



Clinical trial results:

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

Summary

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

Results information

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

Trial information

Trial identification

| | |
|-----------------------|----------|
| Sponsor protocol code | 1200.125 |
|-----------------------|----------|

Additional study identifiers

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

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Boehringer Ingelheim |
| Sponsor organisation address | Binger Strasse 173, Ingelheim am Rhein, Germany, 55216 |
| Public contact | QRPE Processes and Systems Coordination, Clinical Trial Information Disclosure, Boehringer Ingelheim, 001 8002430127, clintriage.rdg@boehringer-ingelheim.com |
| Scientific contact | QRPE Processes and Systems Coordination, Clinical Trial Information Disclosure, Boehringer Ingelheim, 001 8002430127, clintriage.rdg@boehringer-ingelheim.com |

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

| | |
|--|------------------|
| Analysis stage | Final |
| Date of interim/final analysis | 20 February 2018 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 23 October 2013 |
| Global end of trial reached? | Yes |
| Global end of trial date | 27 December 2017 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

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

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

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

Notes:

Population of trial subjects

Subjects enrolled per country

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

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

Notes:

Subjects enrolled per age group

| | |
|---|-----|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 496 |
| From 65 to 84 years | 478 |
| 85 years and over | 3 |

Subject disposition

Recruitment

Recruitment details:

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

Pre-assignment

Screening details:

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

Period 1

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

Blinding implementation details:

This was an open-label trial.

Arms

| | |
|------------------------------|----------|
| Are arms mutually exclusive? | Yes |
| Arm title | Afatinib |

Arm description:

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

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

Dosage and administration details:

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

| | |
|------------------|-----------|
| Arm title | Erlotinib |
|------------------|-----------|

Arm description:

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

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

Dosage and administration details:

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

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

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

Notes:

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

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

Baseline characteristics

Reporting groups

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

| Reporting group values | Afatinib | Erlotinib | Total |
|------------------------|----------|-----------|-------|
| Number of subjects | 398 | 397 | 795 |
| Age categorical | | | |
| Units: Subjects | | | |

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

End points

End points reporting groups

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

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

| | |
|--|---|
| End point title | Progression-free survival, based on central independent review as determined by Response Evaluation Criteria in Solid Tumours 1.1 |
| End point description: | |
| Progression Free Survival (PFS) was defined as the time from randomization to disease progression (or death if the patient died before progression) by central independent review according to Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1. RECIST is a set of published rules that define when tumors in cancer patients improve ("respond"), stay the same ("stabilize") or worsen ("progress") during treatment. Per RECIST v1.1 for target lesions and assessed by MRI: Complete Response (CR), Disappearance of all target lesions; Partial Response (PR), $\geq 30\%$ decrease in the sum of the longest diameter of target lesions; Overall Response (OR) = CR + PR. Randomized Set (RS): All patients who were randomized, regardless of whether they received investigational treatment. | |
| End point type | Primary |
| End point timeframe: | |
| First treatment administration up until cut off date of 02 March 2015 (up to 1058 days). | |

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

Notes:

[1] - RS

[2] - RS

Statistical analyses

| | |
|---|------------------------|
| Statistical analysis title | Statistical Analysis 1 |
| Statistical analysis description: | |
| A Cox proportional hazards model without the randomization stratification variable was used for each subgroup category, along with the corresponding log-rank test. | |
| Comparison groups | Erlotinib v Afatinib |

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

Notes:

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

Secondary: Overall Survival

| | |
|---|------------------|
| End point title | Overall Survival |
| End point description: | |
| Overall Survival is defined as the time from randomisation to death. It was a key secondary endpoint. | |
| End point type | Secondary |
| End point timeframe: | |
| First treatment administration up until cut off date of 27 Dec 2017 (up to 2089 days). | |

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

Notes:

[4] - RS

[5] - RS

Statistical analyses

| | |
|--|-------------------------|
| Statistical analysis title | Statistical Analysis 1 |
| Statistical analysis description: | |
| A Cox proportional-hazards model, stratified by race, was used to estimate the hazard ratio and 95% confidence interval (CI) between the two treatment groups. | |
| Comparison groups | Afatinib v Erlotinib |
| Number of subjects included in analysis | 795 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0193 ^[6] |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.841 |

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

Notes:

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

Secondary: Objective Response according to RECIST 1.1

| | |
|-----------------|--|
| End point title | Objective Response according to RECIST 1.1 |
|-----------------|--|

End point description:

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

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

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

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

Notes:

[7] - RS

[8] - RS

Statistical analyses

| | |
|----------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 1 |
|----------------------------|------------------------|

Statistical analysis description:

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

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

Secondary: Disease Control according to RECIST 1.1

| | |
|-----------------|---|
| End point title | Disease Control according to RECIST 1.1 |
|-----------------|---|

End point description:

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

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

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

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

Notes:

[9] - RS

[10] - RS

Statistical analyses

| | |
|----------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 1 |
|----------------------------|------------------------|

Statistical analysis description:

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

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

Secondary: Tumour Shrinkage

| | |
|-----------------|------------------|
| End point title | Tumour Shrinkage |
|-----------------|------------------|

End point description:

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

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

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

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

Notes:

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

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

Statistical analyses

| | |
|----------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 1 |
|----------------------------|------------------------|

Statistical analysis description:

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

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

Notes:

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

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

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

End point description:

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

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

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

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

Notes:

[14] - RS

[15] - RS

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

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

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

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

Notes:

[16] - RS

[17] - RS

Statistical analyses

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 1 |
|-----------------------------------|------------------------|

Statistical analysis description:

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

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

Notes:

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

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 2 |
|-----------------------------------|------------------------|

Statistical analysis description:

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

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

Notes:

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

| | |
|-----------------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 3 |
|-----------------------------------|------------------------|

Statistical analysis description:

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

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

Notes:

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

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

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

End point description:

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

Questionnaires have items relating to Cough, Dyspnoea and Pain. Overall Scores are transformed to a standardised scale of 0 to 100 with the larger value indicating a worse outcome. A change of (+/-) 10 points is considered to be relevant. The change in cough, dyspnea and pain will be assessed using a mixed effects growth curve model with the average profile over time for each endpoint described by a piecewise linear model (presented as post baseline in data table). Post-baseline mean is adjusted for baseline and race.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

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

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

Notes:

[21] - RS

[22] - RS

Statistical analyses

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

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

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

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

Adverse events

Adverse events information

Timeframe for reporting adverse events:

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

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 20.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|-----------|
| Reporting group title | Erlotinib |
|-----------------------|-----------|

Reporting group description:

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

| | |
|-----------------------|----------|
| Reporting group title | Afatinib |
|-----------------------|----------|

Reporting group description:

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

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

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported