



Clinical trial results:

A Phase 3, Randomized, Double-Blinded, Placebo-Controlled Study of ARQ 197 Plus Erlotinib Versus Placebo Plus Erlotinib in Previously Treated Subjects with Locally Advanced or Metastatic, Non-Squamous, Non-Small-Cell Lung Cancer (NSCLC)

Summary

EudraCT number	2010-022365-10
Trial protocol	HU CZ DE ES IT SE GB DK AT BE
Global end of trial date	06 October 2016

Results information

Result version number	v1 (current)
This version publication date	20 March 2018
First version publication date	20 March 2018

Trial information

Trial identification

Sponsor protocol code	ARQ197-A-U302
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01244191
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Daiichi Sankyo, Inc.
Sponsor organisation address	211 Mt. Airy Road, Basking Ridge, United States, 07920
Public contact	Clinical Trial Information, Daiichi Sankyo Development Limited, +44 1753482800, info@dsd-eu.com
Scientific contact	Clinical Trial Information, Daiichi Sankyo Development Limited, +44 1753482800, info@dsd-eu.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	30 November 2017
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	06 October 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to evaluate overall survival (OS) in the intent-to-treat (ITT) subject population defined by this protocol.

Protection of trial subjects:

This study was conducted in compliance with the protocol, the ethical principles that have their origin in the Declaration of Helsinki, the International Conference on Harmonisation (ICH) consolidated Guideline E6 for Good Clinical Practice (GCP) (CPMP/ICH/135/95), and applicable regulatory requirement(s). Dose delays and/or reductions were permitted.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	11 January 2011
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	4 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Russian Federation: 67
Country: Number of subjects enrolled	United States: 229
Country: Number of subjects enrolled	Chile: 17
Country: Number of subjects enrolled	Argentina: 14
Country: Number of subjects enrolled	Australia: 17
Country: Number of subjects enrolled	Brazil: 45
Country: Number of subjects enrolled	Canada: 39
Country: Number of subjects enrolled	Mexico: 10
Country: Number of subjects enrolled	Peru: 11
Country: Number of subjects enrolled	Poland: 78
Country: Number of subjects enrolled	Romania: 13
Country: Number of subjects enrolled	Spain: 79
Country: Number of subjects enrolled	Netherlands: 12
Country: Number of subjects enrolled	Sweden: 2
Country: Number of subjects enrolled	United Kingdom: 10
Country: Number of subjects enrolled	Austria: 1

Country: Number of subjects enrolled	Belgium: 5
Country: Number of subjects enrolled	Czech Republic: 8
Country: Number of subjects enrolled	Denmark: 14
Country: Number of subjects enrolled	France: 101
Country: Number of subjects enrolled	Germany: 93
Country: Number of subjects enrolled	Hungary: 31
Country: Number of subjects enrolled	Italy: 152
Worldwide total number of subjects	1048
EEA total number of subjects	599

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)	646
From 65 to 84 years	399
85 years and over	3

Subject disposition

Recruitment

Recruitment details:

Between Jan 2011 and July 2012, of the 1624 patients screened, 1048 were randomized to treatment and formed the Intent-to-treat (ITT) Population.

Results of the interim analysis met the protocol-defined stopping criteria.

Protocol amendment 4 allowed only the EGFR mutant subgroup to continue (indicated here as Period 2).

Pre-assignment

Screening details:

A total of 1624 subjects were screened for this study in 23 countries.

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Erlotinib plus tivantinib

Arm description:

Patients received 1 commercially available erlotinib 150 mg tablet once daily without food, plus 3 tivantinib 120 mg tablets twice daily with meals (for a daily dose of 720 mg).

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 tablet once daily at least 1 hour before or at least 2 hours after food.

Investigational medicinal product name	Tivantinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Three 120 mg tablets twice daily with meals, for a total daily dose of 720 mg.

Arm title	Erlotinib plus placebo
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Arm description:

Patients received 1 commercially available erlotinib 150 mg tablet once daily without food, plus 3 placebo tablets twice daily with meals.

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

Dosage and administration details:

Single tablet once daily at least 1 hour before or at least 2 hours after food.

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Three tablets twice daily with meals.

Number of subjects in period 1	Erlotinib plus tivantinib	Erlotinib plus placebo
Started	526	522
Treated - safety analysis set	520	517
Completed	46	24
Not completed	480	498
Consent withdrawn by subject	31	23
Missing or study terminated by sponsor	12	8
Adverse event, non-fatal	65	48
Death	22	29
Clinical disease progression	54	36
Progressive disease	295	350
Lost to follow-up	-	2
Protocol deviation	1	2

Baseline characteristics

Reporting groups

Reporting group title	Erlotinib plus tivantinib
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Reporting group description:

Patients received 1 commercially available erlotinib 150 mg tablet once daily without food, plus 3 tivantinib 120 mg tablets twice daily with meals (for a daily dose of 720 mg).

Reporting group title	Erlotinib plus placebo
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Reporting group description:

Patients received 1 commercially available erlotinib 150 mg tablet once daily without food, plus 3 placebo tablets twice daily with meals.

Reporting group values	Erlotinib plus tivantinib	Erlotinib plus placebo	Total
Number of subjects	526	522	1048
Age categorical			
Units: Subjects			
Adults (18-64 years)	320	326	646
From 65-84 years	204	195	399
85 years and over	2	1	3
Age continuous			
Units: years			
arithmetic mean	61.2	61.1	
standard deviation	± 10.10	± 9.84	-
Gender categorical			
Units: Subjects			
Female	216	213	429
Male	310	309	619

End points

End points reporting groups

Reporting group title	Erlotinib plus tivantinib
Reporting group description: Patients received 1 commercially available erlotinib 150 mg tablet once daily without food, plus 3 tivantinib 120 mg tablets twice daily with meals (for a daily dose of 720 mg).	
Reporting group title	Erlotinib plus placebo
Reporting group description: Patients received 1 commercially available erlotinib 150 mg tablet once daily without food, plus 3 placebo tablets twice daily with meals.	

Primary: Overall survival (OS) in Original Intent-to-treat (ITT) Population

End point title	Overall survival (OS) in Original Intent-to-treat (ITT) Population
End point description: Median length of time patients survived	
End point type	Primary
End point timeframe: by study completion, within 5 years, 9 months	

End point values	Erlotinib plus tivantinib	Erlotinib plus placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	526	522		
Units: months				
median (confidence interval 95%)	8.5 (7.1 to 9.3)	7.8 (7.0 to 9.0)		

Statistical analyses

Statistical analysis title	Original ITT - OS Analysis
Comparison groups	Erlotinib plus tivantinib v Erlotinib plus placebo
Number of subjects included in analysis	1048
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.8086 ^[1]
Method	Logrank

Notes:

[1] - p-value from the stratified log-rank test [adjusting for number of prior therapies, gender, and smoking history using the IXRS (Randomization) data set] provides an overall comparison of the OS survival curves.

Secondary: Progression-Free Survival (PFS) in the Original ITT Population

End point title	Progression-Free Survival (PFS) in the Original ITT Population
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End point description:	
Kaplan-Meier estimates of the median PFS times for each treatment group	
End point type	Secondary
End point timeframe:	
by study completion, within 5 years, 9 months	

End point values	Erlotinib plus tivantinib	Erlotinib plus placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	526	522		
Units: months				
median (confidence interval 95%)	3.6 (2.8 to 3.7)	1.9 (1.9 to 2.0)		

Statistical analyses

Statistical analysis title	Period 1 Original ITT
Comparison groups	Erlotinib plus tivantinib v Erlotinib plus placebo
Number of subjects included in analysis	1048
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001 ^[2]
Method	Logrank

Notes:

[2] - p-value from the stratified log-rank test (adjusting for number of prior therapies, gender, and smoking history using the IXRS data set) provides an overall comparison of the PFS survival curves

Other pre-specified: Overall Survival in the EGFR Mutant Subpopulation (ITT)

End point title	Overall Survival in the EGFR Mutant Subpopulation (ITT)
End point description:	
Median length of time patients survived who were in the EGFR-mutant sub-population that continued until November 2014	
End point type	Other pre-specified
End point timeframe:	
by study completion, within 5 years, 9 months	

End point values	Erlotinib plus tivantinib	Erlotinib plus placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	56	53		
Units: months				
median (confidence interval 95%)	25.5 (15.6 to 38.9)	20.3 (16.6 to 24.3)		

Statistical analyses

Statistical analysis title	EGFR-Mutant Analysis
Statistical analysis description: Analysis of EGFR-mutant patients who continued during Amended Protocol 4	
Comparison groups	Erlotinib plus tivantinib v Erlotinib plus placebo
Number of subjects included in analysis	109
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1013 ^[3]
Method	Logrank

Notes:

[3] - p-value from the stratified log-rank test (adjusting for number of prior therapies, gender, and smoking history) provides an overall comparison of the PFS survival curves

Other pre-specified: Progression-Free Survival in the EGFR Mutant Subpopulation (ITT)

End point title	Progression-Free Survival in the EGFR Mutant Subpopulation (ITT)
End point description: Kaplan-Meier estimates of the median PFS times for each treatment group	
End point type	Other pre-specified
End point timeframe: by study completion, within 5 years, 9 months	

End point values	Erlotinib plus tivantinib	Erlotinib plus placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	56	53		
Units: months				
median (confidence interval 95%)	13.0 (7.3 to 17.7)	7.5 (5.6 to 11.9)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Treatment emergent adverse events (TEAEs) were collected until 30 days after completing treatment, within 5 years, 9 months.

TEAEs that occurred more than 30 days after the last dose of study medication are not included unless related to treatment.

Adverse event reporting additional description:

At each level of summarizing TEAEs, a patient was counted only once if he/she reported one or more adverse events in this older trial. Therefore, the number of events mirrors the number of patients. Relatedness is based on the experimental products placebo and tivantinib only.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	13.1

Reporting groups

Reporting group title	Erlotinib plus placebo
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Reporting group description: -

Reporting group title	Erlotinib plus tivantinib
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Reporting group description: -

Serious adverse events	Erlotinib plus placebo	Erlotinib plus tivantinib	
Total subjects affected by serious adverse events			
subjects affected / exposed	198 / 517 (38.30%)	228 / 520 (43.85%)	
number of deaths (all causes)	300	314	
number of deaths resulting from adverse events	67	82	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			
subjects affected / exposed	4 / 517 (0.77%)	3 / 520 (0.58%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant ascites			
subjects affected / exposed	0 / 517 (0.00%)	1 / 520 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Malignant pleural effusion			
subjects affected / exposed	1 / 517 (0.19%)	1 / 520 (0.19%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Metastases to central nervous system			
subjects affected / exposed	3 / 517 (0.58%)	1 / 520 (0.19%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Metastases to lung			
subjects affected / exposed	0 / 517 (0.00%)	1 / 520 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to lymph nodes			
subjects affected / exposed	0 / 517 (0.00%)	1 / 520 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to spleen			
subjects affected / exposed	1 / 517 (0.19%)	0 / 520 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastatic pain			
subjects affected / exposed	3 / 517 (0.58%)	0 / 520 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Neoplasm malignant			
subjects affected / exposed	0 / 517 (0.00%)	1 / 520 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasm progression			
subjects affected / exposed	1 / 517 (0.19%)	2 / 520 (0.38%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Paraneoplastic syndrome			
subjects affected / exposed	1 / 517 (0.19%)	0 / 520 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal cord neoplasm			

subjects affected / exposed	0 / 517 (0.00%)	1 / 520 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour compression			
subjects affected / exposed	1 / 517 (0.19%)	2 / 520 (0.38%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour haemorrhage			
subjects affected / exposed	0 / 517 (0.00%)	1 / 520 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Tumour pain			
subjects affected / exposed	1 / 517 (0.19%)	4 / 520 (0.77%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Aortic aneurysm			
subjects affected / exposed	0 / 517 (0.00%)	1 / 520 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	2 / 517 (0.39%)	4 / 520 (0.77%)	
occurrences causally related to treatment / all	0 / 2	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolism arterial			
subjects affected / exposed	1 / 517 (0.19%)	0 / 520 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	0 / 517 (0.00%)	2 / 520 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jugular vein thrombosis			

subjects affected / exposed	0 / 517 (0.00%)	1 / 520 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Phlebitis			
subjects affected / exposed	0 / 517 (0.00%)	1 / 520 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shock			
subjects affected / exposed	0 / 517 (0.00%)	1 / 520 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Superior vena caval occlusion			
subjects affected / exposed	3 / 517 (0.58%)	0 / 520 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous insufficiency			
subjects affected / exposed	0 / 517 (0.00%)	1 / 520 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous thrombosis limb			
subjects affected / exposed	0 / 517 (0.00%)	1 / 520 (0.19%)	
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			
Asthenia			
subjects affected / exposed	5 / 517 (0.97%)	3 / 520 (0.58%)	
occurrences causally related to treatment / all	0 / 5	1 / 3	
deaths causally related to treatment / all	0 / 3	0 / 1	
Fatigue			
subjects affected / exposed	2 / 517 (0.39%)	4 / 520 (0.77%)	
occurrences causally related to treatment / all	1 / 2	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			

subjects affected / exposed	13 / 517 (2.51%)	16 / 520 (3.08%)	
occurrences causally related to treatment / all	0 / 13	0 / 16	
deaths causally related to treatment / all	0 / 7	0 / 10	
Malaise			
subjects affected / exposed	1 / 517 (0.19%)	0 / 520 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucosal inflammation			
subjects affected / exposed	0 / 517 (0.00%)	1 / 520 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multi-organ disorder			
subjects affected / exposed	1 / 517 (0.19%)	0 / 520 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multi-organ failure			
subjects affected / exposed	2 / 517 (0.39%)	0 / 520 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	1 / 2	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	3 / 517 (0.58%)	1 / 520 (0.19%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Oedema peripheral			
subjects affected / exposed	1 / 517 (0.19%)	0 / 520 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	0 / 517 (0.00%)	3 / 520 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 2	
Performance status decreased			

subjects affected / exposed	3 / 517 (0.58%)	5 / 520 (0.96%)	
occurrences causally related to treatment / all	0 / 3	0 / 5	
deaths causally related to treatment / all	0 / 3	0 / 3	
Pyrexia			
subjects affected / exposed	5 / 517 (0.97%)	1 / 520 (0.19%)	
occurrences causally related to treatment / all	0 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden cardiac death			
subjects affected / exposed	1 / 517 (0.19%)	0 / 520 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Sudden death			
subjects affected / exposed	1 / 517 (0.19%)	0 / 520 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute lung injury			
subjects affected / exposed	1 / 517 (0.19%)	0 / 520 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory distress syndrome			
subjects affected / exposed	1 / 517 (0.19%)	0 / 520 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Acute respiratory failure			
subjects affected / exposed	0 / 517 (0.00%)	3 / 520 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthma			
subjects affected / exposed	0 / 517 (0.00%)	1 / 520 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atelectasis			

subjects affected / exposed	1 / 517 (0.19%)	1 / 520 (0.19%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchial obstruction			
subjects affected / exposed	1 / 517 (0.19%)	1 / 520 (0.19%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Bronchospasm			
subjects affected / exposed	0 / 517 (0.00%)	1 / 520 (0.19%)	
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 / 517 (0.77%)	4 / 520 (0.77%)	
occurrences causally related to treatment / all	0 / 4	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cough			
subjects affected / exposed	1 / 517 (0.19%)	0 / 520 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diffuse alveolar damage			
subjects affected / exposed	0 / 517 (0.00%)	1 / 520 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Dyspnoea			
subjects affected / exposed	24 / 517 (4.64%)	28 / 520 (5.38%)	
occurrences causally related to treatment / all	2 / 24	0 / 28	
deaths causally related to treatment / all	0 / 8	0 / 11	
Dyspnoea exertional			
subjects affected / exposed	1 / 517 (0.19%)	0 / 520 (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	4 / 517 (0.77%)	4 / 520 (0.77%)	
occurrences causally related to treatment / all	0 / 4	0 / 4	
deaths causally related to treatment / all	0 / 2	0 / 2	
Hypoxia			
subjects affected / exposed	0 / 517 (0.00%)	3 / 520 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 2	
Lung disorder			
subjects affected / exposed	0 / 517 (0.00%)	1 / 520 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mediastinal disorder			
subjects affected / exposed	1 / 517 (0.19%)	0 / 520 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orthopnoea			
subjects affected / exposed	0 / 517 (0.00%)	1 / 520 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	9 / 517 (1.74%)	13 / 520 (2.50%)	
occurrences causally related to treatment / all	0 / 9	0 / 13	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pleurisy			
subjects affected / exposed	0 / 517 (0.00%)	1 / 520 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumomediastinum			
subjects affected / exposed	1 / 517 (0.19%)	0 / 520 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			

subjects affected / exposed	0 / 517 (0.00%)	1 / 520 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	2 / 517 (0.39%)	0 / 520 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	0 / 517 (0.00%)	5 / 520 (0.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 1	
Productive cough			
subjects affected / exposed	0 / 517 (0.00%)	1 / 520 (0.19%)	
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	20 / 517 (3.87%)	17 / 520 (3.27%)	
occurrences causally related to treatment / all	4 / 20	2 / 17	
deaths causally related to treatment / all	0 / 4	0 / 4	
Pulmonary haemorrhage			
subjects affected / exposed	0 / 517 (0.00%)	2 / 520 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary hypertension			
subjects affected / exposed	0 / 517 (0.00%)	1 / 520 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory arrest			
subjects affected / exposed	0 / 517 (0.00%)	1 / 520 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory failure			

subjects affected / exposed	9 / 517 (1.74%)	12 / 520 (2.31%)	
occurrences causally related to treatment / all	1 / 9	1 / 12	
deaths causally related to treatment / all	0 / 8	1 / 8	
Tracheal stenosis			
subjects affected / exposed	1 / 517 (0.19%)	1 / 520 (0.19%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 517 (0.00%)	1 / 520 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Confusional state			
subjects affected / exposed	1 / 517 (0.19%)	1 / 520 (0.19%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental disorder due to a general medical condition			
subjects affected / exposed	0 / 517 (0.00%)	1 / 520 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental status changes			
subjects affected / exposed	0 / 517 (0.00%)	1 / 520 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 517 (0.19%)	0 / 520 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood bilirubin increased			
subjects affected / exposed	1 / 517 (0.19%)	0 / 520 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Blood creatinine increased			
subjects affected / exposed	0 / 517 (0.00%)	3 / 520 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood lactate dehydrogenase increased			
subjects affected / exposed	1 / 517 (0.19%)	0 / 520 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood magnesium decreased			
subjects affected / exposed	1 / 517 (0.19%)	0 / 520 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coagulation test abnormal			
subjects affected / exposed	0 / 517 (0.00%)	1 / 520 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical condition abnormal			
subjects affected / exposed	2 / 517 (0.39%)	0 / 520 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Hepatic enzyme increased			
subjects affected / exposed	0 / 517 (0.00%)	1 / 520 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutrophil count decreased			
subjects affected / exposed	0 / 517 (0.00%)	3 / 520 (0.58%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelet count decreased			
subjects affected / exposed	1 / 517 (0.19%)	0 / 520 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Weight decreased			

subjects affected / exposed	0 / 517 (0.00%)	1 / 520 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
White blood cell count decreased			
subjects affected / exposed	0 / 517 (0.00%)	2 / 520 (0.38%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
White blood cell count increased			
subjects affected / exposed	0 / 517 (0.00%)	1 / 520 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	0 / 517 (0.00%)	1 / 520 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Collapse of lung			
subjects affected / exposed	1 / 517 (0.19%)	0 / 520 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug toxicity			
subjects affected / exposed	1 / 517 (0.19%)	0 / 520 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	0 / 517 (0.00%)	1 / 520 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			
subjects affected / exposed	1 / 517 (0.19%)	0 / 520 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar vertebral fracture			

subjects affected / exposed	0 / 517 (0.00%)	2 / 520 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal compression fracture			
subjects affected / exposed	1 / 517 (0.19%)	0 / 520 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sternal fracture			
subjects affected / exposed	1 / 517 (0.19%)	0 / 520 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 517 (0.00%)	1 / 520 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Arrhythmia supraventricular			
subjects affected / exposed	1 / 517 (0.19%)	0 / 520 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	2 / 517 (0.39%)	1 / 520 (0.19%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			
subjects affected / exposed	0 / 517 (0.00%)	1 / 520 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	1 / 517 (0.19%)	0 / 520 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac failure			

subjects affected / exposed	3 / 517 (0.58%)	2 / 520 (0.38%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 2	0 / 1	
Cardiac tamponade			
subjects affected / exposed	2 / 517 (0.39%)	0 / 520 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardio-respiratory arrest			
subjects affected / exposed	2 / 517 (0.39%)	1 / 520 (0.19%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 2	1 / 1	
Cardiopulmonary failure			
subjects affected / exposed	0 / 517 (0.00%)	1 / 520 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pericardial effusion			
subjects affected / exposed	1 / 517 (0.19%)	3 / 520 (0.58%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pericardial haemorrhage			
subjects affected / exposed	1 / 517 (0.19%)	0 / 520 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericarditis			
subjects affected / exposed	0 / 517 (0.00%)	1 / 520 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericarditis constrictive			
subjects affected / exposed	0 / 517 (0.00%)	1 / 520 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus bradycardia			

subjects affected / exposed	0 / 517 (0.00%)	1 / 520 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Aphasia			
subjects affected / exposed	1 / 517 (0.19%)	1 / 520 (0.19%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Balance disorder			
subjects affected / exposed	0 / 517 (0.00%)	1 / 520 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain compression			
subjects affected / exposed	0 / 517 (0.00%)	1 / 520 (0.19%)	
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	1 / 517 (0.19%)	0 / 520 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain stem infarction			
subjects affected / exposed	0 / 517 (0.00%)	1 / 520 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral ischaemia			
subjects affected / exposed	1 / 517 (0.19%)	0 / 520 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	4 / 517 (0.77%)	3 / 520 (0.58%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 2	0 / 1	
Coma			

subjects affected / exposed	0 / 517 (0.00%)	1 / 520 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Convulsion			
subjects affected / exposed	5 / 517 (0.97%)	1 / 520 (0.19%)	
occurrences causally related to treatment / all	0 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Demyelination			
subjects affected / exposed	1 / 517 (0.19%)	0 / 520 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depressed level of consciousness			
subjects affected / exposed	2 / 517 (0.39%)	0 / 520 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	0 / 517 (0.00%)	2 / 520 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epiduritis			
subjects affected / exposed	0 / 517 (0.00%)	1 / 520 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Headache			
subjects affected / exposed	1 / 517 (0.19%)	0 / 520 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemiparesis			
subjects affected / exposed	1 / 517 (0.19%)	2 / 520 (0.38%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemiplegia			

subjects affected / exposed	1 / 517 (0.19%)	0 / 520 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intracranial pressure increased			
subjects affected / exposed	1 / 517 (0.19%)	1 / 520 (0.19%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	2 / 517 (0.39%)	0 / 520 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorder			
subjects affected / exposed	0 / 517 (0.00%)	1 / 520 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neurological decompensation			
subjects affected / exposed	0 / 517 (0.00%)	1 / 520 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neurological symptom			
subjects affected / exposed	0 / 517 (0.00%)	1 / 520 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Post herpetic neuralgia			
subjects affected / exposed	0 / 517 (0.00%)	1 / 520 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychomotor hyperactivity			
subjects affected / exposed	0 / 517 (0.00%)	1 / 520 (0.19%)	
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 / 517 (0.19%)	0 / 520 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal cord compression			
subjects affected / exposed	0 / 517 (0.00%)	1 / 520 (0.19%)	
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 / 517 (0.19%)	0 / 520 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	0 / 517 (0.00%)	1 / 520 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	7 / 517 (1.35%)	16 / 520 (3.08%)	
occurrences causally related to treatment / all	2 / 7	11 / 16	
deaths causally related to treatment / all	0 / 1	0 / 0	
Febrile bone marrow aplasia			
subjects affected / exposed	0 / 517 (0.00%)	1 / 520 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	2 / 517 (0.39%)	15 / 520 (2.88%)	
occurrences causally related to treatment / all	0 / 2	11 / 15	
deaths causally related to treatment / all	0 / 0	0 / 0	
Idiopathic thrombocytopenic purpura			
subjects affected / exposed	1 / 517 (0.19%)	0 / 520 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukocytosis			

subjects affected / exposed	0 / 517 (0.00%)	1 / 520 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			
subjects affected / exposed	0 / 517 (0.00%)	2 / 520 (0.38%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	1 / 2	
Lymphadenopathy			
subjects affected / exposed	0 / 517 (0.00%)	1 / 520 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	1 / 517 (0.19%)	12 / 520 (2.31%)	
occurrences causally related to treatment / all	0 / 1	12 / 12	
deaths causally related to treatment / all	0 / 0	1 / 1	
Pancytopenia			
subjects affected / exposed	1 / 517 (0.19%)	1 / 520 (0.19%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Thrombocytopenia			
subjects affected / exposed	0 / 517 (0.00%)	3 / 520 (0.58%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 517 (0.19%)	0 / 520 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Diplopia			
subjects affected / exposed	2 / 517 (0.39%)	0 / 520 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			

Abdominal pain			
subjects affected / exposed	1 / 517 (0.19%)	1 / 520 (0.19%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Abdominal pain lower			
subjects affected / exposed	0 / 517 (0.00%)	1 / 520 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	0 / 517 (0.00%)	1 / 520 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colonic obstruction			
subjects affected / exposed	1 / 517 (0.19%)	0 / 520 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	0 / 517 (0.00%)	4 / 520 (0.77%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	7 / 517 (1.35%)	4 / 520 (0.77%)	
occurrences causally related to treatment / all	2 / 7	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal perforation			
subjects affected / exposed	0 / 517 (0.00%)	1 / 520 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer			
subjects affected / exposed	1 / 517 (0.19%)	0 / 520 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			

subjects affected / exposed	2 / 517 (0.39%)	3 / 520 (0.58%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Gastric ulcer			
subjects affected / exposed	1 / 517 (0.19%)	1 / 520 (0.19%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	0 / 517 (0.00%)	1 / 520 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 517 (0.00%)	1 / 520 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	0 / 517 (0.00%)	1 / 520 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Intestinal infarction			
subjects affected / exposed	1 / 517 (0.19%)	0 / 520 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Intestinal obstruction			
subjects affected / exposed	2 / 517 (0.39%)	0 / 520 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine perforation			
subjects affected / exposed	1 / 517 (0.19%)	0 / 520 (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	0 / 517 (0.00%)	1 / 520 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	6 / 517 (1.16%)	1 / 520 (0.19%)	
occurrences causally related to treatment / all	2 / 6	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal disorder			
subjects affected / exposed	1 / 517 (0.19%)	0 / 520 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal stenosis			
subjects affected / exposed	0 / 517 (0.00%)	1 / 520 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophagitis			
subjects affected / exposed	1 / 517 (0.19%)	1 / 520 (0.19%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pancreatitis			
subjects affected / exposed	1 / 517 (0.19%)	0 / 520 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	1 / 517 (0.19%)	0 / 520 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Periodontal disease			
subjects affected / exposed	0 / 517 (0.00%)	1 / 520 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			

subjects affected / exposed	0 / 517 (0.00%)	1 / 520 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subileus			
subjects affected / exposed	0 / 517 (0.00%)	1 / 520 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Vomiting			
subjects affected / exposed	5 / 517 (0.97%)	1 / 520 (0.19%)	
occurrences causally related to treatment / all	3 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Bile duct obstruction			
subjects affected / exposed	1 / 517 (0.19%)	0 / 520 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	1 / 517 (0.19%)	0 / 520 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			
subjects affected / exposed	0 / 517 (0.00%)	1 / 520 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic failure			
subjects affected / exposed	1 / 517 (0.19%)	1 / 520 (0.19%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hepatic function abnormal			
subjects affected / exposed	1 / 517 (0.19%)	0 / 520 (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	0 / 517 (0.00%)	1 / 520 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaundice			
subjects affected / exposed	1 / 517 (0.19%)	0 / 520 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaundice cholestatic			
subjects affected / exposed	1 / 517 (0.19%)	1 / 520 (0.19%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Skin and subcutaneous tissue disorders			
Nail toxicity			
subjects affected / exposed	0 / 517 (0.00%)	1 / 520 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash			
subjects affected / exposed	2 / 517 (0.39%)	1 / 520 (0.19%)	
occurrences causally related to treatment / all	1 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subcutaneous nodule			
subjects affected / exposed	0 / 517 (0.00%)	1 / 520 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute prerenal failure			
subjects affected / exposed	0 / 517 (0.00%)	1 / 520 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	1 / 517 (0.19%)	0 / 520 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oliguria			

subjects affected / exposed	1 / 517 (0.19%)	0 / 520 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	2 / 517 (0.39%)	3 / 520 (0.58%)	
occurrences causally related to treatment / all	1 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 517 (0.19%)	0 / 520 (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	3 / 517 (0.58%)	5 / 520 (0.96%)	
occurrences causally related to treatment / all	0 / 3	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 1	
Bone pain			
subjects affected / exposed	2 / 517 (0.39%)	1 / 520 (0.19%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal chest pain			
subjects affected / exposed	0 / 517 (0.00%)	1 / 520 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal pain			
subjects affected / exposed	3 / 517 (0.58%)	2 / 520 (0.38%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neck pain			
subjects affected / exposed	1 / 517 (0.19%)	0 / 520 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteolysis			

subjects affected / exposed	0 / 517 (0.00%)	1 / 520 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteonecrosis			
subjects affected / exposed	1 / 517 (0.19%)	0 / 520 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	1 / 517 (0.19%)	1 / 520 (0.19%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pathological fracture			
subjects affected / exposed	0 / 517 (0.00%)	2 / 520 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bacteraemia			
subjects affected / exposed	1 / 517 (0.19%)	0 / 520 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial infection			
subjects affected / exposed	1 / 517 (0.19%)	0 / 520 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	5 / 517 (0.97%)	1 / 520 (0.19%)	
occurrences causally related to treatment / all	0 / 5	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Bronchopneumonia			
subjects affected / exposed	2 / 517 (0.39%)	3 / 520 (0.58%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 2	0 / 1	
Cystitis			

subjects affected / exposed	1 / 517 (0.19%)	0 / 520 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	0 / 517 (0.00%)	1 / 520 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Empyema			
subjects affected / exposed	1 / 517 (0.19%)	0 / 520 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Escherichia infection			
subjects affected / exposed	0 / 517 (0.00%)	1 / 520 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Genital infection			
subjects affected / exposed	1 / 517 (0.19%)	0 / 520 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes virus infection			
subjects affected / exposed	1 / 517 (0.19%)	0 / 520 (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 / 517 (0.19%)	0 / 520 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	1 / 517 (0.19%)	0 / 520 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			

subjects affected / exposed	4 / 517 (0.77%)	1 / 520 (0.19%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Perirectal abscess			
subjects affected / exposed	1 / 517 (0.19%)	1 / 520 (0.19%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	13 / 517 (2.51%)	22 / 520 (4.23%)	
occurrences causally related to treatment / all	1 / 13	2 / 22	
deaths causally related to treatment / all	1 / 3	1 / 3	
Pyelonephritis acute			
subjects affected / exposed	0 / 517 (0.00%)	1 / 520 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyothorax			
subjects affected / exposed	0 / 517 (0.00%)	1 / 520 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	3 / 517 (0.58%)	0 / 520 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	2 / 517 (0.39%)	6 / 520 (1.15%)	
occurrences causally related to treatment / all	1 / 2	1 / 6	
deaths causally related to treatment / all	0 / 0	0 / 4	
Septic shock			
subjects affected / exposed	1 / 517 (0.19%)	1 / 520 (0.19%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Skin infection			

subjects affected / exposed	0 / 517 (0.00%)	1 / 520 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	0 / 517 (0.00%)	1 / 520 (0.19%)	
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	3 / 517 (0.58%)	0 / 520 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			
subjects affected / exposed	1 / 517 (0.19%)	0 / 520 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	7 / 517 (1.35%)	2 / 520 (0.38%)	
occurrences causally related to treatment / all	2 / 7	1 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Dehydration			
subjects affected / exposed	4 / 517 (0.77%)	5 / 520 (0.96%)	
occurrences causally related to treatment / all	1 / 4	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Failure to thrive			
subjects affected / exposed	0 / 517 (0.00%)	1 / 520 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hypercalcaemia			
subjects affected / exposed	0 / 517 (0.00%)	1 / 520 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			

subjects affected / exposed	0 / 517 (0.00%)	1 / 520 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	0 / 517 (0.00%)	2 / 520 (0.38%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Erlotinib plus placebo	Erlotinib plus tivantinib	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	496 / 517 (95.94%)	505 / 520 (97.12%)	
Investigations			
Weight decreased			
subjects affected / exposed	59 / 517 (11.41%)	59 / 520 (11.35%)	
occurrences (all)	59	59	
Nervous system disorders			
Headache			
subjects affected / exposed	29 / 517 (5.61%)	43 / 520 (8.27%)	
occurrences (all)	29	43	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	113 / 517 (21.86%)	139 / 520 (26.73%)	
occurrences (all)	113	139	
Asthenia			
subjects affected / exposed	91 / 517 (17.60%)	101 / 520 (19.42%)	
occurrences (all)	91	101	
Pyrexia			
subjects affected / exposed	41 / 517 (7.93%)	62 / 520 (11.92%)	
occurrences (all)	41	62	
Oedema peripheral			
subjects affected / exposed	30 / 517 (5.80%)	40 / 520 (7.69%)	
occurrences (all)	30	40	
Non-cardiac chest pain			

subjects affected / exposed occurrences (all)	23 / 517 (4.45%) 23	35 / 520 (6.73%) 35	
Mucosal inflammation subjects affected / exposed occurrences (all)	24 / 517 (4.64%) 24	29 / 520 (5.58%) 29	
Blood and lymphatic system disorders			
Anaemia subjects affected / exposed occurrences (all)	48 / 517 (9.28%) 48	78 / 520 (15.00%) 78	
Neutropenia subjects affected / exposed occurrences (all)	11 / 517 (2.13%) 11	57 / 520 (10.96%) 57	
Gastrointestinal disorders			
Diarrhoea subjects affected / exposed occurrences (all)	215 / 517 (41.59%) 215	181 / 520 (34.81%) 181	
Nausea subjects affected / exposed occurrences (all)	123 / 517 (23.79%) 123	123 / 520 (23.65%) 123	
Vomiting subjects affected / exposed occurrences (all)	81 / 517 (15.67%) 81	77 / 520 (14.81%) 77	
Constipation subjects affected / exposed occurrences (all)	54 / 517 (10.44%) 54	58 / 520 (11.15%) 58	
Abdominal pain subjects affected / exposed occurrences (all)	26 / 517 (5.03%) 26	35 / 520 (6.73%) 35	
Dyspepsia subjects affected / exposed occurrences (all)	24 / 517 (4.64%) 24	31 / 520 (5.96%) 31	
Abdominal pain upper subjects affected / exposed occurrences (all)	19 / 517 (3.68%) 19	33 / 520 (6.35%) 33	
Respiratory, thoracic and mediastinal disorders			

Dyspnoea subjects affected / exposed occurrences (all)	102 / 517 (19.73%) 102	128 / 520 (24.62%) 128	
Cough subjects affected / exposed occurrences (all)	95 / 517 (18.38%) 95	115 / 520 (22.12%) 115	
Haemoptysis subjects affected / exposed occurrences (all)	15 / 517 (2.90%) 15	30 / 520 (5.77%) 30	
Skin and subcutaneous tissue disorders			
Rash subjects affected / exposed occurrences (all)	193 / 517 (37.33%) 193	173 / 520 (33.27%) 173	
Dermatitis acneiform subjects affected / exposed occurrences (all)	98 / 517 (18.96%) 98	91 / 520 (17.50%) 91	
Dry skin subjects affected / exposed occurrences (all)	57 / 517 (11.03%) 57	42 / 520 (8.08%) 42	
Pruritus subjects affected / exposed occurrences (all)	45 / 517 (8.70%) 45	32 / 520 (6.15%) 32	
Alopecia subjects affected / exposed occurrences (all)	14 / 517 (2.71%) 14	27 / 520 (5.19%) 27	
Psychiatric disorders			
Insomnia subjects affected / exposed occurrences (all)	29 / 517 (5.61%) 29	34 / 520 (6.54%) 34	
Musculoskeletal and connective tissue disorders			
Back pain subjects affected / exposed occurrences (all)	47 / 517 (9.09%) 47	55 / 520 (10.58%) 55	
Pain in extremity subjects affected / exposed occurrences (all)	19 / 517 (3.68%) 19	31 / 520 (5.96%) 31	

Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	149 / 517 (28.82%)	152 / 520 (29.23%)	
occurrences (all)	149	152	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 October 2010	- Revised to require prior platinum-doublet therapy, and clarify eligibility requirements for subjects with prior adjuvant or maintenance therapy - Specified that subjects who experienced $\geq$ Grade 3 neutropenia were to be monitored closely throughout study and offered hematopoietic growth factor therapy as per ASCO guidelines. Also, increased frequency of ANC monitoring for Cycles 3+ from every 4 weeks to every 2 weeks for all subjects, not only those receiving CYP 2C19 or CYP 3A4 inhibitors. - Added precaution for potential of concomitant medications altering gastric pH to affect erlotinib absorption - Added fluconazole, ticlopidine, rabeprazole, and fluoxetine to list of example CYP 2C19 inhibitors to be used with caution concomitantly - Clarified that AEs recorded at Screening visit were to include only those AEs occurring after consent was signed - Removed qualification "if not restricted by local regulation" to require collection of pharmacogenomic data at all sites - Modified language to specify that hematology testing would be performed for all subjects every 2 weeks rather than every 4 weeks in Cycle 3 and beyond - Removed limit of precaution to only "strong" CYP 2C19 inhibitors, but clarified limit to precaution for only strong inhibitors of CYP 3A4 - Specified requirement for biomarker testing for tumor MET, EGFR, and KRAS for all subjects, as well as testing for pre- and posttreatment circulating HGF - Added language specifying data sets and analyses for pharmacogenomic data and PK-pharmacodynamic analyses
01 June 2011	- Added exception for enrollment of subjects with $\leq$ Grade 2 neuropathy - Reduced window for prior surgical procedure, prior systemic anti-tumor therapy, and prior radiotherapy from 4 weeks to 3 weeks - Clarified description of exploratory objectives, endpoints, and analyses with regard to MET status as determined by IHC and FISH. Specifically, the exploratory analysis for evaluating OS and PFS by MET/MET was to be performed using both IHC and FISH analytical methods instead of FISH method only. - Clarified that either archival or fresh tissue biopsy samples would qualify for study eligibility; documented EGFR and KRAS status must have been from an accredited lab; specified that tissue must be provided to central laboratories for MET analysis even if EGFR, KRAS results were obtained locally - Noted that EGFR status was required for study eligibility; in the absence of confirmation of a subject's KRAS status, the subject was to be categorized as "indeterminate" for KRAS - Added exception to the prohibition of highdose corticosteroids for short-term treatment of COPD or other inflammation exacerbation

28 November 2012	- Revised text to indicate that only subjects with EGFR-mutant disease would be included in survival followup evaluations - Revised text to indicate that study closure was to be defined as the final subject visit/contact rather than when the pre-specified 735 deaths have occurred The interim results for this study met the protocol-defined stopping boundary for futility based on overall survival (OS). After reviewing the interim analysis, the data management committee (DMC) concluded that the study would not meet its primary endpoint of improved OS in the intent to treat (ITT) population, and therefore recommended that the study be stopped early. However, the DMC noted that there was no unexpected safety concern requiring immediate treatment discontinuation, and there was a trend toward improvement in progression free survival (PFS) in the ITT population at the interim analysis. Based upon this result, the data were cut on 15 Dec 2012 for the main study analyses included in the original CSR. Patients receiving clinical benefit were allowed to continue. At the time of the data-cut for the main study analyses, the results for EGFR mutant subgroup, which responds well to erlotinib therapy, were not mature. The clinical trial protocol was amended to allow these subjects to continue with follow-up assessments in order to provide mature results for this subgroup. The results posted herein incorporate the tables, figures, and listings for the pre-specified data-cut (Nov 2014) for the EGFR mutant subgroup. This clinical study has now been completed and the full database is locked. This record also includes the isolated EGFR mutant data that were collected during the study.
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Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported