



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 | v1 |
| This version publication date | 24 March 2018 |
| First version publication date | 24 March 2018 |

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 | 293 |

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/m² lyophilised powder as intravenous infusion after Cisplatin 75 mg/m² 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 | 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/m² solution for infusion as intravenous infusion on Day 1 of each 21-day treatment course up to 6 cycles.

| | |
|--|--|
| 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/m² lyophilised powder 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 |
| Other Adverse Event [AE] | 28 | 17 |
| Completed 6 courses of chemotherapy | - | 60 |
| Refusal to continue medication | 7 | 11 |
| Other not specified above | 5 | - |
| Progressive disease | 188 | 19 |
| Protocol deviation | 1 | 4 |
| 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: Baseline characteristics are based on patients who were randomised after successfully completing the screening period and received at least one dose of the trial medication.

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 occurred 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 | 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 [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 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.

| | |
|---|--|
| 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 |

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/Ci splat 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/Ci splat 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 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.

| | |
|-----------------------------------|------------------------|
| 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 |

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 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.

| | |
|---|--|
| 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 |

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: Only those arms for which the comparisons are presented in the clinical trial report thus, those that would yield meaningful results were reported.

| 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 subjects 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: Only those arms for which the comparisons are presented in the clinical trial report thus, those that would yield meaningful results were reported.

| 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: Only those arms for which the comparisons are presented in the clinical trial report thus, those that would yield meaningful results were reported.

| 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/m² lyophilised powder as intravenous infusion after Cisplatin 75 mg/m² 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) | 15 | 3 | |
| number of deaths resulting from adverse events | 4 | 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 | |
| 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 | |
| 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 | |
| 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 | |
| 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 | |
| General disorders and administration site conditions | | | |
| 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 | |

| | | | |
|---|-----------------|-----------------|--|
| 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 | |
| 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 | |
| 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 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 | |
| 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 | |
| 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 | |
| Investigations | | | |
| 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 | |
| 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 | |
| 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 | |
| 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 | |
| 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 | |
| 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 | |

| | | | |
|---|-----------------|-----------------|--|
| 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 | |
| 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 | |
| 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 | |
| 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 | |
| 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 | |
| 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 | |
| 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 | |

| | | | |
|---|-----------------|-----------------|--|
| 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 | |
| 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 | |
| Metabolism and nutrition disorders | | | |
| 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 | |
| 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 | |
| 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 | |

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 | | | |
| Asthenia | | | |
| subjects affected / exposed | 16 / 229 (6.99%) | 14 / 111 (12.61%) | |
| occurrences (all) | 21 | 17 | |
| Chest pain | | | |
| subjects affected / exposed | 16 / 229 (6.99%) | 14 / 111 (12.61%) | |
| occurrences (all) | 19 | 15 | |
| 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 | |

| | | | |
|--|--------------------------|-------------------------|--|
| Mucosal inflammation subjects affected / exposed occurrences (all) | 67 / 229 (29.26%) 110 | 5 / 111 (4.50%) 6 | |
| Oedema subjects affected / exposed occurrences (all) | 7 / 229 (3.06%) 8 | 13 / 111 (11.71%) 27 | |
| Oedema peripheral subjects affected / exposed occurrences (all) | 17 / 229 (7.42%) 17 | 8 / 111 (7.21%) 10 | |
| Pyrexia subjects affected / exposed occurrences (all) | 28 / 229 (12.23%) 34 | 6 / 111 (5.41%) 7 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough subjects affected / exposed occurrences (all) | 39 / 229 (17.03%) 54 | 21 / 111 (18.92%) 23 | |
| Dyspnoea subjects affected / exposed occurrences (all) | 18 / 229 (7.86%) 19 | 12 / 111 (10.81%) 13 | |
| Epistaxis subjects affected / exposed occurrences (all) | 41 / 229 (17.90%) 52 | 1 / 111 (0.90%) 1 | |
| Hiccups subjects affected / exposed occurrences (all) | 5 / 229 (2.18%) 5 | 10 / 111 (9.01%) 21 | |
| Nasal inflammation subjects affected / exposed occurrences (all) | 15 / 229 (6.55%) 16 | 0 / 111 (0.00%) 0 | |
| Oropharyngeal pain subjects affected / exposed occurrences (all) | 13 / 229 (5.68%) 17 | 3 / 111 (2.70%) 3 | |
| Rhinorrhoea subjects affected / exposed occurrences (all) | 16 / 229 (6.99%) 21 | 7 / 111 (6.31%) 9 | |
| Psychiatric disorders | | | |

| | | | |
|--|-------------------------|-------------------------|--|
| Insomnia subjects affected / exposed occurrences (all) | 37 / 229 (16.16%) 53 | 10 / 111 (9.01%) 10 | |
| Investigations | | | |
| Alanine aminotransferase increased subjects affected / exposed occurrences (all) | 27 / 229 (11.79%) 43 | 3 / 111 (2.70%) 5 | |
| Aspartate aminotransferase increased subjects affected / exposed occurrences (all) | 22 / 229 (9.61%) 32 | 1 / 111 (0.90%) 3 | |
| Blood creatinine increased subjects affected / exposed occurrences (all) | 5 / 229 (2.18%) 6 | 10 / 111 (9.01%) 16 | |
| Haemoglobin decreased subjects affected / exposed occurrences (all) | 3 / 229 (1.31%) 7 | 13 / 111 (11.71%) 20 | |
| Neutrophil count decreased subjects affected / exposed occurrences (all) | 1 / 229 (0.44%) 3 | 8 / 111 (7.21%) 19 | |
| Weight decreased subjects affected / exposed occurrences (all) | 44 / 229 (19.21%) 59 | 16 / 111 (14.41%) 16 | |
| Nervous system disorders | | | |
| Dizziness subjects affected / exposed occurrences (all) | 28 / 229 (12.23%) 36 | 12 / 111 (10.81%) 16 | |
| Dysgeusia subjects affected / exposed occurrences (all) | 18 / 229 (7.86%) 20 | 9 / 111 (8.11%) 9 | |
| Headache subjects affected / exposed occurrences (all) | 37 / 229 (16.16%) 55 | 19 / 111 (17.12%) 25 | |
| Blood and lymphatic system disorders | | | |
| Anaemia subjects affected / exposed occurrences (all) | 19 / 229 (8.30%) 24 | 29 / 111 (26.13%) 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 | |
| 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 |
| Dermatitis acneiform | | |
| subjects affected / exposed | 32 / 229 (13.97%) | 0 / 111 (0.00%) |
| occurrences (all) | 47 | 0 |
| Dry skin | | |
| subjects affected / exposed | 72 / 229 (31.44%) | 2 / 111 (1.80%) |
| occurrences (all) | 85 | 2 |
| Nail disorder | | |
| subjects affected / exposed | 14 / 229 (6.11%) | 0 / 111 (0.00%) |
| occurrences (all) | 14 | 0 |
| Palmar-plantar erythrodysesthesia syndrome | | |
| subjects affected / exposed | 19 / 229 (8.30%) | 0 / 111 (0.00%) |
| occurrences (all) | 44 | 0 |
| Pruritus | | |
| subjects affected / exposed | 50 / 229 (21.83%) | 1 / 111 (0.90%) |
| occurrences (all) | 66 | 1 |
| Rash | | |

| | | | |
|--|---------------------------|-------------------------|--|
| subjects affected / exposed occurrences (all) | 145 / 229 (63.32%) 243 | 11 / 111 (9.91%) 12 | |
| Skin exfoliation subjects affected / exposed occurrences (all) | 13 / 229 (5.68%) 14 | 0 / 111 (0.00%) 0 | |
| Skin fissures subjects affected / exposed occurrences (all) | 16 / 229 (6.99%) 20 | 0 / 111 (0.00%) 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia subjects affected / exposed occurrences (all) | 21 / 229 (9.17%) 27 | 6 / 111 (5.41%) 6 | |
| Back pain subjects affected / exposed occurrences (all) | 37 / 229 (16.16%) 44 | 13 / 111 (11.71%) 13 | |
| Muscle spasms subjects affected / exposed occurrences (all) | 20 / 229 (8.73%) 22 | 0 / 111 (0.00%) 0 | |
| Musculoskeletal pain subjects affected / exposed occurrences (all) | 21 / 229 (9.17%) 24 | 2 / 111 (1.80%) 2 | |
| Myalgia subjects affected / exposed occurrences (all) | 12 / 229 (5.24%) 18 | 1 / 111 (0.90%) 1 | |
| Pain in extremity subjects affected / exposed occurrences (all) | 20 / 229 (8.73%) 24 | 4 / 111 (3.60%) 5 | |
| Infections and infestations | | | |
| Conjunctivitis subjects affected / exposed occurrences (all) | 28 / 229 (12.23%) 35 | 3 / 111 (2.70%) 3 | |
| Cystitis subjects affected / exposed occurrences (all) | 15 / 229 (6.55%) 18 | 1 / 111 (0.90%) 1 | |
| Folliculitis | | | |

| | | | |
|---|---------------------------|--------------------------|--|
| subjects affected / exposed occurrences (all) | 12 / 229 (5.24%) 12 | 0 / 111 (0.00%) 0 | |
| Nasopharyngitis subjects affected / exposed occurrences (all) | 39 / 229 (17.03%) 67 | 9 / 111 (8.11%) 9 | |
| Paronychia subjects affected / exposed occurrences (all) | 132 / 229 (57.64%) 188 | 0 / 111 (0.00%) 0 | |
| Upper respiratory tract infection subjects affected / exposed occurrences (all) | 29 / 229 (12.66%) 47 | 4 / 111 (3.60%) 5 | |
| Urinary tract infection subjects affected / exposed occurrences (all) | 19 / 229 (8.30%) 26 | 5 / 111 (4.50%) 5 | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite subjects affected / exposed occurrences (all) | 70 / 229 (30.57%) 96 | 61 / 111 (54.95%) 111 | |
| Hypokalaemia subjects affected / exposed occurrences (all) | 21 / 229 (9.17%) 35 | 4 / 111 (3.60%) 8 | |
| Hyponatraemia subjects affected / exposed occurrences (all) | 4 / 229 (1.75%) 4 | 6 / 111 (5.41%) 12 | |

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 25°C 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