Clinical trial results:
A prospective double-blind randomized Phase III study of 300 mg vs. 150 mg erlotinib in current smokers with locally advanced or metastatic NSCLC in second-line setting after failure on chemotherapy

Summary

EudraCT number	2010-018476-24
Trial protocol	NL ES DE DK
Global end of trial date	07 February 2014

Results information

Result version number	v1 (current)
This version publication date	25 April 2016
First version publication date	08 August 2015

Trial information

Trial identification

Sponsor protocol code	MO22162

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01183858
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	29 October 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	28 October 2013
Global end of trial reached?	Yes
Global end of trial date	07 February 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the efficacy of two dose levels of erlotinib (150 mg and 300 mg) on progression-free survival (PFS) in current smokers with stage IIIB/IV NSCLC after failure of first-line platinum-based chemotherapy.

Protection of trial subjects:

All study participants were required to read and sign an Informed Consent Form.
Patients received full supportive care throughout the study, including transfusion of blood products, treatment with antibiotics, anti-emetics, anti-diarrheals, and analgesics as appropriate.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	14 October 2010
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 11
Country: Number of subjects enrolled	Spain: 29
Country: Number of subjects enrolled	Denmark: 12
Country: Number of subjects enrolled	France: 19
Country: Number of subjects enrolled	Germany: 97
Country: Number of subjects enrolled	China: 95
Country: Number of subjects enrolled	Egypt: 11
Country: Number of subjects enrolled	Switzerland: 5
Country: Number of subjects enrolled	Turkey: 34
Worldwide total number of subjects	313
EEA total number of subjects	168

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)	217
From 65 to 84 years	96
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

315 participants were randomized. 313 participants were included in the Intent-to -treat (ITT) population. The ITT population excluded 2 randomized participants: 1 participant randomized in error and 1 participant with missing source data.

Pre-assignment period milestones

Number of subjects started	315[1]
Number of subjects completed	313

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Randomized in error: 1
Reason: Number of subjects	Missing Source Documentation: 1

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: The worldwide number of 313 participants is based on the Intent-to -treat (ITT)population. The ITT population excluded 2 randomized participants: 1 participant randomized in error and 1 participant with missing source data who are included in the Pre-Assignment period.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Erlotinib 150 mg

Arm description:

Erlotinib 150 mg single daily oral dose until disease progression.

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:

Single daily oral dose.

Arm title	Erlotinib 300 mg

Arm description:

Erlotinib 300 mg single daily oral dose until disease progression.

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:

Single daily oral dose.

Number of subjects in period 1	Erlotinib 150 mg	Erlotinib 300 mg
Started	154	159
Intent-to-treat Population	154	159
Safety Population	154	158
Completed	1	3
Not completed	153	156
Discontinued Smoking	3	1
Withdrew Consent	4	4
Death not related to PD	5	6
Investigator's Decision	-	3
Refused Treatment	1	4
Progressive Disease	112	115
Other Protocol Violation	1	-
Death related to Progressive Disease (PD)	4	5
Adverse Event(s)	14	11
Administrative/Other	6	6
Lost to follow-up	1	1
Insufficient Therapeutic Response	2	-

Baseline characteristics

Reporting groups	
Reporting group title	Erlotinib 150 mg
Reporting group description:	
Erlotinib 150 mg single daily oral dose until disease progression.	
Reporting group title	Erlotinib 300 mg
Reporting group description:	
Erlotinib 300 mg single daily oral dose until disease progression.	

Reporting group values	Erlotinib 150 mg	Erlotinib 300 mg	Total
Number of subjects	154	159	313
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	106	111	217
From 65-84 years	48	48	96
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	59.7	59.2	
standard deviation	± 9.25	± 9.14	-
Gender categorical Units: Subjects			
Female	34	35	69
Male	120	124	244

End points

End points reporting groups

Reporting group title	Erlotinib 150 mg
Reporting group description:	
Erlotinib 150 mg single daily oral dose until disease progression.	
Reporting group title	Erlotinib 300 mg
Reporting group description:	
Erlotinib 300 mg single daily oral dose until disease progression.	

Primary: Progression-Free Survival (PFS)

End point title	Progression-Free Survival (PFS)
End point description:	
PFS is defined as the time from randomization to the date of first occurrence of disease progression or death. For target lesions, Progressive Disease (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 Intent-to-treat Population included all randomized participants. 2 participants were excluded from analysis: 1 participant randomized in error and 1 participant with missing source data.	
End point type	Primary
End point timeframe:	
Randomization to Clinical Cutoff: 28 October 2013 (Up to 36.5 months)	

End point values	Erlotinib 150 mg	Erlotinib 300 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	154	159		
Units: weeks				
median (confidence interval 95%)	6.86 (6.29 to 12)	7 (6.29 to 11)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Erlotinib 150 mg v Erlotinib 300 mg
Number of subjects included in analysis	313
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.671 [1]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.05

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.83
upper limit	1.33

Notes:

[1] - Unstratified analysis.

Primary: Progression-Free Survival at the End of Study

End point title	Progression-Free Survival at the End of Study

End point description:

PFS is defined as the time from randomization to the date of first occurrence of disease progression or death. For target lesions, Progressive Disease (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
Intent-to-treat Population included all randomized participants. 2 participants were excluded from analysis: 1 participant randomized in error and 1 participant with missing source data.

End point type	Primary

End point timeframe:

Randomization to End of Study: 14 October 2010 – 7 February 2014 (Up to 39.8 months)

End point values	Erlotinib 150 mg	Erlotinib 300 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	154	159		
Units: weeks				
median (confidence interval 95%)	6.86 (6.29 to 12)	7 (6.29 to 11.43)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Erlotinib 300 mg v Erlotinib 150 mg
Number of subjects included in analysis	313
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.625 [2]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.84
upper limit	1.33

Notes:
[2] - Unstratified Analysis

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

OS defined as the time from randomization to the date of death due to any cause.
Intent-to-treat Population included all randomized participants. 2 participants were excluded from analysis: 1 participant randomized in error and 1 participant with missing source data.

End point type	Secondary

End point timeframe:

Randomization to Clinical Cutoff: 28 October 2013 (Up to 36.5 months)

End point values	Erlotinib 150 mg	Erlotinib 300 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	154	159		
Units: months				
median (confidence interval 95%)	6.77 (5.65 to 8.77)	6.83 (5.39 to 8.48)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Response Rate (ORR)

End point title	Overall Response Rate (ORR)

End point description:

Tumor response was assessed by the investigator using computer tomography (CT) or magnetic resonance imaging (MRI) scans according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. A participant was defined as a responder if they sustained a complete response (CR) or partial response (PR) for at least 4 weeks during randomized treatment (confirmed response). Patients with no tumor assessment after the start of study treatment were to be considered as non-responders. The percentage of participants in each best response category is presented.
Intent-to-treat Population included all randomized participants. 2 participants were excluded from analysis: 1 participant randomized in error and 1 participant with missing source data.

End point type	Secondary

End point timeframe:

Randomization to Clinical Cutoff: 28 October 2013 (Up to 36.5 months)

End point values	Erlotinib 150 mg	Erlotinib 300 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	154	159		
Units: participants				
number (confidence interval 95%)				
Complete Response	0 (0 to 0)	0 (0 to 0)		
Partial Response	7.1 (3.6 to 12.4)	2.5 (0.7 to 6.3)		
Stable Disease	33.1 (25.8 to 41.1)	34 (26.6 to 41.9)		
Progressive Disease	44.8 (36.8 to 53)	45.9 (38 to 54)		
Not Evaluable	14.9 (9.7 to 21.6)	17.6 (12 to 24.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Control Rate (DCR)

End point title	Disease Control Rate (DCR)

End point description:

Tumor response was assessed by the investigator using computer tomography (CT) or magnetic resonance imaging (MRI) scans. Disease control rates were measured according to RECIST version 1.1 criteria. A participant was defined as having controlled disease if they sustained a Complete Response (CR) or Partial Response (PR) for at least 4 weeks during randomized treatment (confirmed response), or Stable Disease (SD) for at least 6 weeks. Patients with no tumor assessment after the start of study treatment were considered as having uncontrolled disease. The percentage of participants with Disease Control is presented.
Intent-to-treat Population included all randomized participants. 2 participants were excluded from analysis: 1 participant randomized in error and 1 participant with missing source data.

End point type	Secondary

End point timeframe:

Randomization to Clinical Cutoff: 28 October 2013 (Up to 36.5 months)

End point values	Erlotinib 150 mg	Erlotinib 300 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	154	159		
Units: percentage of participants				
number (confidence interval 95%)	40.3 (32.4 to 48.5)	36.5 (29 to 44.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Progression (TTP)

End point title	Time to Progression (TTP)

End point description:

Tumor response was assessed by the investigator using computer tomography (CT) or magnetic resonance imaging (MRI) scans according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 criteria. Time to progression (TTP) in weeks was defined as the time from randomization to the date of disease progression. Participants without event were censored at the date of the last tumor assessment when the patient was known to be progression free.
Intent-to-treat Population included all randomized participants. 2 participants were excluded from analysis: 1 participant randomized in error and 1 participant with missing source data.

End point type	Secondary

End point timeframe:

Randomization to Clinical Cutoff: 28 October 2013 (Up to 36.5 months)

End point values	Erlotinib 150 mg	Erlotinib 300 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	154	159		
Units: weeks				
median (confidence interval 95%)	9.86 (6.43 to 12.14)	9.14 (6.43 to 12)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Adverse Events (AEs) at the End of the Study

End point title	Number of Participants With Adverse Events (AEs) at the End of the Study

End point description:

An adverse event was considered any unfavorable and unintended sign, symptom, or disease associated with the use of the study drug, whether or not considered related to the study drug. Preexisting conditions that worsened during the study were reported as adverse events.
A serious adverse event is any experience that suggests a significant hazard, contraindication, side effect or precaution that: results in death, is life-threatening, required in-patient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect or is medically significant.
Adverse Events in the following categories are presented: Adverse Events, Serious Adverse Events, AEs leading to withdrawal from treatment and AEs leading to death.
Safety population included all randomized participants who received at least one dose of study drug.

End point type	Secondary

End point timeframe:

Randomization to End of Study: 14 October 2010 – 7 February 2014 (Up to 39.8 months)

End point values	Erlotinib 150 mg	Erlotinib 300 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	154	158		
Units: participants				
Adverse Events (AEs)	130	141		
Serious Adverse Events	29	35		
AEs leading to withdrawal	18	15		
AEs leading to death	12	13		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS) at the End of Study

End point title	Overall Survival (OS) at the End of Study

End point description:

OS defined as the time from randomization to the date of death due to any cause.
Intent-to-treat Population included all randomized participants. 2 participants were excluded from analysis: 1 participant randomized in error and 1 participant with missing source data.

End point type	Secondary

End point timeframe:

Randomization to End of Study: 14 October 2010 – 7 February 2014 (Up to 39.8 months)

End point values	Erlotinib 150 mg	Erlotinib 300 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	154	159		
Units: months				
median (confidence interval 95%)	7 (5.65 to 8.84)	6.9 (5.62 to 8.64)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Randomization to End of Study: 14 October 2010 – 7 February 2014 (Up to 39.8 months)

Adverse event reporting additional description:

Safety population: All participants who received at least 1 dose of study drug.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups

Reporting group title	Erlotinib 150 mg

Reporting group description:

Erlotinib 150 mg single daily oral dose until disease progression.

Reporting group title	Erlotinib 300 mg

Reporting group description:

Erlotinib 300 mg single daily oral dose until disease progression.

Serious adverse events	Erlotinib 150 mg	Erlotinib 300 mg	
Total subjects affected by serious adverse events			
subjects affected / exposed	29 / 154 (18.83%)	35 / 158 (22.15%)	
number of deaths (all causes)	123	125	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Gastric cancer			
subjects affected / exposed	1 / 154 (0.65%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial effusion malignant			
subjects affected / exposed	1 / 154 (0.65%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 154 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Peripheral ischaemia			
subjects affected / exposed	0 / 154 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
General physical health deterioration			
subjects affected / exposed	1 / 154 (0.65%)	3 / 158 (1.90%)	
occurrences causally related to treatment / all	0 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Fatigue			
subjects affected / exposed	1 / 154 (0.65%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	1 / 154 (0.65%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Mucosal inflammation			
subjects affected / exposed	1 / 154 (0.65%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden death			
subjects affected / exposed	0 / 154 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	3 / 154 (1.95%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory failure			

subjects affected / exposed	0 / 154 (0.00%)	2 / 158 (1.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Acute respiratory failure			
subjects affected / exposed	1 / 154 (0.65%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 154 (0.65%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	0 / 154 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hydropneumothorax			
subjects affected / exposed	1 / 154 (0.65%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	0 / 154 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	0 / 154 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pulmonary haemorrhage			
subjects affected / exposed	0 / 154 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Injury, poisoning and procedural complications			

Femur fracture			
subjects affected / exposed	0 / 154 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	0 / 154 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Overdose			
subjects affected / exposed	1 / 154 (0.65%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Myocardial infarction			
subjects affected / exposed	1 / 154 (0.65%)	3 / 158 (1.90%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 2	
Arteriospasm coronary			
subjects affected / exposed	0 / 154 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	1 / 154 (0.65%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Intracardiac thrombus			
subjects affected / exposed	0 / 154 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Right ventricular failure			
subjects affected / exposed	1 / 154 (0.65%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Nervous system disorders			

Cerebral infarction			
subjects affected / exposed	1 / 154 (0.65%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage intracranial			
subjects affected / exposed	0 / 154 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hypoxic-ischaemic encephalopathy			
subjects affected / exposed	0 / 154 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Ischaemic stroke			
subjects affected / exposed	0 / 154 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Neuralgia			
subjects affected / exposed	0 / 154 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Somnolence			
subjects affected / exposed	1 / 154 (0.65%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	1 / 154 (0.65%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 154 (0.65%)	2 / 158 (1.27%)	
occurrences causally related to treatment / all	1 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Haematemesis			
subjects affected / exposed	1 / 154 (0.65%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Vomiting			
subjects affected / exposed	0 / 154 (0.00%)	2 / 158 (1.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer			
subjects affected / exposed	0 / 154 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			
subjects affected / exposed	0 / 154 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	0 / 154 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			
subjects affected / exposed	0 / 154 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 154 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatic failure			
subjects affected / exposed	1 / 154 (0.65%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Renal and urinary disorders			

Renal failure			
subjects affected / exposed	1 / 154 (0.65%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Renal failure acute			
subjects affected / exposed	1 / 154 (0.65%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure chronic			
subjects affected / exposed	1 / 154 (0.65%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 154 (0.65%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	6 / 154 (3.90%)	3 / 158 (1.90%)	
occurrences causally related to treatment / all	0 / 7	0 / 4	
deaths causally related to treatment / all	0 / 3	0 / 0	
Respiratory tract infection			
subjects affected / exposed	0 / 154 (0.00%)	3 / 158 (1.90%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Anal abscess			
subjects affected / exposed	0 / 154 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection bacterial			

subjects affected / exposed	0 / 154 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	1 / 154 (0.65%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Septic shock			
subjects affected / exposed	1 / 154 (0.65%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	2 / 154 (1.30%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Erlotinib 150 mg	Erlotinib 300 mg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	115 / 154 (74.68%)	128 / 158 (81.01%)	
Investigations			
Weight decreased			
subjects affected / exposed	7 / 154 (4.55%)	15 / 158 (9.49%)	
occurrences (all)	7	16	
Nervous system disorders			
Headache			
subjects affected / exposed	9 / 154 (5.84%)	2 / 158 (1.27%)	
occurrences (all)	9	2	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	21 / 154 (13.64%)	26 / 158 (16.46%)	
occurrences (all)	28	30	
Chest pain			

subjects affected / exposed	7 / 154 (4.55%)	14 / 158 (8.86%)	
occurrences (all)	7	18	
Asthenia			
subjects affected / exposed	9 / 154 (5.84%)	12 / 158 (7.59%)	
occurrences (all)	10	14	
Pain			
subjects affected / exposed	8 / 154 (5.19%)	5 / 158 (3.16%)	
occurrences (all)	8	5	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	6 / 154 (3.90%)	8 / 158 (5.06%)	
occurrences (all)	6	8	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	29 / 154 (18.83%)	46 / 158 (29.11%)	
occurrences (all)	36	56	
Nausea			
subjects affected / exposed	20 / 154 (12.99%)	17 / 158 (10.76%)	
occurrences (all)	21	19	
Vomiting			
subjects affected / exposed	13 / 154 (8.44%)	14 / 158 (8.86%)	
occurrences (all)	14	15	
Constipation			
subjects affected / exposed	9 / 154 (5.84%)	11 / 158 (6.96%)	
occurrences (all)	9	11	
Dyspepsia			
subjects affected / exposed	3 / 154 (1.95%)	8 / 158 (5.06%)	
occurrences (all)	5	8	
Abdominal pain upper			
subjects affected / exposed	1 / 154 (0.65%)	8 / 158 (5.06%)	
occurrences (all)	1	8	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	26 / 154 (16.88%)	19 / 158 (12.03%)	
occurrences (all)	29	19	
Cough			

subjects affected / exposed	23 / 154 (14.94%)	19 / 158 (12.03%)	
occurrences (all)	25	25	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	43 / 154 (27.92%)	75 / 158 (47.47%)	
occurrences (all)	53	101	
Dry skin			
subjects affected / exposed	13 / 154 (8.44%)	17 / 158 (10.76%)	
occurrences (all)	14	19	
Pruritus			
subjects affected / exposed	8 / 154 (5.19%)	16 / 158 (10.13%)	
occurrences (all)	9	17	
Dermatitis acneiform			
subjects affected / exposed	11 / 154 (7.14%)	9 / 158 (5.70%)	
occurrences (all)	11	9	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	8 / 154 (5.19%)	6 / 158 (3.80%)	
occurrences (all)	11	6	
Pain in extremity			
subjects affected / exposed	3 / 154 (1.95%)	8 / 158 (5.06%)	
occurrences (all)	3	8	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	26 / 154 (16.88%)	32 / 158 (20.25%)	
occurrences (all)	28	33	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 May 2011	•Clarified exclusion criteria to allow the prior use of bevacizumab as standard first-line treatment for Non-small cell lung cancer (NSCLC). •Clarified exclusion criteria to exclude patients with previously diagnosed and treated brain metastases with symptomatic evidence. •Allowed screening evaluations to be performed on the same day as the patient's inclusion provided all the results were obtained prior to inclusion and visit descriptions were aligned for consistency with the laboratory manual, Interactive web response system (IWRS) Electronic case report form (eCRF). •Allowed the results of screening laboratory assessments done within 3 days prior to inclusion to be used for the Baseline laboratory assessment.
09 July 2013	•The primary endpoint of Progression-free survival (PFS), as well as response, was updated to be solely based on the investigator-assessed response evaluation; an independent review committee was no longer used due to accumulating evidence pointing to limited value of independent reviews in double-blind, randomized clinical studies. •The protocol originally specified a randomized stratification by geographical region (Eastern Europe, Western Europe and Asia). However during the study only two strata were used (Europe and Asia) for randomization. •The original recruitment period was estimated to be approximately 18 months. Due to slower than expected recruitment, the recruitment period was changed so that it would be closed when approximately 300 patients had been randomized into the study. •This study was event-driven. The primary analysis was scheduled to be undertaken once approximately 277 PFS events (corresponding to the needed number of PFS events for the primary analysis) had occurred. Data were collected and queries answered until database lock, following the receipt of the 277th PFS event. Originally it was thought that this required number of events would be achieved approximately 6 months after the last patient was recruited; however as timing could not be predicted, this reference to the 6-month time frame was removed. Study treatment continued until disease progression, death, unacceptable toxicity or clinician/patient decision to stop study treatment. It was deemed to be likely that some patients would still be on study drug at the end of the study (upon database lock). Patients still receiving treatment were unblinded and patients who were receiving the experimental dose of erlotinib at the end of the study continued to be provided with erlotinib on an ongoing basis through clinical study supply, until disease progression, death, unacceptable toxicity or clinician/patient decision to stop this therapy.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported