Clinical trial results:
LUX-Lung 3; A randomised, open-label, phase III study of BIBW 2992 versus chemotherapy as first-line treatment for patients with stage IIIB or IV adenocarcinoma of the lung harbouring an EGFR-activating mutation

Summary

EudraCT number	2008-005615-18
Trial protocol	IE FR GB BE AT DE HU IT
Global end of trial date	17 March 2017

Results information

Result version number	v2 (current)
This version publication date	14 November 2021
First version publication date	24 March 2018
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	1200.32

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00949650
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, +1 8002430127, clintriage.rdg@boehringer-ingelheim.com
Scientific contact	QRPE Processes and Systems Coordination, Clinical Trial Information Disclosure, Boehringer Ingelheim, +1 8002430127, clintriage.rdg@boehringer-ingelheim.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	07 April 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	09 February 2012
Global end of trial reached?	Yes
Global end of trial date	17 March 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the efficacy and safety of Afatinib monotherapy with Pemetrexed/Cisplatin chemotherapy as first-line treatment in Epidermal Growth Factor Receptor (EGFR) Tyrosine Kinase Inhibitor (TKI)-naïve patients with stage IIIB (with cytologically proven pleural effusion or pericardial effusion) or IV adenocarcinoma of the lung harbouring an EGFR mutation.

Protection of trial subjects:

Only subjects that met all the study inclusion and none of the 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. If a subject continued to take trial medication, close monitoring was adhered to and all adverse events recorded. Rules were implemented in all trials whereby doses would be reduced if required. Thereafter, if further events were reported, the subject would be withdrawn from the trial. Symptomatic treatment of tumour associated symptoms were allowed throughout.

Background therapy: -

Evidence for comparator:

The comparator treatment was Pemetrexed/Cisplatin Chemotherapy.

Actual start date of recruitment	17 August 2009
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy
Long term follow-up duration	86 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Austria: 19
Country: Number of subjects enrolled	Belgium: 45
Country: Number of subjects enrolled	France: 58
Country: Number of subjects enrolled	Germany: 71
Country: Number of subjects enrolled	Hungary: 11
Country: Number of subjects enrolled	Ireland: 32
Country: Number of subjects enrolled	Italy: 9
Country: Number of subjects enrolled	Romania: 16
Country: Number of subjects enrolled	Russian Federation: 78
Country: Number of subjects enrolled	Ukraine: 30
Country: Number of subjects enrolled	United Kingdom: 32
Country: Number of subjects enrolled	Canada: 40
Country: Number of subjects enrolled	United States: 39
Country: Number of subjects enrolled	Hong Kong: 11

Country: Number of subjects enrolled	Japan: 185
Country: Number of subjects enrolled	Korea, Democratic People's Republic of: 57
Country: Number of subjects enrolled	Malaysia: 55
Country: Number of subjects enrolled	Philippines: 40
Country: Number of subjects enrolled	Taiwan: 129
Country: Number of subjects enrolled	Thailand: 147
Country: Number of subjects enrolled	Argentina: 28
Country: Number of subjects enrolled	Australia: 64
Country: Number of subjects enrolled	Brazil: 26
Country: Number of subjects enrolled	Chile: 21
Country: Number of subjects enrolled	Peru: 26
Worldwide total number of subjects	1269
EEA total number of subjects	261

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)	779
From 65 to 84 years	485
85 years and over	5

Subject disposition

Recruitment

Recruitment details:

Two-arm, randomised (2:1 ratio), open-label, active-controlled, parallel-group comparison. 345 patients were randomised, 5 patients were not treated: 4 patients were not eligible for treatment and 1 patient in the chemotherapy arm refused to take study medication.

Pre-assignment

Screening details:

All subjects were screened for eligibility to participate in the trial. Subjects attended specialist sites which would then ensure that they (the subjects) met all strictly implemented 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	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Afatinib 40 mg

Arm description:

Patients received Afatinib monotherapy 40 mg film-coated tablets orally once daily.

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

Dosage and administration details:

Patients received Afatinib monotherapy 40 mg film-coated tablets orally once daily.

Arm title	Pemetrexed/Cisplatin Chemotherapy

Arm description:

Patients received Pemetrexed 500 mg/m^2 lyophilised powder as intravenous infusion after Cisplatin 75 mg/m^2 solution for infusion as intravenous infusion on Day 1 of each 21-day treatment course up to 6 cycles.

Arm type	Active comparator
Investigational medicinal product name	Pemetrexed
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Patients received Pemetrexed 500 mg/m^2 lyophilised powder as intravenous infusion on Day 1 of each 21-day treatment course up to 6 cycles.

Investigational medicinal product name	Cisplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Patients received Cisplatin 75 mg/m^2 solution for infusion as intravenous infusion on Day 1 of each 21-day treatment course up to 6 cycles.

Number of subjects in period 1[1]	Afatinib 40 mg	Pemetrexed/Cisplatin Chemotherapy
Started	230	115
Completed	0	0
Not completed	230	115
Progressive disease	188	19
Refusal to continue medication	7	11
Protocol deviation	1	4
Other Adverse Event [AE]	28	17
Completed 6 courses of chemotherapy	-	60
Other not specified above	5	-
Not treated	1	4

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: Out of 1269 enrolled subjects only 345 were treated.

Baseline characteristics

Reporting groups	
Reporting group title	Overall Study

Reporting group description: -

Reporting group values	Overall Study	Total	
Number of subjects	345	345	
Age categorical Units: Subjects			
Age Continuous			
Randomised Set (RS): The randomised set includes all patients who were randomised to receive treatment, whether treated or not.			
Units: years			
arithmetic mean	60.3		
standard deviation	± 10.1	-	
Gender, Male/Female Units: Subjects			
Female	224	224	
Male	121	121	
Race/Ethnicity, Customized			
Race (Asian/non-Asian) was a stratification factor.			
Units: Subjects			
Asian	249	249	
Non-Asian	96	96	
Epidermal Growth Factor Receptor (EGFR) mutation group			
EGFR mutation group (L858R/Deletion Exon 19/Other) was a stratification factor.			
Units: Subjects			
EGFR mutation category: L858R	138	138	
EGFR mutation category: Deletion Exon 19	169	169	
EGFR mutation category: Other	38	38	
Eastern Cooperative Oncology Group (ECOG) Performance Status (PS)			
ECOG PS measured on 6 point scale to assess participant's performance status. 0=Fully active, able to carry on all pre-disease activities without restriction. 1=Restricted in physically strenuous activity, but ambulatory and able to carry out light or sedentary work. 2=Ambulatory (>50 percent of waking hours), capable of all self-care, unable to carry out any work activities. 3=Capable of only limited self-care, confined to bed or chair more than 50 percent of waking hours. 4=Completely disabled, cannot carry on any self-care, totally confined to bed or chair. 5=Dead.			
Units: Subjects			
ECOG PS 0 (baseline)	133	133	
ECOG PS 1 (baseline)	211	211	
ECOG PS 2 (baseline)	1	1	

End points

End points reporting groups

Reporting group title	Afatinib 40 mg
Reporting group description:	
Patients received Afatinib monotherapy 40 mg film-coated tablets orally once daily.	
Reporting group title	Pemetrexed/Cisplatin Chemotherapy
Reporting group description:	
Patients received Pemetrexed 500 mg/m^2 lyophilised powder as intravenous infusion after Cisplatin 75 mg/m^2 solution for infusion as intravenous infusion on Day 1 of each 21-day treatment course up to 6 cycles.	
Subject analysis set title	Afatinib 20 mg
Subject analysis set type	Full analysis
Subject analysis set description:	
Patients receiving Afatinib monotherapy 20 mg once daily (q.d.)	
Subject analysis set title	Afatinib 30 mg
Subject analysis set type	Full analysis
Subject analysis set description:	
Patients receiving Afatinib monotherapy 30 mg once daily (q.d.)	
Subject analysis set title	Afatinib 50 mg
Subject analysis set type	Full analysis
Subject analysis set description:	
Patients receiving Afatinib monotherapy 50 mg once daily (q.d.)	

Primary: Progression-Free Survival (PFS) Time

End point title	Progression-Free Survival (PFS) Time
End point description:	
PFS was defined as time from randomisation to disease progression or death whichever occured first. Assessed by central independent review according to the Response Evaluation Criteria in Solid Tumours (RECIST 1.1). Median time results from unstratified Kaplan-Meier estimates. Randomised Set (RS): The randomised set includes all patients who were randomised to receive treatment, whether treated or not.	
End point type	Primary
End point timeframe:	
Tumour assessments were performed at Screening, Week 6, Week 12, Week 18 and then every 12-18 weeks until disease progression	

End point values	Afatinib 40 mg	Pemetrexed/Cisplatin Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	230[1]	115[2]		
Units: Months.				
median (confidence interval 95%)	11.17 (9.63 to 13.70)	6.90 (5.39 to 8.25)		

Notes:

[1] - RS.

[2] - RS.

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Pemetrexed/Cisplatin Chemotherapy v Afatinib 40 mg
Number of subjects included in analysis	345
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0002 [3]
Method	Logrank

Notes:

[3] - Two-sided p-value from log-rank test stratified by EGFR mutation group and race.

Statistical analysis title	Statistical analysis 2

Statistical analysis description:

Cox Proportional Hazard (PH) regression stratified by epidermal growth factor receptor (EGFR) mutation group and race.
Hazard Ratio (HR) was calculated as Afatinib 40 mg versus Pemetrexed/Cisplatin Chemotherapy.

Comparison groups	Afatinib 40 mg v Pemetrexed/Cisplatin Chemotherapy
Number of subjects included in analysis	345
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0002
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.576
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.426
upper limit	0.778

Secondary: Percentage of Patients with Objective Response (OR)

End point title	Percentage of Patients with Objective Response (OR)

End point description:

OR was defined as Complete Response (CR) or Partial Response (PR). Assessed by central independent review according to RECIST 1.1.
Randomised Set (RS): The randomised set includes all patients who were randomised to receive treatment, whether treated or not.

End point type	Secondary

End point timeframe:

Tumour assessments were performed at Screening, Week 6, Week 12, Week 18 and then every 12-18 weeks until disease progression

End point values	Afatinib 40 mg	Pemetrexed/Cisplatin Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	230[4]	115[5]		
Units: Percentage of patients with OR.				
number (confidence interval 95%)	56.5 (49.8 to 63.0)	22.6 (15.3 to 31.3)		

Notes:

[4] - RS.

[5] - RS.

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Logistic regression stratified for EGFR mutation group and race.
Odds Ratio (OR) was calculated as Afatinib 40 mg-Pemetrexed/Cisplatin Chemotherapy.

Comparison groups	Afatinib 40 mg v Pemetrexed/Cisplatin Chemotherapy
Number of subjects included in analysis	345
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	4.802
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.855
upper limit	8.075

Secondary: Percentage of Participants with Disease Control (DC)

End point title	Percentage of Participants with Disease Control (DC)

End point description:

DC was defined as a patient with OR or Stable Disease (SD). Assessed by central independent review according to the RECIST 1.1.
Randomised Set (RS): The randomised set includes all patients who were randomised to receive treatment, whether treated or not.

End point type	Secondary

End point timeframe:

Tumour assessments were performed at Screening, Week 6, Week 12, Week 18 and then every 12-18 weeks until disease progression

End point values	Afatinib 40 mg	Pemetrexed/Cisplatin Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	230[6]	115[7]		
Units: Percentage of participants with DC.				
number (confidence interval 95%)	90.4 (85.9 to 93.9)	80.9 (72.5 to 87.6)		

Notes:

[6] - RS.

[7] - RS.

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Logistic regression stratified for EGFR mutation group and race.
OR was calculated as Afatinib 40 mg-Pemetrexed/Cisplatin Chemotherapy.

Comparison groups	Afatinib 40 mg v Pemetrexed/Cisplatin Chemotherapy
Number of subjects included in analysis	345
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0118
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.288
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.202
upper limit	4.356

Secondary: Overall Survival (OS) Time

End point title	Overall Survival (OS) Time

End point description:

OS was defined as time from randomisation to death.
Randomised Set (RS): The randomised set includes all patients who were randomised to receive treatment, whether treated or not.

End point type	Secondary

End point timeframe:

From randomisation to cut-off date (17MAR2017).

End point values	Afatinib 40 mg	Pemetrexed/Cisplatin Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	230[8]	115[9]		
Units: Months.				
median (confidence interval 95%)	28.16 (24.64 to 33.58)	28.22 (20.73 to 33.22)		

Notes:

[8] - RS.

[9] - RS.

Statistical analyses

Statistical analysis title	Statistical analysis 2

Statistical analysis description:

Cox PH regression stratified by EGFR mutation group and race.

Comparison groups	Afatinib 40 mg v Pemetrexed/Cisplatin Chemotherapy
Number of subjects included in analysis	345
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.385
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.88
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.66
upper limit	1.174

Statistical analysis title	Statistical analysis 1
Comparison groups	Afatinib 40 mg v Pemetrexed/Cisplatin Chemotherapy
Number of subjects included in analysis	345
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.7916 [10]
Method	Logrank

Notes:

[10] - Two-sided p-value from log-rank test stratified by EGFR mutation group and race.

Secondary: Tumour Shrinkage

End point title	Tumour Shrinkage

End point description:

Tumour shrinkage was calculated as the minimum Sum of Diameters (SoD) of target lesions from all post-baseline tumour assessments, as read by the central independent review. The mean of these minimum values were presented after adjusting for baseline SoD, EGFR mutation group and race.
RS. There were only 203 patients in the Afatinib 40 mg arm and 101 patients in the Pemetrexed/Cisplatin Chemotherapy with tumour measurements.

End point type	Secondary

End point timeframe:

Tumour assessments were performed at Screening, Week 6, Week 12, Week 18 and then every 12-18 weeks until disease progression

End point values	Afatinib 40 mg	Pemetrexed/Cisplatin Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	203[11]	101[12]		
Units: mm.				
arithmetic mean (standard error)	33.19 (± 1.12)	43.00 (± 1.59)		

Notes:

[11] - RS.

[12] - RS.

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Adjusted for baseline SoD, EGFR mutation group and race.
Mean Difference (Final Values) was calculated as Afatinib 40 mg-Pemetrexed/Cisplatin Chemotherapy.

Comparison groups	Afatinib 40 mg v Pemetrexed/Cisplatin Chemotherapy
Number of subjects included in analysis	304
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-9.82
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.64
upper limit	-5.99

Secondary: Change from Baseline in Body Weight

End point title	Change from Baseline in Body Weight

End point description:

Because the PFS was longer for patients in the Afatinib arm than for patients in the chemotherapy arm, the period of data collection for ECOG status and body weight continued for a longer time in the Afatinib arm.
RS. Only patients with baseline and at least one post-baseline assessment were included.

End point type	Secondary

End point timeframe:

Baseline and throughout the trial until progression (every 3 weeks), up to 28 months.

End point values	Afatinib 40 mg	Pemetrexed/Cisplatin Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	224[13]	109[14]		
Units: Kg.				
arithmetic mean (standard deviation)				
Change from baseline at lowest value	-3.95 (± 3.91)	-2.68 (± 2.90)		
Change from baseline at last value	-1.19 (± 5.36)	-0.29 (± 4.02)		

Notes:

[13] - RS.

[14] - RS.

Statistical analyses

No statistical analyses for this end point

Secondary: Eastern Cooperative Oncology Group (ECOG) Performance Status (PS)

End point title	Eastern Cooperative Oncology Group (ECOG) Performance Status (PS)

End point description:

ECOG PS measured on 6 point scale to assess participant's performance status. 0=Fully active, able to carry on all pre-disease activities without restriction. 1=Restricted in physically strenuous activity, but ambulatory and able to carry out light or sedentary work. 2=Ambulatory (>50 percent of waking hours), capable of all self-care, unable to carry out any work activities. 3=Capable of only limited self-care, confined to bed or chair more than 50 percent of waking hours. 4=Completely disabled, cannot carry on any self-care, totally confined to bed or chair. 5=Dead.
RS. Only patients with baseline and at least one post-baseline assessment were included.

End point type	Secondary

End point timeframe:

Throughout the trial until progression (every 3 weeks), up to 28 months.

End point values	Afatinib 40 mg	Pemetrexed/Cisplatin Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	228[15]	111[16]		
Units: Participants				
ECOG PS 0 (last value)	92	41		
ECOG PS 1 (last value)	138	73		
ECOG PS 2 (last value)	0	1		

Notes:

[15] - RS.

[16] - RS.

Statistical analyses

No statistical analyses for this end point

Secondary: Health Related Quality of Life (HRQOL): Time to Deterioration in Coughing

End point title	Health Related Quality of Life (HRQOL): Time to Deterioration in Coughing

End point description:

HRQOL was measured by European Organisation for Research and Treatment of Cancer (EORTC) quality of life questionnaire C30 (QLQ-C30) and its lung cancer specific module LC13 (QLQ-LC13). Analysis for cough is based on QLQ-LC13 question 1. Time to deterioration was defined as the time from randomisation to a score increased (worsened) by at least 10 points from baseline (0-100 point scale). Patients were considered deteriorated at time of death. Median time results from unstratified Kaplan-Meier estimates.
Afatinib 40 mg [99999]: As only 82 patients (35.7 percent) in the Afatinib 40 mg deteriorated, the upper limit of CI was not estimable.
Pemetrexed/Cisplatin Chemotherapy [99999]: As only 44 patients (38.3 percent) in the Pemetrexed/Cisplatin Chemotherapy deteriorated, the upper limit of the CI was not estimable.
Randomised Set (RS): The randomised set includes all patients who were randomised to receive treatment, whether treated or not.

End point type	Secondary

End point timeframe:

Throughout the trial until progression (every 3 weeks).

End point values	Afatinib 40 mg	Pemetrexed/Cisplatin Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	230[17]	115[18]		
Units: Months.				
median (confidence interval 95%)	26.97 (19.22 to 99999)	8.02 (4.44 to 99999)		

Notes:

[17] - RS.

[18] - RS.

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Afatinib 40 mg v Pemetrexed/Cisplatin Chemotherapy
Number of subjects included in analysis	345
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0062 [19]
Method	Logrank

Notes:

[19] - Two-sided p-value from log-rank test stratified by EGFR mutation group and race.

Statistical analysis title	Statistical analysis 2

Statistical analysis description:

Cox PH regression stratified by EGFR mutation group and race.
HR was calculated as Afatinib 40 mg vs. Pemetrexed/Cisplatin Chemotherapy, if HR<1 then favours Afatinib 40 mg.

Comparison groups	Afatinib 40 mg v Pemetrexed/Cisplatin Chemotherapy
Number of subjects included in analysis	345
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.2133
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)

Point estimate	0.589
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.401
upper limit	0.866

Secondary: HRQOL: Time to Deterioration in Dyspnoea

End point title	HRQOL: Time to Deterioration in Dyspnoea

End point description:

HRQOL was measured by EORTC QLQ-C30 and its lung cancer specific module QLQ-LC13. Analysis for dyspnoea is based on composite of QLQ-LC13 questions 3-5. Time to deterioration was defined as the time from randomisation to a score increased (worsened) by at least 10 points from baseline (0-100 point scale). Patients were considered deteriorated at time of death. Median time results from unstratified Kaplan-Meier estimates.
Randomised Set (RS): The randomised set includes all patients who were randomised to receive treatment, whether treated or not.

End point type	Secondary

End point timeframe:

Throughout the trial until progression (every 3 weeks).

End point values	Afatinib 40 mg	Pemetrexed/Cisplatin Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	230[20]	115[21]		
Units: Months.				
median (confidence interval 95%)	10.41 (5.59 to 15.93)	2.86 (2.17 to 4.90)		

Notes:

[20] - RS.

[21] - RS.

Statistical analyses

Statistical analysis title	Statistical analysis 2

Statistical analysis description:

Cox PH regression stratified by EGFR mutation group and race.
HR was calculated as Afatinib 40 mg vs. Pemetrexed/Cisplatin Chemotherapy, if HR<1 then favours Afatinib 40 mg.

Comparison groups	Afatinib 40 mg v Pemetrexed/Cisplatin Chemotherapy
Number of subjects included in analysis	345
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0078
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.68
Confidence interval	
level	95 %

sides	2-sided
lower limit	0.499
upper limit	0.927

Statistical analysis title	Statistical analysis 1
Comparison groups	Afatinib 40 mg v Pemetrexed/Cisplatin Chemotherapy
Number of subjects included in analysis	345
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0129 [22]
Method	Logrank

Notes:

[22] - Two-sided p-value from log-rank test stratified by EGFR mutation group and race.

Secondary: HRQOL: Time to Deterioration in Pain

End point title	HRQOL: Time to Deterioration in Pain

End point description:

HRQOL was measured by EORTC QLQ-C30 and its lung cancer specific module QLQ-LC13. Analysis for pain is based on composite of QLQ-C30 questions 9 and 19. Time to deterioration was defined as the time from randomisation to a score increased (worsened) by at least 10 points from baseline (0-100 point scale). Patients were considered deteriorated at time of death. Median time results from unstratified Kaplan-Meier estimates.
Randomised Set (RS): The randomised set includes all patients who were randomised to receive treatment, whether treated or not.

End point type	Secondary

End point timeframe:

Throughout the trial until progression (every 3 weeks).

End point values	Afatinib 40 mg	Pemetrexed/Cisplatin Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	230[23]	115[24]		
Units: Months.				
median (confidence interval 95%)	4.17 (2.79 to 5.59)	3.09 (2.17 to 3.98)		

Notes:

[23] - RS.

[24] - RS.

Statistical analyses

Statistical analysis title	Statistical analysis 2

Statistical analysis description:

Cox PH regression stratified by EGFR mutation group and race.
HR was calculated as Afatinib 40 mg vs. Pemetrexed/Cisplatin Chemotherapy, if HR<1 then favours Afatinib 40 mg.

Comparison groups	Afatinib 40 mg v Pemetrexed/Cisplatin Chemotherapy
Number of subjects included in analysis	345

Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0427
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.826
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.618
upper limit	1.104

Statistical analysis title	Statistical analysis 1
Comparison groups	Afatinib 40 mg v Pemetrexed/Cisplatin Chemotherapy
Number of subjects included in analysis	345
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1882 [25]
Method	Logrank

Notes:

[25] - Two-sided p-value from log-rank test stratified by EGFR mutation group and race.

Secondary: Trough Plasma Concentrations of Afatinib at Day 22

End point title	Trough Plasma Concentrations of Afatinib at Day 22[26]

End point description:

Trough plasma concentrations of Afatinib at Day 22 (course 2, visit 1) after multiple daily dosing of 40 mg Afatinib and after dose escalation to 50 mg or dose reduction to 30 mg or 20 mg.
Patients from the treated set (The treated set included all randomised patients who were documented to have taken at least 1 dose of study medication (i.e. Afatinib or Pemetrexed / Cisplatin)) with evaluable data and who had at least 1 valid Afatinib plasma concentration available on this time point.

End point type	Secondary

End point timeframe:

Day 22.

Notes:

[26] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was defined only for the group "Aftainib 40mg".

End point values	Afatinib 40 mg	Afatinib 20 mg	Afatinib 30 mg	Afatinib 50 mg
Subject group type	Reporting group	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	165[27]	0[28]	11[29]	3[30]
Units: ng/mL.				
geometric mean (geometric coefficient of variation)	28.0 (± 85.0)	()	21.8 (± 36.6)	29.9 (± 46.1)

Notes:

[27] - TS.

[28] - TS.
No subjets analysed.
[29] - TS.

[30] - TS.

Statistical analyses

No statistical analyses for this end point

Secondary: Trough Plasma Concentrations of Afatinib at Day 29

End point title	Trough Plasma Concentrations of Afatinib at Day 29[31]

End point description:

Trough plasma concentrations of Afatinib at day 29 (course 2, visit 2) after multiple daily dosing of 40 mg Afatinib and after dose escalation to 50 mg or dose reduction to 30 mg or 20 mg.
Patients from the treated set (The treated set included all randomised patients who were documented to have taken at least 1 dose of study medication (i.e. Afatinib or Pemetrexed / Cisplatin)) with evaluable data and who had at least 1 valid Afatinib plasma concentration available on this time point.

End point type	Secondary

End point timeframe:

Day 29.

Notes:

[31] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was defined only for the group "Aftainib 40mg".

End point values	Afatinib 40 mg	Afatinib 20 mg	Afatinib 30 mg	Afatinib 50 mg
Subject group type	Reporting group	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	143[32]	0[33]	25[34]	16[35]
Units: ng/mL.				
geometric mean (geometric coefficient of variation)	25.8 (± 69.5)	()	28.0 (± 82.4)	29.6 (± 79.2)

Notes:

[32] - TS.

[33] - TS.
No subjects analysed.

[34] - TS.

[35] - TS.

Statistical analyses

No statistical analyses for this end point

Secondary: Trough Plasma Concentrations of Afatinib at Day 43

End point title	Trough Plasma Concentrations of Afatinib at Day 43[36]

End point description:

Trough plasma concentrations of Afatinib at Day 43 (course 3, visit 1) after multiple daily dosing of 40 mg Afatinib and after dose escalation to 50 mg or dose reduction to 30 mg or 20 mg.
Patients from the treated set (The treated set included all randomised patients who were documented to have taken at least 1 dose of study medication (i.e. Afatinib or Pemetrexed / Cisplatin)) with evaluable data and who had at least 1 valid Afatinib plasma concentration available on this time point.

End point type	Secondary

End point timeframe:

Day 43.

Notes:

[36] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint was defined only for the group "Aftainib 40mg".

End point values	Afatinib 40 mg	Afatinib 20 mg	Afatinib 30 mg	Afatinib 50 mg
Subject group type	Reporting group	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	126[37]	2[38]	39[39]	14[40]
Units: ng/mL.				
geometric mean (geometric coefficient of variation)	23.5 (± 66.2)	24.4 (± 260)	24.7 (± 63.9)	27.5 (± 64.4)

Notes:

[37] - TS.

[38] - TS.

[39] - TS.

[40] - TS.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From the first drug administration until 28 days after the last drug administration.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups	
Reporting group title	Afatinib 40
Reporting group description:	
Patients received Afatinib monotherapy 40 mg film-coated tablets orally once daily.	
Reporting group title	Pe500+Cis75
Reporting group description:	
Patients received Pemetrexed 500 mg/m^2 lyophilised powder as intravenous infusion after Cisplatin 75 mg/m^2 solution for infusion as intravenous infusion on Day 1 of each 21-day treatment course up to 6 cycles.	

Serious adverse events	Afatinib 40	Pe500+Cis75	
Total subjects affected by serious adverse events			
subjects affected / exposed	72 / 229 (31.44%)	25 / 111 (22.52%)	
number of deaths (all causes)	193	88	
number of deaths resulting from adverse events	15	3	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	2 / 229 (0.87%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Superior vena cava syndrome			
subjects affected / exposed	1 / 229 (0.44%)	0 / 111 (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	1 / 229 (0.44%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombosis			
subjects affected / exposed	0 / 229 (0.00%)	1 / 111 (0.90%)	

occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous thrombosis			
subjects affected / exposed	1 / 229 (0.44%)	1 / 111 (0.90%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant neoplasm progression			
subjects affected / exposed	3 / 229 (1.31%)	2 / 111 (1.80%)	
occurrences causally related to treatment / all	1 / 3	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 1	
Metastases to central nervous system			
subjects affected / exposed	3 / 229 (1.31%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Metastases to lung			
subjects affected / exposed	0 / 229 (0.00%)	1 / 111 (0.90%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to meninges			
subjects affected / exposed	1 / 229 (0.44%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Neoplasm progression			
subjects affected / exposed	2 / 229 (0.87%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 229 (0.44%)	2 / 111 (1.80%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Abasia			
subjects affected / exposed	0 / 229 (0.00%)	1 / 111 (0.90%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	2 / 229 (0.87%)	1 / 111 (0.90%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	1 / 2	0 / 1	
Disease progression			
subjects affected / exposed	2 / 229 (0.87%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Fatigue			
subjects affected / exposed	3 / 229 (1.31%)	1 / 111 (0.90%)	
occurrences causally related to treatment / all	2 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	1 / 229 (0.44%)	1 / 111 (0.90%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hernia			
subjects affected / exposed	1 / 229 (0.44%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malaise			
subjects affected / exposed	0 / 229 (0.00%)	1 / 111 (0.90%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucosal inflammation			
subjects affected / exposed	2 / 229 (0.87%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	2 / 229 (0.87%)	1 / 111 (0.90%)	

occurrences causally related to treatment / all	2 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Confusional state			
subjects affected / exposed	3 / 229 (1.31%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Schizophreniform disorder			
subjects affected / exposed	0 / 229 (0.00%)	1 / 111 (0.90%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	1 / 229 (0.44%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower limb fracture			
subjects affected / exposed	1 / 229 (0.44%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Splenic rupture			
subjects affected / exposed	1 / 229 (0.44%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Synovial rupture			
subjects affected / exposed	0 / 229 (0.00%)	1 / 111 (0.90%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thoracic vertebral fracture			
subjects affected / exposed	1 / 229 (0.44%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tibia fracture			

subjects affected / exposed	1 / 229 (0.44%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 229 (0.00%)	1 / 111 (0.90%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Alanine aminotransferase increased			
subjects affected / exposed	0 / 229 (0.00%)	1 / 111 (0.90%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood sodium decreased			
subjects affected / exposed	0 / 229 (0.00%)	1 / 111 (0.90%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver function test abnormal			
subjects affected / exposed	1 / 229 (0.44%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 229 (0.00%)	1 / 111 (0.90%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mitral valve incompetence			
subjects affected / exposed	1 / 229 (0.44%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	0 / 229 (0.00%)	1 / 111 (0.90%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pericardial effusion			
subjects affected / exposed	1 / 229 (0.44%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	2 / 229 (0.87%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	1 / 2	0 / 0	
Bronchospasm			
subjects affected / exposed	0 / 229 (0.00%)	1 / 111 (0.90%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	4 / 229 (1.75%)	2 / 111 (1.80%)	
occurrences causally related to treatment / all	1 / 4	0 / 2	
deaths causally related to treatment / all	1 / 1	0 / 1	
Epistaxis			
subjects affected / exposed	0 / 229 (0.00%)	1 / 111 (0.90%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	1 / 229 (0.44%)	1 / 111 (0.90%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial lung disease			
subjects affected / exposed	1 / 229 (0.44%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	2 / 229 (0.87%)	3 / 111 (2.70%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pneumothorax			
subjects affected / exposed	1 / 229 (0.44%)	1 / 111 (0.90%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary artery thrombosis			
subjects affected / exposed	0 / 229 (0.00%)	1 / 111 (0.90%)	
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	2 / 229 (0.87%)	1 / 111 (0.90%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory failure			
subjects affected / exposed	1 / 229 (0.44%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory arrest			
subjects affected / exposed	1 / 229 (0.44%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 229 (0.00%)	2 / 111 (1.80%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	0 / 229 (0.00%)	1 / 111 (0.90%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Depressed level of consciousness			
subjects affected / exposed	1 / 229 (0.44%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Epilepsy			
subjects affected / exposed	1 / 229 (0.44%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	1 / 229 (0.44%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Loss of consciousness			
subjects affected / exposed	1 / 229 (0.44%)	0 / 111 (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 / 229 (0.44%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Partial seizures			
subjects affected / exposed	1 / 229 (0.44%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	3 / 229 (1.31%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	0 / 229 (0.00%)	1 / 111 (0.90%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Cataract			
subjects affected / exposed	1 / 229 (0.44%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			

Abdominal discomfort			
subjects affected / exposed	1 / 229 (0.44%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	1 / 229 (0.44%)	0 / 111 (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	15 / 229 (6.55%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	15 / 15	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	1 / 229 (0.44%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 229 (0.44%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoids			
subjects affected / exposed	1 / 229 (0.44%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	0 / 229 (0.00%)	2 / 111 (1.80%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	1 / 229 (0.44%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			
subjects affected / exposed	1 / 229 (0.44%)	1 / 111 (0.90%)	

occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	11 / 229 (4.80%)	3 / 111 (2.70%)	
occurrences causally related to treatment / all	9 / 13	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 229 (0.00%)	1 / 111 (0.90%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute prerenal failure			
subjects affected / exposed	1 / 229 (0.44%)	1 / 111 (0.90%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	1 / 229 (0.44%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	2 / 229 (0.87%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaundice			
subjects affected / exposed	1 / 229 (0.44%)	0 / 111 (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			
subjects affected / exposed	1 / 229 (0.44%)	0 / 111 (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	0 / 229 (0.00%)	1 / 111 (0.90%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone pain			
subjects affected / exposed	1 / 229 (0.44%)	0 / 111 (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	0 / 229 (0.00%)	1 / 111 (0.90%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	1 / 229 (0.44%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	3 / 229 (1.31%)	1 / 111 (0.90%)	
occurrences causally related to treatment / all	2 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Decreased appetite			
subjects affected / exposed	2 / 229 (0.87%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes with hyperosmolarity			
subjects affected / exposed	0 / 229 (0.00%)	1 / 111 (0.90%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	4 / 229 (1.75%)	1 / 111 (0.90%)	
occurrences causally related to treatment / all	3 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			

subjects affected / exposed	1 / 229 (0.44%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Cellulitis			
subjects affected / exposed	1 / 229 (0.44%)	1 / 111 (0.90%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	1 / 229 (0.44%)	0 / 111 (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	2 / 229 (0.87%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	1 / 229 (0.44%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis aseptic			
subjects affected / exposed	1 / 229 (0.44%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Meningoencephalitis herpetic			
subjects affected / exposed	0 / 229 (0.00%)	1 / 111 (0.90%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	4 / 229 (1.75%)	1 / 111 (0.90%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Sepsis			
subjects affected / exposed	1 / 229 (0.44%)	0 / 111 (0.00%)	

occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	2 / 229 (0.87%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	2 / 229 (0.87%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Afatinib 40	Pe500+Cis75	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	229 / 229 (100.00%)	108 / 111 (97.30%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	14 / 229 (6.11%)	14 / 111 (12.61%)	
occurrences (all)	14	15	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	16 / 229 (6.99%)	14 / 111 (12.61%)	
occurrences (all)	19	15	
Asthenia			
subjects affected / exposed	16 / 229 (6.99%)	14 / 111 (12.61%)	
occurrences (all)	21	17	
Fatigue			
subjects affected / exposed	45 / 229 (19.65%)	39 / 111 (35.14%)	
occurrences (all)	55	59	
Malaise			
subjects affected / exposed	7 / 229 (3.06%)	6 / 111 (5.41%)	
occurrences (all)	7	6	
Oedema			

subjects affected / exposed	7 / 229 (3.06%)	13 / 111 (11.71%)	
occurrences (all)	8	27	
Mucosal inflammation			
subjects affected / exposed	67 / 229 (29.26%)	5 / 111 (4.50%)	
occurrences (all)	110	6	
Oedema peripheral			
subjects affected / exposed	17 / 229 (7.42%)	8 / 111 (7.21%)	
occurrences (all)	17	10	
Pyrexia			
subjects affected / exposed	28 / 229 (12.23%)	6 / 111 (5.41%)	
occurrences (all)	34	7	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	37 / 229 (16.16%)	10 / 111 (9.01%)	
occurrences (all)	53	10	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	27 / 229 (11.79%)	3 / 111 (2.70%)	
occurrences (all)	43	5	
Aspartate aminotransferase increased			
subjects affected / exposed	22 / 229 (9.61%)	1 / 111 (0.90%)	
occurrences (all)	32	3	
Blood creatinine increased			
subjects affected / exposed	5 / 229 (2.18%)	10 / 111 (9.01%)	
occurrences (all)	6	16	
Haemoglobin decreased			
subjects affected / exposed	3 / 229 (1.31%)	13 / 111 (11.71%)	
occurrences (all)	7	20	
Neutrophil count decreased			
subjects affected / exposed	1 / 229 (0.44%)	8 / 111 (7.21%)	
occurrences (all)	3	19	
Weight decreased			
subjects affected / exposed	44 / 229 (19.21%)	16 / 111 (14.41%)	
occurrences (all)	59	16	
Blood and lymphatic system disorders			

Anaemia			
subjects affected / exposed	19 / 229 (8.30%)	29 / 111 (26.13%)	
occurrences (all)	24	30	
Leukopenia			
subjects affected / exposed	6 / 229 (2.62%)	21 / 111 (18.92%)	
occurrences (all)	6	53	
Neutropenia			
subjects affected / exposed	4 / 229 (1.75%)	35 / 111 (31.53%)	
occurrences (all)	4	86	
Thrombocytopenia			
subjects affected / exposed	1 / 229 (0.44%)	8 / 111 (7.21%)	
occurrences (all)	1	21	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	39 / 229 (17.03%)	21 / 111 (18.92%)	
occurrences (all)	54	23	
Dyspnoea			
subjects affected / exposed	18 / 229 (7.86%)	12 / 111 (10.81%)	
occurrences (all)	19	13	
Epistaxis			
subjects affected / exposed	41 / 229 (17.90%)	1 / 111 (0.90%)	
occurrences (all)	52	1	
Nasal inflammation			
subjects affected / exposed	15 / 229 (6.55%)	0 / 111 (0.00%)	
occurrences (all)	16	0	
Hiccups			
subjects affected / exposed	5 / 229 (2.18%)	10 / 111 (9.01%)	
occurrences (all)	5	21	
Rhinorrhoea			
subjects affected / exposed	16 / 229 (6.99%)	7 / 111 (6.31%)	
occurrences (all)	21	9	
Oropharyngeal pain			
subjects affected / exposed	13 / 229 (5.68%)	3 / 111 (2.70%)	
occurrences (all)	17	3	
Nervous system disorders			

Dizziness			
subjects affected / exposed	28 / 229 (12.23%)	12 / 111 (10.81%)	
occurrences (all)	36	16	
Headache			
subjects affected / exposed	37 / 229 (16.16%)	19 / 111 (17.12%)	
occurrences (all)	55	25	
Dysgeusia			
subjects affected / exposed	18 / 229 (7.86%)	9 / 111 (8.11%)	
occurrences (all)	20	9	
Eye disorders			
Dry eye			
subjects affected / exposed	14 / 229 (6.11%)	0 / 111 (0.00%)	
occurrences (all)	14	0	
Vision blurred			
subjects affected / exposed	12 / 229 (5.24%)	2 / 111 (1.80%)	
occurrences (all)	12	2	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	13 / 229 (5.68%)	5 / 111 (4.50%)	
occurrences (all)	17	5	
Abdominal pain upper			
subjects affected / exposed	15 / 229 (6.55%)	8 / 111 (7.21%)	
occurrences (all)	25	9	
Cheilitis			
subjects affected / exposed	22 / 229 (9.61%)	0 / 111 (0.00%)	
occurrences (all)	27	0	
Constipation			
subjects affected / exposed	37 / 229 (16.16%)	39 / 111 (35.14%)	
occurrences (all)	44	54	
Diarrhoea			
subjects affected / exposed	216 / 229 (94.32%)	25 / 111 (22.52%)	
occurrences (all)	535	31	
Dyspepsia			
subjects affected / exposed	21 / 229 (9.17%)	7 / 111 (6.31%)	
occurrences (all)	25	10	
Mouth ulceration			
subjects affected / exposed	24 / 229 (10.48%)	3 / 111 (2.70%)	

occurrences (all)	36	3	
Nausea			
subjects affected / exposed	65 / 229 (28.38%)	75 / 111 (67.57%)	
occurrences (all)	98	174	
Stomatitis			
subjects affected / exposed	88 / 229 (38.43%)	10 / 111 (9.01%)	
occurrences (all)	144	13	
Vomiting			
subjects affected / exposed	53 / 229 (23.14%)	50 / 111 (45.05%)	
occurrences (all)	79	83	
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	52 / 229 (22.71%)	0 / 111 (0.00%)	
occurrences (all)	67	0	
Alopecia			
subjects affected / exposed	30 / 229 (13.10%)	20 / 111 (18.02%)	
occurrences (all)	33	20	
Dry skin			
subjects affected / exposed	72 / 229 (31.44%)	2 / 111 (1.80%)	
occurrences (all)	85	2	
Dermatitis acneiform			
subjects affected / exposed	32 / 229 (13.97%)	0 / 111 (0.00%)	
occurrences (all)	47	0	
Nail disorder			
subjects affected / exposed	14 / 229 (6.11%)	0 / 111 (0.00%)	
occurrences (all)	14	0	
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	19 / 229 (8.30%)	0 / 111 (0.00%)	
occurrences (all)	44	0	
Rash			
subjects affected / exposed	145 / 229 (63.32%)	11 / 111 (9.91%)	
occurrences (all)	243	12	
Pruritus			
subjects affected / exposed	50 / 229 (21.83%)	1 / 111 (0.90%)	
occurrences (all)	66	1	

Skin exfoliation			
subjects affected / exposed	13 / 229 (5.68%)	0 / 111 (0.00%)	
occurrences (all)	14	0	
Skin fissures			
subjects affected / exposed	16 / 229 (6.99%)	0 / 111 (0.00%)	
occurrences (all)	20	0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	21 / 229 (9.17%)	6 / 111 (5.41%)	
occurrences (all)	27	6	
Muscle spasms			
subjects affected / exposed	20 / 229 (8.73%)	0 / 111 (0.00%)	
occurrences (all)	22	0	
Back pain			
subjects affected / exposed	37 / 229 (16.16%)	13 / 111 (11.71%)	
occurrences (all)	44	13	
Musculoskeletal pain			
subjects affected / exposed	21 / 229 (9.17%)	2 / 111 (1.80%)	
occurrences (all)	24	2	
Myalgia			
subjects affected / exposed	12 / 229 (5.24%)	1 / 111 (0.90%)	
occurrences (all)	18	1	
Pain in extremity			
subjects affected / exposed	20 / 229 (8.73%)	4 / 111 (3.60%)	
occurrences (all)	24	5	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	70 / 229 (30.57%)	61 / 111 (54.95%)	
occurrences (all)	96	111	
Hypokalaemia			
subjects affected / exposed	21 / 229 (9.17%)	4 / 111 (3.60%)	
occurrences (all)	35	8	
Hyponatraemia			
subjects affected / exposed	4 / 229 (1.75%)	6 / 111 (5.41%)	
occurrences (all)	4	12	
Infections and infestations			

Conjunctivitis			
subjects affected / exposed	28 / 229 (12.23%)	3 / 111 (2.70%)	
occurrences (all)	35	3	
Cystitis			
subjects affected / exposed	15 / 229 (6.55%)	1 / 111 (0.90%)	
occurrences (all)	18	1	
Nasopharyngitis			
subjects affected / exposed	39 / 229 (17.03%)	9 / 111 (8.11%)	
occurrences (all)	67	9	
Folliculitis			
subjects affected / exposed	12 / 229 (5.24%)	0 / 111 (0.00%)	
occurrences (all)	12	0	
Paronychia			
subjects affected / exposed	132 / 229 (57.64%)	0 / 111 (0.00%)	
occurrences (all)	188	0	
Upper respiratory tract infection			
subjects affected / exposed	29 / 229 (12.66%)	4 / 111 (3.60%)	
occurrences (all)	47	5	
Urinary tract infection			
subjects affected / exposed	19 / 229 (8.30%)	5 / 111 (4.50%)	
occurrences (all)	26	5	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 May 2010	Exclusion criterion 21 was changed; it originally referred to patients randomised to treatment with chemotherapy only. As the consent process took place before randomisation, it was necessary to cover both treatment arms with this exclusion criterion. The restricted medications during treatment with Afatinib were changed. It was specified that the list of restricted medications refers to all patients randomised. An additional explanatory paragraph was added that the concomitant use of potent P-gp inhibitors and inducers was to be avoided during treatment with Afatinib. The background was that a trial [1200.79] in healthy volunteers indicated that co-administration of these drugs affected the pharmacokinetics of Afatinib.
09 May 2011	Several changes and corrections were introduced with the second amendment to the protocol; major changes are presented. It was specified that the trial had 2 screening visits. During the first screening visit, the patient signed the first informed consent and agreed to the EGFR mutation testing. During the second screening visit patients with positive EGFR mutation testing signed a second informed consent and agreed to participate in the main part of the trial. The strict time window for Afatinib intake was removed to accommodate individual patient's daily schedule preference because Afatinib has a long half-life. The storage conditions for Afatinib were corrected to match the labelling in the USA and Canada. Tablets were to be stored at the temperature specified in the label [i.e. between 15°C and 30°C in the USA and Canada and not above 25ºC in all other countries]. It was specified how data in HRQOL questionnaires were to be handled for Adverse Event [AE] reporting. The length of the observation period of this trial was specified. The focus of the analysis of HRQOL was broadened to include all summary scales and items measuring cough, dyspnoea, and pain measured by the EORTC QLQ-C30 and QLQ-LC13 questionnaires. The time window of the on-treatment period was modified to match the planned safety analysis with other Afatinib trials. It was specified that the decision of whether to proceed to full accrual was based on the first 40 patients randomised to treatment with Afatinib whether or not they had stopped treatment before the Week 6 assessment. New information was added to the appendix of the protocol. The appendix was updated with the current Summary of Product Characteristics [SPC] of Cisplatin provided for the trial. In addition, the RECIST version 1.1 criteria in the appendix were updated to ensure consistency with the imaging charter for the central independent review of radiological imaging.
01 August 2012	The third amendment to the protocol introduced several changes; the key changes are presented. Amendment 3 changed the frequency of Electro Cardio Gram [ECG] assessments from once every third course to "as clinically indicated". The amendment was released after at least 18 months of collection of centrally assessed ECG data for all randomised patients. The data showed that Afatinib did not have any effect on QTc or other ECG parameters; therefore routine monitoring of ECG was no longer required. The requirements for collection of biopsy and blood samples at the time of Progressive Disease [PD] were changed for both treatment arms. Based on the review of already collected data, further follow-up biopsy and blood samples were not requested. The frequency of collection of observation-period data was changed. A data snapshot could now be requested at any time; after the analysis of OS, the collection of observation-period data could be reduced in frequency or stopped, as decided by the Trial Clinical Monitor [TCM]. The requirement for reporting 'always serious' adverse events as per new corporate standard was added. The new corporate standard for monitoring and assessment of potential drug-induced liver injury was added. Based on the new clinical data, the recommendation to avoid the use of P-gp inhibitors or inducers in patients treated with Afatinib was modified to allow for their use with caution if clinically indicated.

20 September 2013	Several changes affecting patients still ongoing in the trial were introduced with the fourth amendment to the protocol; the main changes are presented. Routine monitoring of Left Ventricular Ejection Fraction [LVEF] was no longer required after database lock for the analysis of OS. LVEF assessments were now to be performed as clinically indicated. No safety signals indicating an effect of Afatinib on the cardiac contractility had been identified in this trial and using a larger safety database. Routine monitoring of LVEF was therefore no longer required. The frequency of trial visits was reduced after database lock for the analysis of OS. A treatment course now comprised 9 weeks [63 days] and FU visits were to be performed every 9 weeks [63 days] until PD or death. All patients had been on treatment for more than 2 years, therefore the frequency of clinic visits could be reduced. The frequency of imaging assessments was reduced after database lock for the analysis of OS. Assessments were now to be performed every 18 weeks. More frequent assessments were no longer required after assessment of the primary endpoint PFS. Central independent review of tumour imaging was stopped after database lock for the analysis of OS. Central independent review was no longer needed as the primary endpoint PFS had been assessed and reported. Completion of HRQOL questionnaires was no longer requested after database lock for the analysis of OS. Sufficient HRQOL data had been collected for the analysis. Patients could move onto an alternative supply of Afatinib after database lock for the analysis of OS, as Afatinib had been approved for use in patients with EGFR mutation positive Non-Small Cell Lung Cancer [NSCLC] in some countries by the time of the analysis. The follow-up and observation periods were amended to allow for completion of the trial. The follow-up period was to end on 31 Jan 2015 with the exception of FU visit 1 which was still required to assess Adverse Events [AEs].
04 December 2014	The follow-up and observation periods were amended to allow continued collection of data after 31 Jan 2015, until all patients had completed study treatment. Follow-up visit 1 was still required for all patients to assess for AEs.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported