

Paronychia subjects affected / exposed occurrences (all)	7 / 50 (14.00%) 9		
Cystitis subjects affected / exposed occurrences (all)	3 / 50 (6.00%) 3		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	6 / 50 (12.00%) 8		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 January 2013	Amendment 1 introduced a descriptive, interim analysis of clinical characteristics at baseline including the EGFR mutation test results obtained from basal tumor biopsies, from circulating tumor cells and plasma DNA and by immunohistochemical detection. Moreover, a descriptive analysis was performed on data collected up to January 2013 concerning data on demographics, disease history, treatment dose and duration, the incidence of rash, EGFR mutation test, results from both local and central laboratory, at baseline and at progression, stratifying patients according to their undergoing disease progression or not at the date of the analysis. No change in the experimental design was foreseen based on the analysis results. Since no model analyses on primary or secondary end-points were performed, no correction of the overall alpha level was applied.
08 July 2013	Amendment 2 ensured that patients who did not have progressive disease at the end of the study were able to continue to receive the study drug. For these patients, the protocol called for a reduction of dosage to 50 mg. Since the 25 mg dose is not commercialized in Italy, Roche provided the study drug until progression, unacceptable toxicity or consent withdrawal. No further data was to be captured for these patients. Nevertheless, adverse events (SAEs) continued to be collected and were reported as outlined in the study protocol.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported