Clinical trial results:
Phase IIb/III randomized, double-blind trial of BIBW 2992 plus best supportive care (BSC) versus placebo plus BSC in non-small cell lung cancer patients failing erlotinib or gefitinib

Summary

EudraCT number	2007-005983-28
Trial protocol	ES GB BE NL DE FR IT
Global end of trial date	04 October 2013

Results information

Result version number	v1 (current)
This version publication date	20 June 2016
First version publication date	16 July 2015

Trial information

Trial identification

Sponsor protocol code	1200.23

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00656136
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 Pharma GmbH & Co. KG, 001 800 243 0127, clintriage.rdg@boehringer-ingelheim.com
Scientific contact	QRPE Processes and Systems Coordination Clinical Trial Information Disclosure, Boehringer Ingelheim Pharma GmbH & Co. KG, 001 800 243 0127, 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	04 October 2013
Is this the analysis of the primary completion data?	Yes
Primary completion date	04 October 2013
Global end of trial reached?	Yes
Global end of trial date	04 October 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To investigate the efficacy and safety of BIBW 2992 plus BSC versus placebo plus BSC in a double-blind randomized trial in non-small cell lung cancer patients with progressive disease after at least one but not more than two lines of chemotherapy and at least 12 weeks of treatment with erlotinib or gefitinib

Protection of trial subjects:

Only subjects who were considered eligible by investigators based on the protocol-specific inclusion and exclusion criteria were to be entered in the study. All subjects were free to withdraw from the clinical trial at any time for any reason given.Close monitoring of all subjects was adhered to throughout the trial conduct.
Symptomatic treatment of tumour associated symptoms were allowed throughout. Dose reduction was allowed in cases of pre-specified, protocol defined adverse events. For patients who experienced CTCAE (version 3.0) grade ≥3 drug-related adverse events (AEs) despite appropriate supportive care, or grade ≥2 AEs, a dose reduction scheme was followed after a treatment pause to allow the AE to decrease to CTCAE grade ≤1 or baseline (within a maximum of 14 days). Further instructions on managing diarrhoea, nausea and vomiting, and rash, respectively were provided in the protocol.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	19 May 2008
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 15
Country: Number of subjects enrolled	Spain: 19
Country: Number of subjects enrolled	United Kingdom: 20
Country: Number of subjects enrolled	Belgium: 18
Country: Number of subjects enrolled	France: 35
Country: Number of subjects enrolled	Germany: 31
Country: Number of subjects enrolled	Italy: 36
Country: Number of subjects enrolled	Hong Kong: 6
Country: Number of subjects enrolled	China: 124
Country: Number of subjects enrolled	Taiwan: 156
Country: Number of subjects enrolled	Korea, Republic of: 106
Country: Number of subjects enrolled	Singapore: 15
Country: Number of subjects enrolled	Canada: 56
Country: Number of subjects enrolled	Thailand: 26

Country: Number of subjects enrolled	United States: 35
Worldwide total number of subjects	698
EEA total number of subjects	174

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)	462
From 65 to 84 years	234
85 years and over	2

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

All enrolled subjects were screened for eligibility to participate in the trial. Subjects attended specialist sites which would then ensure that they (the subjects) met all inclusion/exclusion criteria. Subjects were not to be randomised to trial treatment if any one of the specific entry criteria were violated.

Period 1

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

Blinding implementation details:

Patients were randomised to receive afatinib plus BSC or matching placebo plus BSC in a double-blind fashion. Patients, investigators and the sponsor's trial team involved in site monitoring, data management and analysing the results of the study remained blinded to the randomised treatment assignments up to the static snapshot created for primary analysis of overall survival in July 2010.. Additionally, readers for the independent central imaging unit were blinded to treatment assignments.

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Patients received matching placebo for 50 mg, 40 mg or 30 mg afatinib tablets starting with 50 mg/day. Dose reductions were managed in the same way as for the afatinib arm.

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

Dosage and administration details:

Patients received matching placebo for 50 mg, 40 mg or 30 mg afatinib tablets starting with 50 mg/day. Dose reductions were managed in the same way as for the afatinib arm.

Arm title	Afatinib 50 mg/Day

Arm description:

Patients started with a 50 mg/day dose. Dose reductions were permitted by the protocol to 40 mg/day plus Best Supportive Care (BSC) or 30 mg /day plus BSC based upon prespecified Adverse Events and Common Terminology Criteria for Adverse Events (CTCAE) grade (Version 3.0).

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

Dosage and administration details:

Patients started with a 50 mg/day dose. Dose reductions were permitted by the protocol to 40 mg/day plus Best Supportive Care (BSC) or 30 mg /day plus BSC based upon prespecified Adverse Events and Common Terminology Criteria for Adverse Events (CTCAE) grade (Version 3.0).

Number of subjects in period 1[1]	Placebo	Afatinib 50 mg/Day
Started	195	390
Completed	0	0
Not completed	195	390
Adverse event, serious fatal	3	22
Other reason not defined above	4	4
Patient refused to continue study medication	7	10
Adverse event, non-fatal	2	29
Progressive disease	177	322
Protocol deviation	2	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 and received at least one of the trial medication.

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Patients received matching placebo for 50 mg, 40 mg or 30 mg afatinib tablets starting with 50 mg/day. Dose reductions were managed in the same way as for the afatinib arm.	
Reporting group title	Afatinib 50 mg/Day
Reporting group description:	
Patients started with a 50 mg/day dose. Dose reductions were permitted by the protocol to 40 mg/day plus Best Supportive Care (BSC) or 30 mg /day plus BSC based upon prespecified Adverse Events and Common Terminology Criteria for Adverse Events (CTCAE) grade (Version 3.0).	

Reporting group values	Placebo	Afatinib 50 mg/Day	Total
Number of subjects	195	390	585
Age categorical			
Units: Subjects			
Adults (18-64 years)	127	275	402
From 65-84 years	68	114	182
85 years and over	0	1	1
Age continuous			
Units: years			
arithmetic mean	59	58	
standard deviation	± 10.4	± 10.8	-
Gender categorical			
Units: Subjects			
Female	117	231	348
Male	78	159	237
Race/Ethnicity			
Units: Subjects			
Caucasian	72	121	193
Eastern Asian	110	227	337
Other Asian	12	38	50
Other	1	4	5
Baselinne Eastern Cooperative Oncology Group (ECOG) Performance Score			
ECOG performance score was measured on a 6 point scale where 0="Fully active", 1="Restricted in physically strenuous activity", 2="Ambulatory and capable of all self care but unable to carry out any work activities', 3="Capable of only limited self care, confined to bed or chair 50% or more of waking hours", 4="bedbound", and 5="Death'.			
Units: Subjects			
ECOG score=0	53	92	145
ECOG score=1	127	268	395
ECOG score=2	15	30	45

End points

End points reporting groups

Reporting group title	Placebo

Reporting group description:

Patients received matching placebo for 50 mg, 40 mg or 30 mg afatinib tablets starting with 50 mg/day. Dose reductions were managed in the same way as for the afatinib arm.

Reporting group title	Afatinib 50 mg/Day

Reporting group description:

Patients started with a 50 mg/day dose. Dose reductions were permitted by the protocol to 40 mg/day plus Best Supportive Care (BSC) or 30 mg /day plus BSC based upon prespecified Adverse Events and Common Terminology Criteria for Adverse Events (CTCAE) grade (Version 3.0).

Primary: Overall Survival

End point title	Overall Survival

End point description:

Overall survival was the duration from the date of randomization to the date of death. Patients who were alive were censored at the last contact date prior to the database lock. For the primary analysis 11 patients were lost to follow-up and were censored at the last contact date when they were known to be still alive. Primary analysis data cut-off date was 08 July 2010. For the final analysis 13 patients were lost to follow-up and were censored at the last contact date when they were known to be still alive. Final analysis data cut-off date was 01 April 2014.

End point type	Primary

End point timeframe:

From randomization until death or the last patient out date (01 April 2014), an average of 12 months

End point values	Placebo	Afatinib 50 mg/Day		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	195[1]	390[2]		
Units: months				
arithmetic mean (confidence interval 95%)				
Primary analysis (358 deaths)	11.96 (10.15 to 14.26)	10.78 (9.95 to 11.99)		
Final analysis (526 deaths)	11.73 (10.05 to 14.06)	10.87 (9.95 to 12.25)		

Notes:

[1] - Randomized Set (RS) includes all randomized patients that received one dose of study medication

[2] - Randomized Set (RS) includes all randomized patients that received one dose of study medication

Statistical analyses

Statistical analysis title	Primary analysis comparison of overall survival

Statistical analysis description:

Primary analysis was performed after 358 deaths were observed among randomized patients. The data cut-off date for the primary analysis was 08 July 2010. The hazard ratio was calculated as Afatinib versus placebo.

Comparison groups	Afatinib 50 mg/Day v Placebo

Number of subjects included in analysis	585
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.7428 [4]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.077
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.862
upper limit	1.346

Notes:

[3] - P-value is one-sided (afatinib vs placebo) log rank test stratified by gender and baseline ECOG score (0,1 vs 2)
[4] - Model stratified by gender and baseline ECOG score (0,1 vs 2)

Statistical analysis title	Final analysis comparison of overall survival

Statistical analysis description:

Final analysis was performed after 526 deaths were observed among randomized patients. The data cut-off date for the final analysis was
01 April 2014. The hazard ratio was calculated as Afatinib versus placebo.

Comparison groups	Placebo v Afatinib 50 mg/Day
Number of subjects included in analysis	585
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	= 0.3955 [6]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.976
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.814
upper limit	1.17

Notes:

[5] - P-value is one-sided (afatinib vs placebo) log rank test stratified by gender and baseline ECOG score (0,1 vs 2)
[6] - Model stratified by gender and baseline ECOG score (0,1 vs 2)

Secondary: Progression-free Survival (PFS)

End point title	Progression-free Survival (PFS)

End point description:

PFS is defined as time from randomisation to disease progression or death whichever occurs first. Assessed by central independent review according to the Response Evaluation Criteria in Solid Tumours version 1.0 (RECIST 1.0).

End point type	Secondary

End point timeframe:

From randomization to disease progression, death or the data cutoff on 07 July 2010, an average of 3.3 months

End point values	Placebo	Afatinib 50 mg/Day		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	195	390		
Units: months				
median (confidence interval 95%)	1.08 (0.95 to 1.68)	3.29 (2.79 to 4.4)		

Statistical analyses

Statistical analysis title	Cox regression for Progression Free Survival

Statistical analysis description:

Cox proportional hazard model, stratified by baseline ECOG performance score (0,1 vs. 2) and gender (male vs. female), was used to estimate the HR (afatinib vs. placebo)

Comparison groups	Placebo v Afatinib 50 mg/Day
Number of subjects included in analysis	585
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [7]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.381
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.306
upper limit	0.475

Notes:

[7] - P-value is one-sided (afatinib vs placebo) log rank test stratified by gender and baseline ECOG score (0,1 vs 2)

Secondary: Objective Response Rate (OR)

End point title	Objective Response Rate (OR)

End point description:

OR is defined as complete response (CR) and partial response (PR). Assessed by central independent review according to RECIST 1.0.

End point type	Secondary

End point timeframe:

From randomization to disease progression, death or the data cutoff on 07 July 2010, an average of 3.3 months

End point values	Placebo	Afatinib 50 mg/Day		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	195	390		
Units: percentage patients				
number (confidence interval 95%)	0.5 (0 to 2.8)	7.4 (5 to 10.5)		

Statistical analyses

Statistical analysis title	Logistic regression for Objective Response Rate
Statistical analysis description:	
Logistic regression model adjusted for stratification factors, gender and baseline ECOG score (0, 1 vs 2)	
Comparison groups	Placebo v Afatinib 50 mg/Day
Number of subjects included in analysis	585
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0071 [8]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	15.61
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.1
upper limit	115

Notes:

[8] - P-value is derived from logistic regression model adjusted for stratification factors, gender and baseline ECOG score (0, 1 vs 2)

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the date of first drug administration up to 28 days after the last drug administration for on-treatment adverse events or the last patient out dated on 4 October 2013.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups

Reporting group title	Afatinib 50 mg/Day

Reporting group description:

Patients started with a 50 mg/day dose. Dose reductions were permitted by the protocol to 40 mg/day plus BSC or 30 mg /day plus BSC based upon prespecified Adverse Events and Common Terminology Criteria for Adverse Events (CTCAE) grade (Version 3.0).

Reporting group title	Placebo

Reporting group description:

Patients received matching placebo for 50 mg, 40 mg or 30 mg afatinib tablets starting with 50 mg/day. Dose reductions were managed in the same way as for the afatinib arm.

Serious adverse events	Afatinib 50 mg/Day	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	136 / 390 (34.87%)	36 / 195 (18.46%)	
number of deaths (all causes)	49	15	
number of deaths resulting from adverse events	3	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	1 / 390 (0.26%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervix carcinoma			
subjects affected / exposed	1 / 390 (0.26%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon cancer			
subjects affected / exposed	1 / 390 (0.26%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung adenocarcinoma metastatic			

subjects affected / exposed	1 / 390 (0.26%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant ascites			
subjects affected / exposed	1 / 390 (0.26%)	0 / 195 (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 / 390 (4.10%)	7 / 195 (3.59%)	
occurrences causally related to treatment / all	0 / 16	0 / 7	
deaths causally related to treatment / all	0 / 14	0 / 7	
Malignant pleural effusion			
subjects affected / exposed	1 / 390 (0.26%)	1 / 195 (0.51%)	
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	11 / 390 (2.82%)	3 / 195 (1.54%)	
occurrences causally related to treatment / all	0 / 12	0 / 3	
deaths causally related to treatment / all	0 / 2	0 / 2	
Metastases to liver			
subjects affected / exposed	1 / 390 (0.26%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to meninges			
subjects affected / exposed	1 / 390 (0.26%)	0 / 195 (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	1 / 390 (0.26%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-small cell lung cancer			

subjects affected / exposed	0 / 390 (0.00%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	5 / 390 (1.28%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	1 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive crisis			
subjects affected / exposed	1 / 390 (0.26%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	2 / 390 (0.51%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombosis			
subjects affected / exposed	2 / 390 (0.51%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 390 (0.26%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest discomfort			
subjects affected / exposed	1 / 390 (0.26%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	0 / 390 (0.00%)	2 / 195 (1.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	

Condition aggravated			
subjects affected / exposed	1 / 390 (0.26%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	3 / 390 (0.77%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 3	0 / 1	
Extravasation			
subjects affected / exposed	1 / 390 (0.26%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Face oedema			
subjects affected / exposed	1 / 390 (0.26%)	0 / 195 (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	3 / 390 (0.77%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	2 / 390 (0.51%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hernia			
subjects affected / exposed	0 / 390 (0.00%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malaise			
subjects affected / exposed	1 / 390 (0.26%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Medical device complication			

subjects affected / exposed	0 / 390 (0.00%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multi-organ failure			
subjects affected / exposed	1 / 390 (0.26%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Oedema peripheral			
subjects affected / exposed	2 / 390 (0.51%)	0 / 195 (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	2 / 390 (0.51%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	7 / 390 (1.79%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	0 / 7	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden cardiac death			
subjects affected / exposed	1 / 390 (0.26%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Sudden death			
subjects affected / exposed	1 / 390 (0.26%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Reproductive system and breast disorders			
Pelvic pain			
subjects affected / exposed	0 / 390 (0.00%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			

Cough			
subjects affected / exposed	0 / 390 (0.00%)	3 / 195 (1.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	8 / 390 (2.05%)	4 / 195 (2.05%)	
occurrences causally related to treatment / all	1 / 9	0 / 4	
deaths causally related to treatment / all	0 / 1	0 / 1	
Dyspnoea at rest			
subjects affected / exposed	1 / 390 (0.26%)	0 / 195 (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	2 / 390 (0.51%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Haemothorax			
subjects affected / exposed	0 / 390 (0.00%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydropneumothorax			
subjects affected / exposed	1 / 390 (0.26%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	14 / 390 (3.59%)	7 / 195 (3.59%)	
occurrences causally related to treatment / all	0 / 14	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	2 / 390 (0.51%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Pneumothorax			

subjects affected / exposed	2 / 390 (0.51%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	5 / 390 (1.28%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	1 / 5	1 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory failure			
subjects affected / exposed	9 / 390 (2.31%)	2 / 195 (1.03%)	
occurrences causally related to treatment / all	0 / 9	0 / 2	
deaths causally related to treatment / all	0 / 6	0 / 2	
Wheezing			
subjects affected / exposed	1 / 390 (0.26%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Delirium			
subjects affected / exposed	1 / 390 (0.26%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood creatinine increased			
subjects affected / exposed	4 / 390 (1.03%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	4 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood culture positive			
subjects affected / exposed	1 / 390 (0.26%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood potassium increased			
subjects affected / exposed	1 / 390 (0.26%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrocardiogram T wave inversion			

subjects affected / exposed	1 / 390 (0.26%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oxygen saturation decreased			
subjects affected / exposed	1 / 390 (0.26%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostatic specific antigen increased			
subjects affected / exposed	1 / 390 (0.26%)	0 / 195 (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			
Fall			
subjects affected / exposed	1 / 390 (0.26%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Head injury			
subjects affected / exposed	0 / 390 (0.00%)	1 / 195 (0.51%)	
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 / 390 (0.26%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple fractures			
subjects affected / exposed	1 / 390 (0.26%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thoracic vertebral fracture			
subjects affected / exposed	1 / 390 (0.26%)	0 / 195 (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 left ventricular failure			
subjects affected / exposed	2 / 390 (0.51%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Atrial fibrillation			
subjects affected / exposed	1 / 390 (0.26%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	2 / 390 (0.51%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Cardiac tamponade			
subjects affected / exposed	1 / 390 (0.26%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardio-respiratory arrest			
subjects affected / exposed	1 / 390 (0.26%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Myocardial infarction			
subjects affected / exposed	1 / 390 (0.26%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial effusion			
subjects affected / exposed	2 / 390 (0.51%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Sick sinus syndrome			
subjects affected / exposed	1 / 390 (0.26%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Supraventricular tachycardia			

subjects affected / exposed	1 / 390 (0.26%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia			
subjects affected / exposed	1 / 390 (0.26%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Altered state of consciousness			
subjects affected / exposed	1 / 390 (0.26%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain mass			
subjects affected / exposed	1 / 390 (0.26%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain oedema			
subjects affected / exposed	2 / 390 (0.51%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haemorrhage			
subjects affected / exposed	0 / 390 (0.00%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral infarction			
subjects affected / exposed	0 / 390 (0.00%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	2 / 390 (0.51%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Convulsion			

subjects affected / exposed	1 / 390 (0.26%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	3 / 390 (0.77%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysarthria			
subjects affected / exposed	0 / 390 (0.00%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolic cerebral infarction			
subjects affected / exposed	1 / 390 (0.26%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	1 / 390 (0.26%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemiparesis			
subjects affected / exposed	1 / 390 (0.26%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydrocephalus			
subjects affected / exposed	1 / 390 (0.26%)	0 / 195 (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	2 / 390 (0.51%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			

subjects affected / exposed	1 / 390 (0.26%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraesthesia			
subjects affected / exposed	1 / 390 (0.26%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraplegia			
subjects affected / exposed	1 / 390 (0.26%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Partial seizures			
subjects affected / exposed	1 / 390 (0.26%)	0 / 195 (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	2 / 390 (0.51%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tremor			
subjects affected / exposed	0 / 390 (0.00%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
VIIth nerve paralysis			
subjects affected / exposed	1 / 390 (0.26%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Disseminated intravascular coagulation			
subjects affected / exposed	1 / 390 (0.26%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			

subjects affected / exposed	2 / 390 (0.51%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphadenopathy			
subjects affected / exposed	1 / 390 (0.26%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	0 / 390 (0.00%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Blindness			
subjects affected / exposed	1 / 390 (0.26%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diplopia			
subjects affected / exposed	1 / 390 (0.26%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye movement disorder			
subjects affected / exposed	0 / 390 (0.00%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vision blurred			
subjects affected / exposed	1 / 390 (0.26%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	1 / 390 (0.26%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			

subjects affected / exposed	2 / 390 (0.51%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	1 / 390 (0.26%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	1 / 390 (0.26%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	18 / 390 (4.62%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	18 / 21	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	0 / 390 (0.00%)	3 / 195 (1.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematemesis			
subjects affected / exposed	1 / 390 (0.26%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	1 / 390 (0.26%)	0 / 195 (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	2 / 390 (0.51%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			

subjects affected / exposed	4 / 390 (1.03%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	2 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	1 / 390 (0.26%)	0 / 195 (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	4 / 390 (1.03%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	2 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Proctalgia			
subjects affected / exposed	1 / 390 (0.26%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			
subjects affected / exposed	2 / 390 (0.51%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			
subjects affected / exposed	3 / 390 (0.77%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	5 / 390 (1.28%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	3 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Acute hepatic failure			
subjects affected / exposed	1 / 390 (0.26%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Hepatitis acute			

subjects affected / exposed	1 / 390 (0.26%)	0 / 195 (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			
Dermatitis allergic			
subjects affected / exposed	1 / 390 (0.26%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash			
subjects affected / exposed	2 / 390 (0.51%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stevens-Johnson syndrome			
subjects affected / exposed	1 / 390 (0.26%)	0 / 195 (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			
Acute prerenal failure			
subjects affected / exposed	1 / 390 (0.26%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oliguria			
subjects affected / exposed	1 / 390 (0.26%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal colic			
subjects affected / exposed	1 / 390 (0.26%)	0 / 195 (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	1 / 390 (0.26%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure acute			

subjects affected / exposed	7 / 390 (1.79%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	3 / 7	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Renal impairment			
subjects affected / exposed	1 / 390 (0.26%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 390 (0.26%)	2 / 195 (1.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone pain			
subjects affected / exposed	2 / 390 (0.51%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Flank pain			
subjects affected / exposed	1 / 390 (0.26%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular weakness			
subjects affected / exposed	3 / 390 (0.77%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal chest pain			
subjects affected / exposed	1 / 390 (0.26%)	0 / 195 (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 / 390 (0.26%)	1 / 195 (0.51%)	
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	2 / 390 (0.51%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Atypical pneumonia			
subjects affected / exposed	1 / 390 (0.26%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			
subjects affected / exposed	1 / 390 (0.26%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Candida infection			
subjects affected / exposed	1 / 390 (0.26%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	1 / 390 (0.26%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 390 (0.26%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	1 / 390 (0.26%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis viral			
subjects affected / exposed	1 / 390 (0.26%)	0 / 195 (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 fungal			

subjects affected / exposed	1 / 390 (0.26%)	0 / 195 (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 / 390 (1.03%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Paronychia			
subjects affected / exposed	1 / 390 (0.26%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis bacterial			
subjects affected / exposed	1 / 390 (0.26%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	10 / 390 (2.56%)	4 / 195 (2.05%)	
occurrences causally related to treatment / all	1 / 10	0 / 4	
deaths causally related to treatment / all	0 / 2	0 / 0	
Sepsis			
subjects affected / exposed	1 / 390 (0.26%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	5 / 390 (1.28%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	0 / 6	0 / 0	
deaths causally related to treatment / all	0 / 3	0 / 0	
Soft tissue infection			
subjects affected / exposed	1 / 390 (0.26%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			

subjects affected / exposed	1 / 390 (0.26%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			
subjects affected / exposed	1 / 390 (0.26%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	3 / 390 (0.77%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	8 / 390 (2.05%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	5 / 9	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypocalcaemia			
subjects affected / exposed	2 / 390 (0.51%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	5 / 390 (1.28%)	0 / 195 (0.00%)	
occurrences causally related to treatment / all	5 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	0 / 390 (0.00%)	1 / 195 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Afatinib 50 mg/Day	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	383 / 390 (98.21%)	167 / 195 (85.64%)	
Investigations			
Weight decreased			
subjects affected / exposed	37 / 390 (9.49%)	2 / 195 (1.03%)	
occurrences (all)	41	3	
Nervous system disorders			
Dizziness			
subjects affected / exposed	20 / 390 (5.13%)	6 / 195 (3.08%)	
occurrences (all)	23	8	
Headache			
subjects affected / exposed	21 / 390 (5.38%)	9 / 195 (4.62%)	
occurrences (all)	23	12	
Dysgeusia			
subjects affected / exposed	22 / 390 (5.64%)	1 / 195 (0.51%)	
occurrences (all)	22	1	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	23 / 390 (5.90%)	3 / 195 (1.54%)	
occurrences (all)	29	4	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	36 / 390 (9.23%)	16 / 195 (8.21%)	
occurrences (all)	41	17	
Chest pain			
subjects affected / exposed	27 / 390 (6.92%)	11 / 195 (5.64%)	
occurrences (all)	30	12	
Fatigue			
subjects affected / exposed	72 / 390 (18.46%)	23 / 195 (11.79%)	
occurrences (all)	82	23	
Mucosal inflammation			
subjects affected / exposed	95 / 390 (24.36%)	2 / 195 (1.03%)	
occurrences (all)	118	3	
Pyrexia			
subjects affected / exposed	36 / 390 (9.23%)	7 / 195 (3.59%)	
occurrences (all)	48	9	

Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	25 / 390 (6.41%)	8 / 195 (4.10%)	
occurrences (all)	28	8	
Constipation			
subjects affected / exposed	43 / 390 (11.03%)	24 / 195 (12.31%)	
occurrences (all)	48	26	
Diarrhoea			
subjects affected / exposed	334 / 390 (85.64%)	18 / 195 (9.23%)	
occurrences (all)	552	22	
Mouth ulceration			
subjects affected / exposed	51 / 390 (13.08%)	0 / 195 (0.00%)	
occurrences (all)	67	0	
Nausea			
subjects affected / exposed	90 / 390 (23.08%)	39 / 195 (20.00%)	
occurrences (all)	105	43	
Stomatitis			
subjects affected / exposed	82 / 390 (21.03%)	2 / 195 (1.03%)	
occurrences (all)	98	2	
Vomiting			
subjects affected / exposed	75 / 390 (19.23%)	25 / 195 (12.82%)	
occurrences (all)	103	35	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	54 / 390 (13.85%)	36 / 195 (18.46%)	
occurrences (all)	65	38	
Dyspnoea			
subjects affected / exposed	54 / 390 (13.85%)	22 / 195 (11.28%)	
occurrences (all)	58	24	
Epistaxis			
subjects affected / exposed	73 / 390 (18.72%)	1 / 195 (0.51%)	
occurrences (all)	93	1	
Productive cough			
subjects affected / exposed	9 / 390 (2.31%)	13 / 195 (6.67%)	
occurrences (all)	9	14	
Rhinorrhoea			

subjects affected / exposed	42 / 390 (10.77%)	2 / 195 (1.03%)	
occurrences (all)	45	2	
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	27 / 390 (6.92%)	0 / 195 (0.00%)	
occurrences (all)	34	0	
Dermatitis acneiform			
subjects affected / exposed	28 / 390 (7.18%)	1 / 195 (0.51%)	
occurrences (all)	36	1	
Dry skin			
subjects affected / exposed	62 / 390 (15.90%)	14 / 195 (7.18%)	
occurrences (all)	64	14	
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	30 / 390 (7.69%)	0 / 195 (0.00%)	
occurrences (all)	31	0	
Pruritus			
subjects affected / exposed	73 / 390 (18.72%)	11 / 195 (5.64%)	
occurrences (all)	90	12	
Rash			
subjects affected / exposed	248 / 390 (63.59%)	23 / 195 (11.79%)	
occurrences (all)	344	25	
Skin fissures			
subjects affected / exposed	32 / 390 (8.21%)	0 / 195 (0.00%)	
occurrences (all)	34	0	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	17 / 390 (4.36%)	10 / 195 (5.13%)	
occurrences (all)	18	10	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	29 / 390 (7.44%)	22 / 195 (11.28%)	
occurrences (all)	33	23	
Pain in extremity			
subjects affected / exposed	27 / 390 (6.92%)	4 / 195 (2.05%)	
occurrences (all)	30	4	
Muscle spasms			

subjects affected / exposed	20 / 390 (5.13%)	3 / 195 (1.54%)	
occurrences (all)	24	3	
Infections and infestations			
Folliculitis			
subjects affected / exposed	25 / 390 (6.41%)	0 / 195 (0.00%)	
occurrences (all)	27	0	
Paronychia			
subjects affected / exposed	131 / 390 (33.59%)	1 / 195 (0.51%)	
occurrences (all)	145	1	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	118 / 390 (30.26%)	22 / 195 (11.28%)	
occurrences (all)	130	23	
Hypokalaemia			
subjects affected / exposed	29 / 390 (7.44%)	4 / 195 (2.05%)	
occurrences (all)	34	4	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 April 2009	• An increase in sample size. Recruitment rate for the study after initiation was higher than initially projected, but the death rate appeared lower than expected. In order to increase expected power for the trial to 90% (initially 85%) Amendment 1 to the CTP increased the randomisation from 400 to 560 patients. The increase in number of deaths to 359 (initially 309) required for analysis provided 90% power. • A pharmacogenetic analysis substudy was added to the protocol; however, this substudy was not conducted. Patient enrolment accrued more quickly than expected; patients were accrued before having the logistics of the amendment implemented entirely. • An additional exclusion criterion. Patients with known interstitial lung disease were to be excluded from the trial. • Clarification of safety monitoring and reporting. A flow chart was added to the CTP which outlined the process for reporting AEs occurring in patients discontinued from the trial. • Removal of the pelvic scan requirement as this scan was not clinically indicated or standard of care for the NSCLC patient population targeted for the trial.
26 July 2010	The key change to the CTP provided by Global Amendment 2, dated 26 July 2010 was the restricted use of potent P-gp inhibitors and inducers concomitantly with study medication during the trial. The results of a Phase I trial indicated increased exposure to afatinib when taken in combination with ritonavir. The amendment provided guidance regarding the exclusion of P-gp inhibitors and inducers as well as management of patients who were already receiving P-gp inhibitors and inducers.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Age of two subjects is missing, as the platform does not provide the option of "missing" category, the two subjects were included to age range Adults (18-64 years): N=460 + N=2 (missing age)

Notes: