Clinical trial results:
LUX-Lung 8: A randomized, open-label Phase III trial of afatinib versus erlotinib in patients with advanced squamous cell carcinoma of the lung as second-line therapy following first-line platinum-based chemotherapy

Summary

EudraCT number	2011-002380-24
Trial protocol	ES DE PT GR DK HU IE GB AT IT NL
Global end of trial date	27 December 2017

Results information

Result version number	v1
This version publication date	05 January 2019
First version publication date	05 January 2019

Trial information

Trial identification

Sponsor protocol code	1200.125

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01523587
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Boehringer Ingelheim
Sponsor organisation address	Binger Strasse 173, Ingelheim am Rhein, Germany, 55216
Public contact	QRPE Processes and Systems Coordination, Clinical Trial Information Disclosure, Boehringer Ingelheim, 001 8002430127, clintriage.rdg@boehringer-ingelheim.com
Scientific contact	QRPE Processes and Systems Coordination, Clinical Trial Information Disclosure, Boehringer Ingelheim, 001 8002430127, clintriage.rdg@boehringer-ingelheim.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	20 February 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	23 October 2013
Global end of trial reached?	Yes
Global end of trial date	27 December 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the efficacy of afatinib with erlotinib as second-line treatment for patients with squamous cell carcinoma (SCC) of the lung, as measured by progression-free survival (PFS)

Protection of trial subjects:

Only patients that met all the study inclusion and none of the exclusion criteria were to be entered in the study. All patients were free to withdraw from the clinical trial at any time for any reason given. Close monitoring of all patients was adhered to throughout the trial conduct. Rescue medication was allowed for all patients as required. The terms and conditions of the insurance coverage were available to the investigator and the patients in the investigator site file (ISF).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	29 March 2012
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy, Safety
Long term follow-up duration	52 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 15
Country: Number of subjects enrolled	Austria: 18
Country: Number of subjects enrolled	Canada: 22
Country: Number of subjects enrolled	Chile: 11
Country: Number of subjects enrolled	China: 69
Country: Number of subjects enrolled	Denmark: 12
Country: Number of subjects enrolled	France: 82
Country: Number of subjects enrolled	Germany: 36
Country: Number of subjects enrolled	Greece: 44
Country: Number of subjects enrolled	Hungary: 81
Country: Number of subjects enrolled	India: 25
Country: Number of subjects enrolled	Ireland: 3
Country: Number of subjects enrolled	Italy: 66
Country: Number of subjects enrolled	Korea, Republic of: 84
Country: Number of subjects enrolled	Mexico: 8
Country: Number of subjects enrolled	Netherlands: 22
Country: Number of subjects enrolled	Portugal: 30

Country: Number of subjects enrolled	Singapore: 5
Country: Number of subjects enrolled	Spain: 89
Country: Number of subjects enrolled	Taiwan: 39
Country: Number of subjects enrolled	Turkey: 82
Country: Number of subjects enrolled	United Kingdom: 51
Country: Number of subjects enrolled	United States: 83
Worldwide total number of subjects	977
EEA total number of subjects	534

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)	496
From 65 to 84 years	478
85 years and over	3

Subject disposition

Recruitment

Recruitment details:

Open-label PhaseIII trial to compare the efficacy of afatinib with erlotinib for the second-line treatment of patients with advanced non-small cell lung cancer,who completed at least 4cycles of platinum-based doublet chemotherapy. Stratification was based on race. 977 patients were enrolled, 795 randomized.

Pre-assignment

Screening details:

Patients screened to ensure that they met all inclusion/exclusion criteria. Patients were not to be entered to trial treatment if any one of the specific entry criteria were not met. Tumor assessments at screening were completed within 21 days and other screening assessments were completed within 28 days, of randomization.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

This was an open-label trial.

Arms

Are arms mutually exclusive?	Yes
Arm title	Afatinib

Arm description:

Patients administered 40 milligram (mg) film-coated tablet once daily orally for the first 28-day treatment course. Dose escalation to 50 mg once daily was allowed at the beginning of the second 28-day treatment course, if patients met specified safety and compliance criteria. Dose reduction to 40 mg/day (if applicable), 30 mg/day, or 20 mg/day, was required in the presence of known drug-related adverse events.

Arm type	Experimental
Investigational medicinal product name	Afatinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Patients administered 40 milligram (mg) film-coated tablet once daily orally for the first 28-day treatment course. Dose escalation to 50 mg once daily was allowed at the beginning of the second 28-day treatment course, if patients met specified safety and compliance criteria. Dose reduction to 40 mg/day (if applicable), 30 mg/day, or 20 mg/day, was required in the presence of known drug-related adverse events.

Arm title	Erlotinib

Arm description:

Patients administered 150 mg film-coated tablet once daily orally, with dose reduction to 100 mg/day or 50 mg/day in the presence of known drug-related adverse events.

Arm type	Active comparator
Investigational medicinal product name	Erlotinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Patients administered 150 mg film-coated tablet once daily orally, with dose reduction to 100 mg/day or

50 mg/day in the presence of known drug-related adverse events.

Number of subjects in period 1[1]	Afatinib	Erlotinib
Started	398	397
Treated	392	395
Completed	0	0
Not completed	398	397
Withdrew due to Progressive disease	265	279
Adverse event, serious fatal	35	27
Consent withdrawn by subject	28	20
Adverse event, non-fatal	33	25
Randomised but bot treated	6	2
Lost to follow-up	2	2
Other than listed	5	5
Worsening of underlying cancer disease	19	34
Protocol deviation	5	3

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: Baseline characteristics are based on patients who were randomised after successfully completing the screening period regardless of whether they received investigational treatment.

Baseline characteristics

Reporting groups	
Reporting group title	Afatinib
Reporting group description:	
Patients administered 40 milligram (mg) film-coated tablet once daily orally for the first 28-day treatment course. Dose escalation to 50 mg once daily was allowed at the beginning of the second 28-day treatment course, if patients met specified safety and compliance criteria. Dose reduction to 40 mg/day (if applicable), 30 mg/day, or 20 mg/day, was required in the presence of known drug-related adverse events.	
Reporting group title	Erlotinib
Reporting group description:	
Patients administered 150 mg film-coated tablet once daily orally, with dose reduction to 100 mg/day or 50 mg/day in the presence of known drug-related adverse events.	

Reporting group values	Afatinib	Erlotinib	Total
Number of subjects	398	397	795
Age categorical			
Units: Subjects			
Age Continuous			
Randomized Set (RS): All patients who were randomized, regardless of whether they received investigational treatment.			
Units: years			
arithmetic mean	64.9	63.4	
standard deviation	± 8.39	± 8.98	-
Sex: Female, Male			
Randomized Set (RS): All patients who were randomized, regardless of whether they received investigational treatment.			
Units: Subjects			
Female	63	66	129
Male	335	331	666
Race (NIH/OMB)			
Ethnicity was not captured in this trial. Randomized Set (RS): All patients who were randomized, regardless of whether they received investigational treatment.			
Units: Subjects			
American Indian or Alaska Native	2	2	4
Asian	97	94	191
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	7	8	15
White	288	291	579
More than one race	0	0	0
Unknown or Not Reported	4	2	6

End points

End points reporting groups

Reporting group title	Afatinib

Reporting group description:

Patients administered 40 milligram (mg) film-coated tablet once daily orally for the first 28-day treatment course. Dose escalation to 50 mg once daily was allowed at the beginning of the second 28-day treatment course, if patients met specified safety and compliance criteria. Dose reduction to 40 mg/day (if applicable), 30 mg/day, or 20 mg/day, was required in the presence of known drug-related adverse events.

Reporting group title	Erlotinib

Reporting group description:

Patients administered 150 mg film-coated tablet once daily orally, with dose reduction to 100 mg/day or 50 mg/day in the presence of known drug-related adverse events.

Primary: Progression-free survival, based on central independent review as determined by Response Evaluation Criteria in Solid Tumours 1.1

End point title	Progression-free survival, based on central independent review as determined by Response Evaluation Criteria in Solid Tumours 1.1

End point description:

Progression Free Survival (PFS) was defined as the time from randomization to disease progression (or death if the patient died before progression) by central independent review according to Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1. RECIST is a set of published rules that define when tumors in cancer patients improve ("respond"), stay the same ("stabilize") or worsen ("progress") during treatment. Per RECIST v1.1 for target lesions and assessed by MRI: Complete Response (CR), Disappearance of all target lesions; Partial Response (PR), >=30% decrease in the sum of the longest diameter of target lesions; Overall Response (OR) = CR + PR. Randomized Set (RS): All patients who were randomized, regardless of whether they received investigational treatment.

End point type	Primary

End point timeframe:

First treatment administration up until cut off date of 02 March 2015 (up to 1058 days).

End point values	Afatinib	Erlotinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	398[1]	397[2]		
Units: Months				
median (confidence interval 95%)	2.63 (2.00 to 2.86)	1.94 (1.87 to 2.10)		

Notes:

[1] - RS

[2] - RS

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

A Cox proportional hazards model without the randomization stratification variable was used for each subgroup category, along with the corresponding log-rank test.

Comparison groups	Erlotinib v Afatinib

Number of subjects included in analysis	795
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0103 [3]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.814
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.693
upper limit	0.956

Notes:

[3] - P−value from log−rank stratified by Race (two−sided). Hazard ratio (Afatinib vs Erlotinib) from Cox proportional hazards model stratified by Race.

Secondary: Overall Survival

End point title	Overall Survival

End point description:

Overall Survival is defined as the time from randomisation to death. It was a key secondary endpoint.

End point type	Secondary

End point timeframe:

First treatment administration up until cut off date of 27 Dec 2017 (up to 2089 days).

End point values	Afatinib	Erlotinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	398[4]	397[5]		
Units: Months				
median (confidence interval 95%)	7.82 (7.19 to 8.71)	6.77 (5.85 to 7.79)		

Notes:

[4] - RS

[5] - RS

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

A Cox proportional-hazards model, stratified by race, was used to estimate the hazard ratio and 95% confidence interval (CI) between the two treatment groups.

Comparison groups	Afatinib v Erlotinib
Number of subjects included in analysis	795
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0193 [6]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.841

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.727
upper limit	0.973

Notes:

[6] - P−value from log−rank stratified by Race (two−sided). Hazard ratio (Afatinib vs Erlotinib) from Cox proportional hazards model stratified by Race.

Secondary: Objective Response according to RECIST 1.1

End point title	Objective Response according to RECIST 1.1

End point description:

A patient with a best overall response of Complete Responder (CR) or Partial Responder (PR) was considered to show objective response to study medication. For patients with an objective response, time to objective response was defined as the time from randomization to the first objective response; duration of objective response was defined as the time from the first objective response to progression (or death if the patient died before progression). Per RECIST v1.1 for target lesions and assessed by MRI: Complete Response (CR), Disappearance of all target lesions; Partial Response (PR), >=30% decrease in the sum of the longest diameter of target lesions; Overall Response (OR) = CR + PR.

End point type	Secondary

End point timeframe:

First treatment administration up until cut off date of 02 March 2015 (up to 1058 days).

End point values	Afatinib	Erlotinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	398[7]	397[8]		
Units: Participants	22	11		

Notes:

[7] - RS

[8] - RS

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Odds ratio (Afatinib vs Erlotinib), 95% CI and p−value (two−sided) from logistic regression stratified by race.

Comparison groups	Afatinib v Erlotinib
Number of subjects included in analysis	795
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0551
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.98
upper limit	4.32

Secondary: Disease Control according to RECIST 1.1

End point title	Disease Control according to RECIST 1.1

End point description:

Disease control was assessed based on Independent Radiologic Review (IRR) and investigator assessment. A patient with a best overall response of CR, PR, or Stable Disease (SD) was considered to have disease control. Patients with no baseline target lesions who had no evidence of disease progression in their non-target lesions and had no new lesions were considered to have disease control. Per RECIST v1.1 for target lesions and assessed by MRI: Complete Response (CR), Disappearance of all target lesions; Partial Response (PR), >=30% decrease in the sum of the longest diameter of target lesions; Overall Response (OR) = CR + PR.

End point type	Secondary

End point timeframe:

First treatment administration up until cut off date of 02 March 2015 (up to 1058 days).

End point values	Afatinib	Erlotinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	398[9]	397[10]		
Units: Participants	201	157		

Notes:

[9] - RS

[10] - RS

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Odds ratio (Afatinib vs Erlotinib), 95% CI and p−value (two−sided) from logistic regression stratified by race.

Comparison groups	Afatinib v Erlotinib
Number of subjects included in analysis	795
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.002
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.56
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.18
upper limit	2.06

Secondary: Tumour Shrinkage

End point title	Tumour Shrinkage

End point description:

Maximum percentage decrease from baseline in the sum of target lesion diameters following independent review. The change in the size (i.e. the sum of diameters (SOD)) of target lesions from baseline was derived. Tumour shrinkage for each patient was measured (based on Independent Radiologic Review (IRR)) as the minimum SOD of target lesions after randomisation. A negative percentage indicates decrease from baseline; positive numbers indicate an increase of tumour size. The mean maximum decrease from baseline of +5 and +9.4 reflect an average increase in tumour size. Post−baseline mean is adjusted for baseline sum of diameters and race. Patients from the randomised set with tumour assessments are considered for the analysis of this endpoint.

End point type	Secondary

End point timeframe:

First treatment administration up until cut off date of 02 March 2015 (up to 1058 days).

End point values	Afatinib	Erlotinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	307[11]	311[12]		
Units: Millimeter (mm)				
least squares mean (standard error)	78.8 (± 1.26)	80.0 (± 1.24)		

Notes:

[11] - Patients from the randomised set with tumour assessments

[12] - Patients from the randomised set with tumour assessments

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

The analysis will compare the treatments using analysis of covariance (ANCOVA) for minimum sum of diameters, using baseline sum of diameters as a covariate. The randomization strata will be included as classification factors.

Comparison groups	Afatinib v Erlotinib
Number of subjects included in analysis	618
Analysis specification	Pre-specified
Analysis type	superiority[13]
P-value	= 0.5
Method	ANCOVA
Parameter estimate	Adjusted mean difference
Point estimate	-1.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.67
upper limit	2.28
Variability estimate	Standard error of the mean
Dispersion value	1.77

Notes:

[13] - Mean was adjusted for baseline sum of diameters and race.

Secondary: Status change in cough, dyspnoea and pain related items over time in Health related Quality of Life Questionnaire

End point title	Status change in cough, dyspnoea and pain related items over time in Health related Quality of Life Questionnaire

End point description:

Health-related quality of life (HRQoL) was measured with the following multi-dimensional questionnaires: the european organization for research and treatment of cancer (eortc) quality of life questionnaire (QLQ-C30) questionnaire and its lung cancer specific supplementary module EORTC QLQ-LC13 and the EQ-5D health status self-assessment questionnaire. The questionnaires were assessed at the first visit of each treatment course, at end of treatment (EOT) and follow up prior to clinical assessment. The results displayed show number of patients with improvement in the relevant criteria. For each of the summary scales and items measuring cough, dyspnoea and pain, the two treatment arms were compared in terms of: The number of patients that were improved: Change in cough; dyspnoea and pain scores over time.

End point type	Secondary

End point timeframe:

First treatment administration up to 28 days after the last intake of study medication.

End point values	Afatinib	Erlotinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	398[14]	397[15]		
Units: Participants				
Improved Cough|	147	120		
Improved Dyspnoea|	174	150		
Improved Pain Related|	138	134		
Improved Global Health Status|	121	96		

Notes:

[14] - RS

[15] - RS

Statistical analyses

No statistical analyses for this end point

Secondary: Summary of Time to Deterioration in Coughing, Dyspnoea and Pain.

End point title	Summary of Time to Deterioration in Coughing, Dyspnoea and Pain.

End point description:

Health-related quality of life (HRQoL) was measured with the following multi-dimensional questionnaires: the EORTC QLQ-C30. The questionnaires were assessed at the first visit of each treatment course. For each of the summary scales and items measuring cough, dyspnoea and pain, the two treatment arms were compared in terms of: Time to deterioration.

End point type	Secondary

End point timeframe:

First treatment administration up to 28 days after the last intake of study medication.

End point values	Afatinib	Erlotinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	398[16]	397[17]		
Units: Months				
median (confidence interval 95%)				
Time to Deterioration - Coughing|	4.53 (2.86 to 4.93)	3.65 (2.79 to 4.66)		

Time to Deterioration - Dyspnoea|	2.63 (1.97 to 2.86)	1.91 (1.87 to 2.33)		
Time to Deterioration - Pain|	2.50 (2.00 to 2.79)	2.37 (1.91 to 2.76)		

Notes:

[16] - RS

[17] - RS

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

The results shown relate to time to deterioration in coughing. Hazard ratio (Afatinib vs Erlotinib) from Cox proportional hazard model stratified by race.

Comparison groups	Afatinib v Erlotinib
Number of subjects included in analysis	795
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2562 [18]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.89
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.72
upper limit	1.09

Notes:

[18] - P-value calculated using log rank test stratified by race.

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

The results shown relate to time to deterioration in dyspnoea. Hazard ratio (Afatinib vs Erlotinib) from Cox proportional hazard model stratified by race.

Comparison groups	Afatinib v Erlotinib
Number of subjects included in analysis	795
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0078 [19]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.79
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.66
upper limit	0.94

Notes:

[19] - P-value calculated using log rank test stratified by race.

Statistical analysis title	Statistical Analysis 3

Statistical analysis description:

The results shown relate to time to Deterioration in pain. Hazard ratio (Afatinib vs Erlotinib) from Cox proportional hazard model stratified by race.

Comparison groups	Afatinib v Erlotinib
Number of subjects included in analysis	795
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.869 [20]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.99
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.82
upper limit	1.18

Notes:

[20] - p-value calculated using log rank test stratified by race

Secondary: Change in score over time in Coughing,Dyspnoea and Pain

End point title	Change in score over time in Coughing,Dyspnoea and Pain

End point description:

Health related quality of life (HRQoL) was measured with the following multi dimensional questionnaires: the EORTC QLQ-C30. The questionnaires were assessed at the first visit of each treatment course. For each of the summary scales and items measuring cough, dyspnoea and pain, the two treatment arms were compared in terms of change in score over time, adjusted for baseline score and race. Questionnaires have items relating to Cough, Dyspnoea and Pain. Overall Scores are transformed to a standardised scale of 0 to 100 with the larger value indicating a worse outcome. A change of (+/-) 10 points is considered to be relevant. The change in cough, dyspnea and pain will be assessed using a mixed effects growth curve model with the average profile over time for each endpoint described by a piecewise linear model (presented as post baseline in data table). Post−baseline mean is adjusted for baseline and race.

End point type	Secondary

End point timeframe:

First treatment administration up to 28 days after last intake of study medication

End point values	Afatinib	Erlotinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	398[21]	397[22]		
Units: Units on a scale				
least squares mean (standard error)				
Coughing|	15.8 (± 2.40)	19.3 (± 2.37)		
Dyspnoea|	11.4 (± 1.83)	14.9 (± 1.85)		
Pain|	10.3 (± 2.13)	13.1 (± 2.17)		

Notes:

[21] - RS

[22] - RS

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
The results shown relate to Change in scores over time for: Coughing.	
Comparison groups	Afatinib v Erlotinib
Number of subjects included in analysis	795
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0091
Method	Regression, Cox
Parameter estimate	Mean difference (final values)
Point estimate	-3.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.15
upper limit	-0.88
Variability estimate	Standard error of the mean
Dispersion value	1.34

Statistical analysis title	Statistical Analysis 2
Statistical analysis description:	
The results shown relate to Change in scores over time for: Dyspnoea.	
Comparison groups	Afatinib v Erlotinib
Number of subjects included in analysis	795
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0024
Method	Regression, Cox
Parameter estimate	Mean difference (final values)
Point estimate	-3.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.75
upper limit	-1.25
Variability estimate	Standard error of the mean
Dispersion value	1.15

Statistical analysis title	Statistical Analysis 3
Statistical analysis description:	
The results shown relate to Change in scores over time for: Pain.	
Comparison groups	Afatinib v Erlotinib

Number of subjects included in analysis	795
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0384
Method	Regression, Cox
Parameter estimate	Mean difference (final values)
Point estimate	-2.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.33
upper limit	-0.15
Variability estimate	Standard error of the mean
Dispersion value	1.32

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From randomisation until 28 days after the discontinuation of trial medication, up to 2071 days.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.1

Reporting groups

Reporting group title	Erlotinib

Reporting group description:

Patients administered 150 mg film-coated tablet once daily orally, with dose reduction to 100 mg/day or 50 mg/day in the presence of known drug-related adverse events.

Reporting group title	Afatinib

Reporting group description:

Patients administered 40 milligram (mg) film-coated tablet once daily orally for the first 28-day treatment course. Dose escalation to 50 mg once daily was allowed at the beginning of the second 28-day treatment course, if patients met specified safety and compliance criteria. Dose reduction to 40 mg/day (if applicable), 30 mg/day, or 20 mg/day, was required in the presence of known drug-related adverse events.

Serious adverse events	Erlotinib	Afatinib	
Total subjects affected by serious adverse events			
subjects affected / exposed	175 / 395 (44.30%)	174 / 392 (44.39%)	
number of deaths (all causes)	82	89	
number of deaths resulting from adverse events	0	1	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma of colon			
subjects affected / exposed	0 / 395 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cancer pain			
subjects affected / exposed	1 / 395 (0.25%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant neoplasm progression			
subjects affected / exposed	16 / 395 (4.05%)	23 / 392 (5.87%)	
occurrences causally related to treatment / all	0 / 16	0 / 23	
deaths causally related to treatment / all	0 / 10	0 / 13	

Metastases to bone			
subjects affected / exposed	1 / 395 (0.25%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to central nervous system			
subjects affected / exposed	6 / 395 (1.52%)	2 / 392 (0.51%)	
occurrences causally related to treatment / all	0 / 6	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to liver			
subjects affected / exposed	1 / 395 (0.25%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Metastases to meninges			
subjects affected / exposed	0 / 395 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasm malignant			
subjects affected / exposed	0 / 395 (0.00%)	2 / 392 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Neoplasm progression			
subjects affected / exposed	1 / 395 (0.25%)	2 / 392 (0.51%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 1	
Non-small cell lung cancer			
subjects affected / exposed	1 / 395 (0.25%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Transitional cell carcinoma			
subjects affected / exposed	0 / 395 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour pain			

subjects affected / exposed	0 / 395 (0.00%)	2 / 392 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureteric cancer			
subjects affected / exposed	1 / 395 (0.25%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Arterial thrombosis			
subjects affected / exposed	1 / 395 (0.25%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage			
subjects affected / exposed	2 / 395 (0.51%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	1 / 395 (0.25%)	2 / 392 (0.51%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	1 / 395 (0.25%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inferior vena cava syndrome			
subjects affected / exposed	0 / 395 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orthostatic hypotension			
subjects affected / exposed	0 / 395 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemia			

subjects affected / exposed	1 / 395 (0.25%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Superior vena cava syndrome			
subjects affected / exposed	1 / 395 (0.25%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombosis			
subjects affected / exposed	1 / 395 (0.25%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	3 / 395 (0.76%)	6 / 392 (1.53%)	
occurrences causally related to treatment / all	1 / 3	2 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest discomfort			
subjects affected / exposed	2 / 395 (0.51%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	6 / 395 (1.52%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 6	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Condition aggravated			
subjects affected / exposed	1 / 395 (0.25%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	2 / 395 (0.51%)	4 / 392 (1.02%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 2	0 / 4	
Device occlusion			

subjects affected / exposed	1 / 395 (0.25%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Discomfort			
subjects affected / exposed	1 / 395 (0.25%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	2 / 395 (0.51%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	6 / 395 (1.52%)	11 / 392 (2.81%)	
occurrences causally related to treatment / all	0 / 6	3 / 14	
deaths causally related to treatment / all	0 / 0	0 / 2	
Mucosal inflammation			
subjects affected / exposed	1 / 395 (0.25%)	2 / 392 (0.51%)	
occurrences causally related to treatment / all	0 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multi-organ failure			
subjects affected / exposed	1 / 395 (0.25%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Necrosis			
subjects affected / exposed	0 / 395 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	0 / 395 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			

subjects affected / exposed	2 / 395 (0.51%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	3 / 395 (0.76%)	2 / 392 (0.51%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Performance status decreased			
subjects affected / exposed	1 / 395 (0.25%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	4 / 395 (1.01%)	3 / 392 (0.77%)	
occurrences causally related to treatment / all	0 / 4	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden death			
subjects affected / exposed	1 / 395 (0.25%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Respiratory, thoracic and mediastinal disorders			
Acute pulmonary oedema			
subjects affected / exposed	1 / 395 (0.25%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory distress syndrome			
subjects affected / exposed	1 / 395 (0.25%)	3 / 392 (0.77%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 0	
Acute respiratory failure			
subjects affected / exposed	0 / 395 (0.00%)	2 / 392 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atelectasis			

subjects affected / exposed	3 / 395 (0.76%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchial fistula			
subjects affected / exposed	0 / 395 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	4 / 395 (1.01%)	5 / 392 (1.28%)	
occurrences causally related to treatment / all	0 / 4	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cough			
subjects affected / exposed	3 / 395 (0.76%)	2 / 392 (0.51%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	30 / 395 (7.59%)	12 / 392 (3.06%)	
occurrences causally related to treatment / all	2 / 35	2 / 12	
deaths causally related to treatment / all	0 / 2	0 / 0	
Dyspnoea exertional			
subjects affected / exposed	0 / 395 (0.00%)	2 / 392 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	10 / 395 (2.53%)	5 / 392 (1.28%)	
occurrences causally related to treatment / all	1 / 10	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hypoxia			
subjects affected / exposed	1 / 395 (0.25%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Interstitial lung disease			

subjects affected / exposed	1 / 395 (0.25%)	4 / 392 (1.02%)	
occurrences causally related to treatment / all	1 / 1	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	6 / 395 (1.52%)	3 / 392 (0.77%)	
occurrences causally related to treatment / all	0 / 6	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung disorder			
subjects affected / exposed	0 / 395 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleurisy			
subjects affected / exposed	0 / 395 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleuritic pain			
subjects affected / exposed	0 / 395 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	0 / 395 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	3 / 395 (0.76%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	2 / 4	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	3 / 395 (0.76%)	2 / 392 (0.51%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary artery thrombosis			

subjects affected / exposed	0 / 395 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	5 / 395 (1.27%)	10 / 392 (2.55%)	
occurrences causally related to treatment / all	0 / 5	1 / 10	
deaths causally related to treatment / all	0 / 0	0 / 2	
Pulmonary haemorrhage			
subjects affected / exposed	0 / 395 (0.00%)	2 / 392 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Pulmonary hypertension			
subjects affected / exposed	1 / 395 (0.25%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary mass			
subjects affected / exposed	0 / 395 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			
subjects affected / exposed	1 / 395 (0.25%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory disorder			
subjects affected / exposed	0 / 395 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory distress			
subjects affected / exposed	2 / 395 (0.51%)	2 / 392 (0.51%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory failure			

subjects affected / exposed	12 / 395 (3.04%)	2 / 392 (0.51%)	
occurrences causally related to treatment / all	1 / 12	1 / 2	
deaths causally related to treatment / all	0 / 4	0 / 0	
Sputum increased			
subjects affected / exposed	0 / 395 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Confusional state			
subjects affected / exposed	1 / 395 (0.25%)	2 / 392 (0.51%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Delirium			
subjects affected / exposed	1 / 395 (0.25%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disorientation			
subjects affected / exposed	2 / 395 (0.51%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Investigations			
Blood calcium increased			
subjects affected / exposed	0 / 395 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood creatinine increased			
subjects affected / exposed	1 / 395 (0.25%)	2 / 392 (0.51%)	
occurrences causally related to treatment / all	0 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood urea increased			
subjects affected / exposed	0 / 395 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
C-reactive protein increased			

subjects affected / exposed	0 / 395 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eastern Cooperative Oncology Group performance status worsened			
subjects affected / exposed	1 / 395 (0.25%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical condition abnormal			
subjects affected / exposed	1 / 395 (0.25%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic enzyme increased			
subjects affected / exposed	1 / 395 (0.25%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelet count decreased			
subjects affected / exposed	0 / 395 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Weight decreased			
subjects affected / exposed	1 / 395 (0.25%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
White blood cell count decreased			
subjects affected / exposed	1 / 395 (0.25%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Cervical vertebral fracture			
subjects affected / exposed	1 / 395 (0.25%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral neck fracture			

subjects affected / exposed	1 / 395 (0.25%)	2 / 392 (0.51%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	1 / 395 (0.25%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fracture			
subjects affected / exposed	1 / 395 (0.25%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury			
subjects affected / exposed	1 / 395 (0.25%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	2 / 395 (0.51%)	4 / 392 (1.02%)	
occurrences causally related to treatment / all	0 / 2	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	1 / 395 (0.25%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Cardiac failure			
subjects affected / exposed	3 / 395 (0.76%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	0 / 395 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac tamponade			

subjects affected / exposed	1 / 395 (0.25%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardio-respiratory arrest			
subjects affected / exposed	1 / 395 (0.25%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiopulmonary failure			
subjects affected / exposed	1 / 395 (0.25%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Myocardial infarction			
subjects affected / exposed	4 / 395 (1.01%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	1 / 4	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Myocardial ischaemia			
subjects affected / exposed	0 / 395 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Palpitations			
subjects affected / exposed	0 / 395 (0.00%)	2 / 392 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial effusion			
subjects affected / exposed	2 / 395 (0.51%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericarditis			
subjects affected / exposed	1 / 395 (0.25%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus tachycardia			

subjects affected / exposed	0 / 395 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	0 / 395 (0.00%)	3 / 392 (0.77%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia			
subjects affected / exposed	0 / 395 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tracheo-oesophageal fistula			
subjects affected / exposed	0 / 395 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Altered state of consciousness			
subjects affected / exposed	1 / 395 (0.25%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Amnesia			
subjects affected / exposed	1 / 395 (0.25%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aphasia			
subjects affected / exposed	0 / 395 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain oedema			
subjects affected / exposed	0 / 395 (0.00%)	3 / 392 (0.77%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			

subjects affected / exposed	1 / 395 (0.25%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Convulsion			
subjects affected / exposed	1 / 395 (0.25%)	4 / 392 (1.02%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	4 / 395 (1.01%)	2 / 392 (0.51%)	
occurrences causally related to treatment / all	1 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysarthria			
subjects affected / exposed	1 / 395 (0.25%)	0 / 392 (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	1 / 395 (0.25%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hemiparesis			
subjects affected / exposed	0 / 395 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoaesthesia			
subjects affected / exposed	2 / 395 (0.51%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Motor dysfunction			
subjects affected / exposed	1 / 395 (0.25%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myoclonus			

subjects affected / exposed	0 / 395 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraparesis			
subjects affected / exposed	1 / 395 (0.25%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polyneuropathy			
subjects affected / exposed	0 / 395 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal cord compression			
subjects affected / exposed	2 / 395 (0.51%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Somnolence			
subjects affected / exposed	0 / 395 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	1 / 395 (0.25%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 395 (0.51%)	5 / 392 (1.28%)	
occurrences causally related to treatment / all	0 / 2	2 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	1 / 395 (0.25%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			

subjects affected / exposed	0 / 395 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	0 / 395 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	0 / 395 (0.00%)	2 / 392 (0.51%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	5 / 395 (1.27%)	5 / 392 (1.28%)	
occurrences causally related to treatment / all	1 / 5	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	2 / 395 (0.51%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal fissure			
subjects affected / exposed	0 / 395 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aphagia			
subjects affected / exposed	0 / 395 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	1 / 395 (0.25%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			

subjects affected / exposed	7 / 395 (1.77%)	18 / 392 (4.59%)	
occurrences causally related to treatment / all	6 / 7	17 / 19	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	3 / 395 (0.76%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric perforation			
subjects affected / exposed	1 / 395 (0.25%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer			
subjects affected / exposed	2 / 395 (0.51%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	0 / 395 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 395 (0.25%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal perforation			
subjects affected / exposed	0 / 395 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal telangiectasia			
subjects affected / exposed	1 / 395 (0.25%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			

subjects affected / exposed	1 / 395 (0.25%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal perforation			
subjects affected / exposed	1 / 395 (0.25%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Melaena			
subjects affected / exposed	1 / 395 (0.25%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	3 / 395 (0.76%)	2 / 392 (0.51%)	
occurrences causally related to treatment / all	2 / 3	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal stenosis			
subjects affected / exposed	1 / 395 (0.25%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatic duct dilatation			
subjects affected / exposed	1 / 395 (0.25%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	1 / 395 (0.25%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Proctalgia			
subjects affected / exposed	0 / 395 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal haemorrhage			

subjects affected / exposed	1 / 395 (0.25%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	1 / 395 (0.25%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			
subjects affected / exposed	0 / 395 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	5 / 395 (1.27%)	4 / 392 (1.02%)	
occurrences causally related to treatment / all	1 / 5	3 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatic function abnormal			
subjects affected / exposed	1 / 395 (0.25%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis toxic			
subjects affected / exposed	1 / 395 (0.25%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatomegaly			
subjects affected / exposed	1 / 395 (0.25%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperbilirubinaemia			
subjects affected / exposed	1 / 395 (0.25%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaundice			

subjects affected / exposed	1 / 395 (0.25%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	1 / 395 (0.25%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dermatitis acneiform			
subjects affected / exposed	0 / 395 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dermatomyositis			
subjects affected / exposed	1 / 395 (0.25%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	0 / 395 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin lesion			
subjects affected / exposed	1 / 395 (0.25%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Azotaemia			
subjects affected / exposed	1 / 395 (0.25%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute prerenal failure			
subjects affected / exposed	0 / 395 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	

Calculus ureteric			
subjects affected / exposed	0 / 395 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder mass			
subjects affected / exposed	1 / 395 (0.25%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	2 / 395 (0.51%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydronephrosis			
subjects affected / exposed	0 / 395 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	2 / 395 (0.51%)	2 / 392 (0.51%)	
occurrences causally related to treatment / all	0 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure acute			
subjects affected / exposed	1 / 395 (0.25%)	9 / 392 (2.30%)	
occurrences causally related to treatment / all	1 / 1	4 / 9	
deaths causally related to treatment / all	0 / 0	1 / 1	
Renal impairment			
subjects affected / exposed	0 / 395 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	1 / 395 (0.25%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary bladder polyp			

subjects affected / exposed	1 / 395 (0.25%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Inappropriate antidiuretic hormone secretion			
subjects affected / exposed	1 / 395 (0.25%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 395 (0.25%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	1 / 395 (0.25%)	3 / 392 (0.77%)	
occurrences causally related to treatment / all	0 / 1	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone pain			
subjects affected / exposed	1 / 395 (0.25%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscle spasms			
subjects affected / exposed	0 / 395 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular weakness			
subjects affected / exposed	2 / 395 (0.51%)	2 / 392 (0.51%)	
occurrences causally related to treatment / all	0 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal chest pain			
subjects affected / exposed	0 / 395 (0.00%)	2 / 392 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Musculoskeletal pain			
subjects affected / exposed	1 / 395 (0.25%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myalgia			
subjects affected / exposed	0 / 395 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neck pain			
subjects affected / exposed	1 / 395 (0.25%)	2 / 392 (0.51%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Anal abscess			
subjects affected / exposed	0 / 395 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	6 / 395 (1.52%)	2 / 392 (0.51%)	
occurrences causally related to treatment / all	0 / 6	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopneumonia			
subjects affected / exposed	1 / 395 (0.25%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocarditis			
subjects affected / exposed	1 / 395 (0.25%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Folliculitis			
subjects affected / exposed	0 / 395 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			

subjects affected / exposed	1 / 395 (0.25%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis C			
subjects affected / exposed	1 / 395 (0.25%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes virus infection			
subjects affected / exposed	1 / 395 (0.25%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	1 / 395 (0.25%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	3 / 395 (0.76%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	5 / 395 (1.27%)	2 / 392 (0.51%)	
occurrences causally related to treatment / all	0 / 5	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oral fungal infection			
subjects affected / exposed	1 / 395 (0.25%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			
subjects affected / exposed	1 / 395 (0.25%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			

subjects affected / exposed	16 / 395 (4.05%)	26 / 392 (6.63%)	
occurrences causally related to treatment / all	2 / 17	1 / 26	
deaths causally related to treatment / all	0 / 1	0 / 2	
Pneumonia bacterial			
subjects affected / exposed	1 / 395 (0.25%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary tuberculosis			
subjects affected / exposed	1 / 395 (0.25%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	0 / 395 (0.00%)	2 / 392 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	2 / 395 (0.51%)	9 / 392 (2.30%)	
occurrences causally related to treatment / all	0 / 2	0 / 10	
deaths causally related to treatment / all	0 / 0	0 / 1	
Septic shock			
subjects affected / exposed	1 / 395 (0.25%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin infection			
subjects affected / exposed	0 / 395 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	0 / 395 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			

subjects affected / exposed	1 / 395 (0.25%)	2 / 392 (0.51%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Cachexia			
subjects affected / exposed	0 / 395 (0.00%)	2 / 392 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Decreased appetite			
subjects affected / exposed	3 / 395 (0.76%)	3 / 392 (0.77%)	
occurrences causally related to treatment / all	2 / 3	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	4 / 395 (1.01%)	12 / 392 (3.06%)	
occurrences causally related to treatment / all	2 / 4	9 / 14	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia			
subjects affected / exposed	6 / 395 (1.52%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	1 / 6	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	2 / 395 (0.51%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	0 / 395 (0.00%)	1 / 392 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperuricaemia			
subjects affected / exposed	1 / 395 (0.25%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			

subjects affected / exposed	0 / 395 (0.00%)	2 / 392 (0.51%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypophagia			
subjects affected / exposed	1 / 395 (0.25%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malnutrition			
subjects affected / exposed	1 / 395 (0.25%)	0 / 392 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Erlotinib	Afatinib	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	371 / 395 (93.92%)	383 / 392 (97.70%)	
Investigations			
Weight decreased			
subjects affected / exposed	51 / 395 (12.91%)	38 / 392 (9.69%)	
occurrences (all)	51	38	
Nervous system disorders			
Dizziness			
subjects affected / exposed	21 / 395 (5.32%)	12 / 392 (3.06%)	
occurrences (all)	21	12	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	41 / 395 (10.38%)	31 / 392 (7.91%)	
occurrences (all)	44	37	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	48 / 395 (12.15%)	61 / 392 (15.56%)	
occurrences (all)	52	68	
Chest pain			

subjects affected / exposed	20 / 395 (5.06%)	14 / 392 (3.57%)	
occurrences (all)	20	14	
Fatigue			
subjects affected / exposed	67 / 395 (16.96%)	65 / 392 (16.58%)	
occurrences (all)	71	69	
Mucosal inflammation			
subjects affected / exposed	14 / 395 (3.54%)	50 / 392 (12.76%)	
occurrences (all)	15	59	
Pyrexia			
subjects affected / exposed	33 / 395 (8.35%)	32 / 392 (8.16%)	
occurrences (all)	35	42	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	42 / 395 (10.63%)	43 / 392 (10.97%)	
occurrences (all)	47	46	
Diarrhoea			
subjects affected / exposed	158 / 395 (40.00%)	284 / 392 (72.45%)	
occurrences (all)	283	568	
Nausea			
subjects affected / exposed	62 / 395 (15.70%)	81 / 392 (20.66%)	
occurrences (all)	70	93	
Vomiting			
subjects affected / exposed	38 / 395 (9.62%)	48 / 392 (12.24%)	
occurrences (all)	46	60	
Stomatitis			
subjects affected / exposed	21 / 395 (5.32%)	54 / 392 (13.78%)	
occurrences (all)	24	63	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	67 / 395 (16.96%)	65 / 392 (16.58%)	
occurrences (all)	73	69	
Dyspnoea			
subjects affected / exposed	69 / 395 (17.47%)	68 / 392 (17.35%)	
occurrences (all)	74	74	
Epistaxis			

subjects affected / exposed	10 / 395 (2.53%)	27 / 392 (6.89%)	
occurrences (all)	12	28	
Productive cough			
subjects affected / exposed	21 / 395 (5.32%)	14 / 392 (3.57%)	
occurrences (all)	23	14	
Haemoptysis			
subjects affected / exposed	39 / 395 (9.87%)	44 / 392 (11.22%)	
occurrences (all)	46	57	
Skin and subcutaneous tissue disorders			
Dermatitis acneiform			
subjects affected / exposed	56 / 395 (14.18%)	38 / 392 (9.69%)	
occurrences (all)	57	41	
Pruritus			
subjects affected / exposed	52 / 395 (13.16%)	38 / 392 (9.69%)	
occurrences (all)	54	45	
Dry skin			
subjects affected / exposed	47 / 395 (11.90%)	36 / 392 (9.18%)	
occurrences (all)	47	36	
Rash			
subjects affected / exposed	187 / 395 (47.34%)	196 / 392 (50.00%)	
occurrences (all)	206	236	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	17 / 395 (4.30%)	20 / 392 (5.10%)	
occurrences (all)	18	21	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	25 / 395 (6.33%)	22 / 392 (5.61%)	
occurrences (all)	25	22	
Musculoskeletal pain			
subjects affected / exposed	20 / 395 (5.06%)	20 / 392 (5.10%)	
occurrences (all)	20	22	
Pain in extremity			
subjects affected / exposed	23 / 395 (5.82%)	14 / 392 (3.57%)	
occurrences (all)	24	14	
Infections and infestations			

Paronychia subjects affected / exposed occurrences (all)	18 / 395 (4.56%) 21	41 / 392 (10.46%) 44	
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	100 / 395 (25.32%) 108	94 / 392 (23.98%) 105	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 October 2012	Inclusion criterion 2 was modified to state that patients intending to receive four cycles of platinum-based doublet chemotherapy but due to toxicity, and not PD, discontinued just the platinum agent after at least 2 cycles of platinum doublet therapy had been administered, were considered to have met inclusion criterion 2. Exclusion criterion 21 was added to align the criterion with the language in Section 3.3.1 of the protocol, specifying patients needed to have disease progression after completion of the first line treatment. Language describing the timing of trial team unblinding was changed to clarify that the trial team will be unblinded at the time of the aggregate data reviews of the database snapshot used for the primary Progression-free Survival (PFS) analysis. The original language stated that the trial team would remain blinded for as long as feasible. Certain medications were added to and deleted from the list of potent inhibitors and inducers of P-glycoprotein (P-gp) in Appendix 10.5 of the protocol, to provide updated information and a disclosure statement was added regarding assessing medications not listed.
24 June 2016	Flow chart was updated to decrease the frequency of Electrocardiogram (ECG), Echocardiography (ECHO)/ Multiple Gated Acquisition Scan (MUGA), and imaging assessments and remove requirements for Quality of Life (QOL) assessments, collection of Health Care Resource Utilization (HCRU) data, and collection of Observation Period data. ECG and Left Ventricular Ejection Fraction (LVEF) assessments during follow-up were only required to be performed if clinically indicated. Following the database lock for the primary analysis of Overall Survival (OS) data (cut-off 02March2015), patients would have been on treatment for more than 2 years, and therefore, sufficient vital status and health related QOL, HCRU data were collected. A more frequent ECG, ECHO/MUGA and imaging assessment was no longer considered necessary. Central imaging review and collection of vital status data were discontinued. Following the database lock for the primary analysis of OS data (cut-off 02 March 2015), there was no longer the requirement for central analysis of imaging, as the primary endpoint of Progression-free Survival (PFS) was assessed and reported. Sufficient vital status data were collected, and therefore, no longer required. Updated terminology and the reporting timeline and requirements for Serious Adverse Event (SAEs) and Adverse Event (AEs) of special interest to be consistent with updated BI reporting guidelines. Safety laboratory samples were no longer required to be sent to the central laboratory for analysis, but were analyzed locally.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported