



Clinical trial results:

A Randomized, Double-Blind, Placebo-Controlled, Phase III Study of First-Line Maintenance Tarceva® Versus Tarceva at the Time of Disease Progression in Patients With Advanced Non-Small Cell Lung Cancer (NSCLC) Who Have Not Progressed Following 4 Cycles of Platinum-Based Chemotherapy

Summary

| | |
|--------------------------|----------------------------|
| EudraCT number | 2010-024468-16 |
| Trial protocol | SK HU CZ LV LT NL FR BG IT |
| Global end of trial date | 22 January 2016 |

Results information

| | |
|--------------------------------|--|
| Result version number | v2 |
| This version publication date | 06 July 2016 |
| First version publication date | 01 May 2016 |
| Version creation reason | • New data added to full data set Final CSR |

Trial information

Trial identification

| | |
|-----------------------|---------|
| Sponsor protocol code | BO25460 |
|-----------------------|---------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01328951 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | F. Hoffmann-La Roche AG |
| Sponsor organisation address | Grenzacherstrasse 124, Basel, Switzerland, CH-4070 |
| Public contact | Roche Trial Information Hotline, F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.com |
| Scientific contact | Roche Trial Information Hotline, F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.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 | 26 February 2016 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 22 January 2016 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The study evaluated the benefit of first-line maintenance erlotinib versus erlotinib at the time of disease progression in participants with advanced non-small cell lung cancer (NSCLC) who have not progressed following 4 cycles of platinum-based chemotherapy and whose tumor does not harbor an epidermal growth factor receptor (EGFR) activating mutation. The study included three periods: a Blinded Period (BP), an Open-Label Period (OLP) and a final Survival Follow-Up (SFU) period.

Protection of trial subjects:

The study was conducted in full conformance with the principles of the Declaration of Helsinki, or the laws and regulations of the country in which the research was conducted, whichever afforded greater protection to the participant. The study has fully adhered to the principles outlined in the Guideline for Good Clinical Practice (GCP) International Conference on Harmonisation (ICH) Tripartite Guideline (January 1997) or with local law if it afforded greater protection to the participant. For study sites in the European Union (EU)/European Economic Area (EEA), the study has also complied with the EU Clinical Trial Directive (2001/20/EC). For study sites in the United States (US) or under the US Investigational New Drug application (IND), the study has also adhered to the basic principles of GCP as outlined in the current version of 21 Code of Federal Regulations (CFR), subchapter D, part 312, "Responsibilities of Sponsors and Investigators"; part 50, "Protection of Human Subjects"; and part 56, "Institutional Review Boards". In other countries where Guidelines for GCP exist, the Sponsor and the investigators have strictly ensured adherence to the stated provision.

Background therapy: -

Evidence for comparator: -

| | |
|---|------------------|
| Actual start date of recruitment | 06 July 2011 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Safety, Efficacy |
| Long term follow-up duration | 51 Months |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-----------------------|
| Country: Number of subjects enrolled | Canada: 4 |
| Country: Number of subjects enrolled | China: 61 |
| Country: Number of subjects enrolled | Korea, Republic of: 4 |
| Country: Number of subjects enrolled | Romania: 53 |
| Country: Number of subjects enrolled | Thailand: 54 |
| Country: Number of subjects enrolled | Taiwan: 18 |
| Country: Number of subjects enrolled | Ukraine: 87 |
| Country: Number of subjects enrolled | United States: 7 |
| Country: Number of subjects enrolled | South Africa: 30 |

| | |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | Brazil: 37 |
| Country: Number of subjects enrolled | Netherlands: 7 |
| Country: Number of subjects enrolled | Poland: 21 |
| Country: Number of subjects enrolled | Slovakia: 13 |
| Country: Number of subjects enrolled | Bulgaria: 80 |
| Country: Number of subjects enrolled | Czech Republic: 32 |
| Country: Number of subjects enrolled | France: 13 |
| Country: Number of subjects enrolled | Hungary: 44 |
| Country: Number of subjects enrolled | Italy: 43 |
| Country: Number of subjects enrolled | Latvia: 7 |
| Country: Number of subjects enrolled | Lithuania: 28 |
| Worldwide total number of subjects | 643 |
| EEA total number of subjects | 341 |

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) | 420 |
| From 65 to 84 years | 220 |
| 85 years and over | 3 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

The study consisted of three periods: a BP, an OLP, and final SFU. These periods were not necessarily sequential, because the OLP could be "skipped" in select participants. Therefore, the reasons for discontinuation are presented altogether within the Overall Study.

Period 1

| | |
|------------------------------|--------------------------------|
| Period 1 title | Overall Study (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator |

Blinding implementation details:

Participants received double-blinded treatment during the BP; however, open-label treatment was administered during the OLP.

Arms

| | |
|------------------------------|----------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Late Erlotinib |

Arm description:

Participants received blinded placebo tablets orally (PO) once daily during the BP in the maintenance setting until disease progression, death, or unacceptable toxicity. Those who demonstrated disease progression were unblinded and could receive second-line erlotinib tablets during the OLP as 150 milligrams (mg) PO once daily, provided by the Sponsor. This treatment continued until disease progression, death, or unacceptable toxicity. If disease progression or unacceptable toxicity occurred during the OLP, the participant entered a final SFU period. Participants could also enter the SFU period directly after the BP if they were unable to receive second-line treatment per protocol.

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

Dosage and administration details:

Placebo was administered as film-coated tablets PO once daily during the BP until disease progression, death, or unacceptable toxicity.

| | |
|--|--------------------|
| 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:

Erlotinib was administered during either the BP (for Early Erlotinib) or the OLP (for Late Erlotinib) as 150 mg PO once daily until disease progression, death, or unacceptable toxicity.

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

Arm description:

Participants received blinded erlotinib tablets, 150 mg PO once daily during the BP in the maintenance setting until disease progression, death, or unacceptable toxicity. Those who demonstrated disease progression were unblinded and could receive an approved second-line therapy (but not EGFR targeted therapies) or best supportive care (BSC) as chosen by the investigator during the OLP. This treatment continued until disease progression, death, or unacceptable toxicity. If disease progression or

unacceptable toxicity occurred during the OLP, the participant entered a final SFU period. Participants could also enter the SFU period directly after the BP if they were unable to receive second-line treatment per protocol.

| | |
|--|--------------------|
| Arm type | Experimental |
| 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:

Erlotinib was administered during either the BP (for Early Erlotinib) or the OLP (for Late Erlotinib) as 150 mg PO once daily until disease progression, death, or unacceptable toxicity.

| Number of subjects in period 1 | Late Erlotinib | Early Erlotinib |
|---------------------------------------|----------------|-----------------|
| Started | 321 | 322 |
| Completed | 0 | 0 |
| Not completed | 321 | 322 |
| Disease progression | 17 | 14 |
| Death | 243 | 258 |
| Not specified | 11 | 6 |
| Adverse event | 2 | - |
| Lost to follow-up | 6 | 7 |
| Withdrawal by subject | 6 | 6 |
| Study closed by the Sponsor | 36 | 31 |

Baseline characteristics

Reporting groups

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

Reporting group description:

Participants received blinded placebo tablets orally (PO) once daily during the BP in the maintenance setting until disease progression, death, or unacceptable toxicity. Those who demonstrated disease progression were unblinded and could receive second-line erlotinib tablets during the OLP as 150 milligrams (mg) PO once daily, provided by the Sponsor. This treatment continued until disease progression, death, or unacceptable toxicity. If disease progression or unacceptable toxicity occurred during the OLP, the participant entered a final SFU period. Participants could also enter the SFU period directly after the BP if they were unable to receive second-line treatment per protocol.

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

Reporting group description:

Participants received blinded erlotinib tablets, 150 mg PO once daily during the BP in the maintenance setting until disease progression, death, or unacceptable toxicity. Those who demonstrated disease progression were unblinded and could receive an approved second-line therapy (but not EGFR targeted therapies) or best supportive care (BSC) as chosen by the investigator during the OLP. This treatment continued until disease progression, death, or unacceptable toxicity. If disease progression or unacceptable toxicity occurred during the OLP, the participant entered a final SFU period. Participants could also enter the SFU period directly after the BP if they were unable to receive second-line treatment per protocol.

| Reporting group values | Late Erlotinib | Early Erlotinib | Total |
|------------------------------------|----------------|-----------------|-------|
| Number of subjects | 321 | 322 | 643 |
| Age categorical Units: Subjects | | | |

| | | | |
|---|---------------|---------------|------------|
| Age continuous Units: years arithmetic mean standard deviation | 60.6 ± 9.1 | 60.8 ± 8.8 | - |
| Gender categorical Units: Subjects Female Male | 77 244 | 84 238 | 161 482 |

End points

End points reporting groups

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

Reporting group description:

Participants received blinded placebo tablets orally (PO) once daily during the BP in the maintenance setting until disease progression, death, or unacceptable toxicity. Those who demonstrated disease progression were unblinded and could receive second-line erlotinib tablets during the OLP as 150 milligrams (mg) PO once daily, provided by the Sponsor. This treatment continued until disease progression, death, or unacceptable toxicity. If disease progression or unacceptable toxicity occurred during the OLP, the participant entered a final SFU period. Participants could also enter the SFU period directly after the BP if they were unable to receive second-line treatment per protocol.

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

Reporting group description:

Participants received blinded erlotinib tablets, 150 mg PO once daily during the BP in the maintenance setting until disease progression, death, or unacceptable toxicity. Those who demonstrated disease progression were unblinded and could receive an approved second-line therapy (but not EGFR targeted therapies) or best supportive care (BSC) as chosen by the investigator during the OLP. This treatment continued until disease progression, death, or unacceptable toxicity. If disease progression or unacceptable toxicity occurred during the OLP, the participant entered a final SFU period. Participants could also enter the SFU period directly after the BP if they were unable to receive second-line treatment per protocol.

| | |
|----------------------------|--------------------------|
| Subject analysis set title | Placebo (Late Erlotinib) |
|----------------------------|--------------------------|

| | |
|---------------------------|---------------|
| Subject analysis set type | Full analysis |
|---------------------------|---------------|

Subject analysis set description:

Participants received blinded placebo tablets PO once daily during the BP in the maintenance setting until disease progression, death, or unacceptable toxicity.

| | |
|----------------------------|-----------------------------|
| Subject analysis set title | Erlotinib (Early Erlotinib) |
|----------------------------|-----------------------------|

| | |
|---------------------------|---------------|
| Subject analysis set type | Full analysis |
|---------------------------|---------------|

Subject analysis set description:

Participants received blinded erlotinib tablets, 150 mg PO once daily during the BP in the maintenance setting until disease progression, death, or unacceptable toxicity.

Primary: Percentage of Participants Who Died During the Overall Study

| | |
|-----------------|---|
| End point title | Percentage of Participants Who Died During the Overall Study ^[1] |
|-----------------|---|

End point description:

Participants were followed for survival until death or premature withdrawal. The percentage of participants who died during the Overall Study (BP, OLP, or SFU) was calculated. Intent-to-Treat (ITT) Population: All participants who were randomized to treatment.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Up to approximately 3.5 years (visits at Baseline and Weeks 6, 12, and 18 and every 12 weeks until/at disease progression during BP; per local standards during OLP; then every 12 weeks during SFU until death)

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: This endpoint reflects the percentage of participants with the event of interest. Statistical analysis was performed on the time-to-event endpoint.

| End point values | Late Erlotinib | Early Erlotinib | | |
|-----------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 321 | 322 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | 73.2 | 75.2 | | |

Statistical analyses

No statistical analyses for this end point

Primary: Overall Survival (OS) as Median Time to Event During the Overall Study

| | |
|-----------------|--|
| End point title | Overall Survival (OS) as Median Time to Event During the Overall Study |
|-----------------|--|

End point description:

Participants were followed for survival until death or premature withdrawal. OS was defined as the interval between date of randomization and date of death from any cause. Median time to event during the Overall Study (BP, OLP, or SFU) was estimated using the Kaplan-Meier method and expressed in months. ITT Population.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Up to approximately 3.5 years (visits at Baseline and Weeks 6, 12, and 18 and every 12 weeks until/at disease progression during BP; per local standards during OLP; then every 12 weeks during SFU until death)

| End point values | Late Erlotinib | Early Erlotinib | | |
|----------------------------------|----------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 321 | 322 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 9.46 (8.38 to 11.33) | 9.72 (8.57 to 11.17) | | |

Statistical analyses

| | |
|---|----------------------------------|
| Statistical analysis title | Unstratified Analysis |
| Comparison groups | Late Erlotinib v Early Erlotinib |
| Number of subjects included in analysis | 643 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[2] |
| P-value | = 0.8183 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.02 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.85 |
| upper limit | 1.22 |

Notes:

[2] - The HR and 95% confidence interval (CI) were estimated by Cox regression.

| | |
|--|----------------------------------|
| Statistical analysis title | Stratified Analysis |
| Statistical analysis description: Stratified according to tumor histology, stage of disease, objective response at Baseline, bevacizumab use, smoking status, and region of enrollment. | |
| Comparison groups | Late Erlotinib v Early Erlotinib |
| Number of subjects included in analysis | 643 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[3] |
| P-value | = 0.5256 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.07 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.87 |
| upper limit | 1.32 |

Notes:

[3] - The HR and 95% CI were estimated by Cox regression.

Primary: Percentage of Participants Event-Free (Alive) at 1 Year During the Overall Study

| | |
|---|--|
| End point title | Percentage of Participants Event-Free (Alive) at 1 Year During the Overall Study |
| End point description: Participants were followed for survival until death or premature withdrawal. The percentage of participants event-free (i.e., still alive) at 1 year during the Overall Study was calculated. ITT Population. | |
| End point type | Primary |
| End point timeframe: At 1 year | |

| | | | | |
|-----------------------------------|----------------------|----------------------|--|--|
| End point values | Late Erlotinib | Early Erlotinib | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 321 | 322 | | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | 41.75 (36.2 to 47.3) | 42.15 (36.6 to 47.7) | | |

Statistical analyses

| | |
|-----------------------------------|----------------------------------|
| Statistical analysis title | Difference in Event-Free Rate |
| Comparison groups | Late Erlotinib v Early Erlotinib |

| | |
|---|-------------------------------|
| Number of subjects included in analysis | 643 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.9207 |
| Method | Chi-squared |
| Parameter estimate | Difference in event-free rate |
| Point estimate | -0.4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -8.25 |
| upper limit | 7.45 |

Secondary: Percentage of Participants Who Died or Experienced Disease Progression During Blinded Treatment

| | |
|-----------------|---|
| End point title | Percentage of Participants Who Died or Experienced Disease Progression During Blinded Treatment |
|-----------------|---|

End point description:

Tumor response was evaluated using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Disease progression was defined as a greater than or equal to (\geq) 20 percent (%) and \geq 5-millimeter (mm) increase in the sum of target lesion diameters in reference to the smallest sum on study and/or substantial worsening in non-target disease. The percentage of participants who died or experienced disease progression during the BP was calculated. ITT Population.

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

End point timeframe:

Up to approximately 3.5 years (visits at Baseline and Weeks 6, 12, and 18 and every 12 weeks until/at disease progression during BP)

| End point values | Placebo (Late Erlotinib) | Erlotinib (Early Erlotinib) | | |
|-----------------------------------|--------------------------|-----------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 321 | 322 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | 95 | 94.1 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-Free Survival (PFS) as Median Time to Event During Blinded Treatment

| | |
|-----------------|--|
| End point title | Progression-Free Survival (PFS) as Median Time to Event During Blinded Treatment |
|-----------------|--|

End point description:

Tumor response was evaluated using RECIST version 1.1. Disease progression was defined as a \geq 20% and \geq 5-mm increase in the sum of target lesion diameters in reference to the smallest sum on study and/or substantial worsening in non-target disease. PFS was defined as the interval between date of

randomization and date of first documented death or disease progression. Median time to event during the BP was estimated using the Kaplan-Meier method and expressed in weeks. ITT Population.

| | |
|--|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Up to approximately 3.5 years (visits at Baseline and Weeks 6, 12, and 18 and every 12 weeks until/at disease progression during BP) | |

| End point values | Placebo (Late Erlotinib) | Erlotinib (Early Erlotinib) | | |
|-------------------------------|--------------------------|-----------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 321 | 322 | | |
| Units: weeks | | | | |
| median (full range (min-max)) | 12 (11.71 to 12.29) | 13 (12.14 to 17.43) | | |

Statistical analyses

| Statistical analysis title | Unstratified Analysis |
|---|--|
| Comparison groups | Placebo (Late Erlotinib) v Erlotinib (Early Erlotinib) |
| Number of subjects included in analysis | 643 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[4] |
| P-value | = 0.4759 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.94 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.8 |
| upper limit | 1.11 |

Notes:

[4] - The HR and 95% CI were estimated by Cox regression.

| Statistical analysis title | Stratified Analysis |
|---|--|
| Statistical analysis description: | |
| Stratified according to tumor histology, stage of disease, objective response at Baseline, bevacizumab use, smoking status, and region of enrollment. | |
| Comparison groups | Placebo (Late Erlotinib) v Erlotinib (Early Erlotinib) |
| Number of subjects included in analysis | 643 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[5] |
| P-value | = 0.1635 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.87 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.72 |
| upper limit | 1.06 |

Notes:

[5] - The HR and 95% CI were estimated by Cox regression.

Secondary: Percentage of Participants Event-Free (Alive and No Disease Progression) at 6 Months During Blinded Treatment

| | |
|-----------------|---|
| End point title | Percentage of Participants Event-Free (Alive and No Disease Progression) at 6 Months During Blinded Treatment |
|-----------------|---|

End point description:

Tumor response was evaluated using RECIST version 1.1. Disease progression was defined as a $\geq 20\%$ and ≥ 5 -mm increase in the sum of target lesion diameters in reference to the smallest sum on study and/or substantial worsening in non-target disease. The percentage of participants event-free (i.e., still alive and without disease progression) at 6 months during the BP was calculated. ITT Population.

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

End point timeframe:

At 6 months

| End point values | Placebo (Late Erlotinib) | Erlotinib (Early Erlotinib) | | |
|-----------------------------------|--------------------------|-----------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 321 | 322 | | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | 24.22 (19.5 to 28.94) | 27.11 (22.19 to 32.02) | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Difference in Event-Free Rate |
| Comparison groups | Placebo (Late Erlotinib) v Erlotinib (Early Erlotinib) |
| Number of subjects included in analysis | 643 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.4069 |
| Method | Chi-squared |
| Parameter estimate | Difference in event-free rate |
| Point estimate | -2.89 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -9.7 |
| upper limit | 3.93 |

Secondary: Percentage of Participants With Complete Response (CR) or Partial Response (PR) According to RECIST During Blinded Treatment

| | |
|-----------------|--|
| End point title | Percentage of Participants With Complete Response (CR) or Partial Response (PR) According to RECIST During Blinded Treatment |
|-----------------|--|

End point description:

Tumor response was evaluated using RECIST version 1.1. CR was defined as disappearance of all target and non-target lesions and short-axis reduction to less than (<) 10 mm of any pathological lymph nodes. PR was defined as a $\geq 30\%$ decrease in the sum of target lesion diameters in reference to the Baseline sum. The percentage of participants with a best overall response of either CR or PR (i.e., the objective response rate [ORR]) during the BP was calculated, and corresponding 95% CI was constructed using the Pearson-Clopper method. ITT Population.

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

End point timeframe:

Up to approximately 3.5 years (visits at Baseline and Weeks 6, 12, and 18 and every 12 weeks until/at disease progression during BP)

| End point values | Placebo (Late Erlotinib) | Erlotinib (Early Erlotinib) | | |
|-----------------------------------|--------------------------|-----------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 321 | 322 | | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | 3.7 (1.95 to 6.44) | 6.5 (4.08 to 9.8) | | |

Statistical analyses

| Statistical analysis title | Difference in Response Rate |
|---|--|
| Comparison groups | Placebo (Late Erlotinib) v Erlotinib (Early Erlotinib) |
| Number of subjects included in analysis | 643 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[6] |
| P-value | = 0.1097 |
| Method | Chi-squared |
| Parameter estimate | Difference in response rate |
| Point estimate | 2.78 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.78 |
| upper limit | 6.35 |

Notes:

[6] - The 95% CI for difference in response rates was constructed using the Anderson-Hauck method.

| Statistical analysis title | Odds Ratio |
|----------------------------|--|
| Comparison groups | Placebo (Late Erlotinib) v Erlotinib (Early Erlotinib) |

| | |
|---|----------------------|
| Number of subjects included in analysis | 643 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[7] |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.8 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.87 |
| upper limit | 3.72 |

Notes:

[7] - The 95% CI for OR was constructed using the Wald method.

Secondary: Percentage of Participants by Best Overall Response According to RECIST During Blinded Treatment

| | |
|-----------------|--|
| End point title | Percentage of Participants by Best Overall Response According to RECIST During Blinded Treatment |
|-----------------|--|

End point description:

Tumor response was evaluated using RECIST version 1.1. CR was defined as disappearance of all target and non-target lesions and short-axis reduction to <10 mm of any pathological lymph nodes. PR was defined as a $\geq 30\%$ decrease in the sum of target lesion diameters in reference to the Baseline sum. Stable disease (SD) was defined as neither sufficient shrinkage in target lesions to qualify for PR nor sufficient growth to qualify for disease progression. Disease progression (progressive disease/PD) was defined as a $\geq 20\%$ and ≥ 5 -mm increase in the sum of target lesion diameters in reference to the smallest sum on study and/or substantial worsening in non-target disease. The percentage of participants with each level of best tumor response during the BP was calculated, and corresponding 95% CI was constructed using the Pearson-Clopper method. ITT Population.

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

End point timeframe:

Up to approximately 3.5 years (visits at Baseline and Weeks 6, 12, and 18 and every 12 weeks until/at disease progression during BP)

| End point values | Placebo (Late Erlotinib) | Erlotinib (Early Erlotinib) | | |
|-----------------------------------|--------------------------|-----------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 321 | 322 | | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | | | | |
| CR | 0.6 (0.08 to 2.23) | 0.9 (0.19 to 2.7) | | |
| PR | 3.1 (1.5 to 5.65) | 5.6 (3.35 to 8.69) | | |
| SD | 55.5 (49.83 to 60.97) | 54.7 (49.04 to 60.19) | | |
| PD | 38.6 (33.27 to 44.2) | 32.3 (27.22 to 37.71) | | |
| Missing | 2.2 (0.88 to 4.44) | 6.5 (4.08 to 9.8) | | |

Statistical analyses

Secondary: Percentage of Participants With CR, PR, or SD According to RECIST During Blinded Treatment

| | |
|-----------------|--|
| End point title | Percentage of Participants With CR, PR, or SD According to RECIST During Blinded Treatment |
|-----------------|--|

End point description:

Tumor response was evaluated using RECIST version 1.1. CR was defined as disappearance of all target and non-target lesions and short-axis reduction to <10 mm of any pathological lymph nodes. PR was defined as a $\geq 30\%$ decrease in the sum of target lesion diameters in reference to the Baseline sum. SD was defined as neither sufficient shrinkage in target lesions to qualify for PR nor sufficient growth to qualify for disease progression. The percentage of participants with a best overall response of CR, PR, or SD (i.e., the disease control rate [DCR]) during the BP was calculated, and corresponding 95% CI was constructed using the Pearson-Clopper method. ITT Population.

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

End point timeframe:

Up to approximately 3.5 years (visits at Baseline and Weeks 6, 12, and 18 and every 12 weeks until/at disease progression during BP)

| End point values | Placebo (Late Erlotinib) | Erlotinib (Early Erlotinib) | | |
|-----------------------------------|--------------------------|-----------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 321 | 322 | | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | 59.2 (53.59 to 64.62) | 61.2 (55.62 to 66.53) | | |

Statistical analyses

| Statistical analysis title | Difference in Response Rate |
|---|--|
| Comparison groups | Placebo (Late Erlotinib) v Erlotinib (Early Erlotinib) |
| Number of subjects included in analysis | 643 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[8] |
| P-value | = 0.6062 |
| Method | Chi-squared |
| Parameter estimate | Difference in response rate |
| Point estimate | 1.99 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -5.74 |
| upper limit | 9.72 |

Notes:

[8] - The 95% CI for difference in response rates was constructed using the Anderson-Hauck method.

| Statistical analysis title | Odds Ratio |
|----------------------------|--|
| Comparison groups | Placebo (Late Erlotinib) v Erlotinib (Early Erlotinib) |

| | |
|---|----------------------|
| Number of subjects included in analysis | 643 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[9] |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.09 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.79 |
| upper limit | 1.49 |

Notes:

[9] - The 95% CI for OR was constructed using the Wald method.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to approximately 4.5 years (visits at Baseline and Weeks 6, 12, and 18 and every 12 weeks until disease progression, death, or unacceptable toxicity during BP; per local standards and 28 days after last visit during OLP)

Adverse event reporting additional description:

Safety Population: All participants who received at least one dose of study treatment, according to the drug actually received. Only serious adverse events (AEs) were collected during OLP. Therefore, the numbers of subjects affected have been entered as 0 under "Non-Serious Adverse Events" with one exception (see "Rash").

| | |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 18.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|--------------------------|
| Reporting group title | Placebo (Late Erlotinib) |
|-----------------------|--------------------------|

Reporting group description:

Participants received blinded placebo tablets PO once daily during the BP in the maintenance setting until disease progression, death, or unacceptable toxicity.

| | |
|-----------------------|--|
| Reporting group title | Second-Line Erlotinib (Late Erlotinib) |
|-----------------------|--|

Reporting group description:

Participants who received blinded placebo and who demonstrated disease progression were unblinded and could receive second-line erlotinib as 150-mg tablets PO once daily, provided by the Sponsor. This treatment continued during the OLP until disease progression, death, or unacceptable toxicity.

| | |
|-----------------------|--|
| Reporting group title | Second-Line Chemotherapy (Early Erlotinib) |
|-----------------------|--|

Reporting group description:

Participants who received blinded erlotinib and who demonstrated disease progression were unblinded and could receive an approved second-line therapy (but not EGFR targeted therapies) or BSC as chosen by the investigator. This treatment continued during the OLP until disease progression, death, or unacceptable toxicity.

| | |
|-----------------------|-----------------------------|
| Reporting group title | Erlotinib (Early Erlotinib) |
|-----------------------|-----------------------------|

Reporting group description:

Participants received blinded erlotinib tablets, 150 mg PO once daily during the BP in the maintenance setting until disease progression, death, or unacceptable toxicity.

| Serious adverse events | Placebo (Late Erlotinib) | Second-Line Erlotinib (Late Erlotinib) | Second-Line Chemotherapy (Early Erlotinib) |
|---|--------------------------|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 27 / 319 (8.46%) | 23 / 248 (9.27%) | 8 / 162 (4.94%) |
| number of deaths (all causes) | 11 | 51 | 31 |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Meningeal neoplasm | | | |

| | | | |
|--|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 319 (0.00%) | 1 / 248 (0.40%) | 0 / 162 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 1 / 319 (0.31%) | 0 / 248 (0.00%) | 1 / 162 (0.62%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypotension | | | |
| subjects affected / exposed | 1 / 319 (0.31%) | 0 / 248 (0.00%) | 0 / 162 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Peripheral ischaemia | | | |
| subjects affected / exposed | 0 / 319 (0.00%) | 1 / 248 (0.40%) | 0 / 162 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Superior vena cava syndrome | | | |
| subjects affected / exposed | 1 / 319 (0.31%) | 0 / 248 (0.00%) | 0 / 162 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Thrombosis | | | |
| subjects affected / exposed | 1 / 319 (0.31%) | 0 / 248 (0.00%) | 0 / 162 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Surgical and medical procedures | | | |
| Finger amputation | | | |
| subjects affected / exposed | 0 / 319 (0.00%) | 0 / 248 (0.00%) | 0 / 162 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 1 / 319 (0.31%) | 1 / 248 (0.40%) | 0 / 162 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|-----------------|-----------------|-----------------|
| Death | | | |
| subjects affected / exposed | 0 / 319 (0.00%) | 1 / 248 (0.40%) | 0 / 162 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Fatigue | | | |
| subjects affected / exposed | 2 / 319 (0.63%) | 0 / 248 (0.00%) | 0 / 162 (0.00%) |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyperthermia | | | |
| subjects affected / exposed | 0 / 319 (0.00%) | 0 / 248 (0.00%) | 1 / 162 (0.62%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Impaired healing | | | |
| subjects affected / exposed | 0 / 319 (0.00%) | 1 / 248 (0.40%) | 0 / 162 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Perforated ulcer | | | |
| subjects affected / exposed | 0 / 319 (0.00%) | 1 / 248 (0.40%) | 0 / 162 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pyrexia | | | |
| subjects affected / exposed | 0 / 319 (0.00%) | 1 / 248 (0.40%) | 0 / 162 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Pneumonia aspiration | | | |
| subjects affected / exposed | 0 / 319 (0.00%) | 1 / 248 (0.40%) | 0 / 162 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Chronic obstructive pulmonary disease | | | |
| subjects affected / exposed | 3 / 319 (0.94%) | 0 / 248 (0.00%) | 0 / 162 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|-----------------|-----------------|-----------------|
| Dyspnoea | | | |
| subjects affected / exposed | 0 / 319 (0.00%) | 3 / 248 (1.21%) | 1 / 162 (0.62%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 3 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Haemoptysis | | | |
| subjects affected / exposed | 0 / 319 (0.00%) | 1 / 248 (0.40%) | 0 / 162 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Interstitial lung disease | | | |
| subjects affected / exposed | 0 / 319 (0.00%) | 0 / 248 (0.00%) | 0 / 162 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pleural effusion | | | |
| subjects affected / exposed | 0 / 319 (0.00%) | 1 / 248 (0.40%) | 0 / 162 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pleuritic pain | | | |
| subjects affected / exposed | 1 / 319 (0.31%) | 0 / 248 (0.00%) | 0 / 162 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary embolism | | | |
| subjects affected / exposed | 0 / 319 (0.00%) | 0 / 248 (0.00%) | 0 / 162 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory failure | | | |
| subjects affected / exposed | 1 / 319 (0.31%) | 0 / 248 (0.00%) | 0 / 162 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Psychiatric disorders | | | |
| Confusional state | | | |
| subjects affected / exposed | 0 / 319 (0.00%) | 0 / 248 (0.00%) | 0 / 162 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Depression | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 319 (0.00%) | 0 / 248 (0.00%) | 0 / 162 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| Spinal compression fracture | | | |
| subjects affected / exposed | 1 / 319 (0.31%) | 0 / 248 (0.00%) | 0 / 162 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Subdural haematoma | | | |
| subjects affected / exposed | 0 / 319 (0.00%) | 0 / 248 (0.00%) | 0 / 162 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tracheal obstruction | | | |
| subjects affected / exposed | 1 / 319 (0.31%) | 0 / 248 (0.00%) | 0 / 162 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Femur fracture | | | |
| subjects affected / exposed | 1 / 319 (0.31%) | 0 / 248 (0.00%) | 0 / 162 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fracture | | | |
| subjects affected / exposed | 0 / 319 (0.00%) | 0 / 248 (0.00%) | 0 / 162 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hip fracture | | | |
| subjects affected / exposed | 1 / 319 (0.31%) | 0 / 248 (0.00%) | 0 / 162 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ilium fracture | | | |
| subjects affected / exposed | 1 / 319 (0.31%) | 0 / 248 (0.00%) | 0 / 162 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Limb injury | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 319 (0.00%) | 0 / 248 (0.00%) | 0 / 162 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 0 / 319 (0.00%) | 1 / 248 (0.40%) | 0 / 162 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Arrhythmia | | | |
| subjects affected / exposed | 0 / 319 (0.00%) | 1 / 248 (0.40%) | 0 / 162 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Atrial fibrillation | | | |
| subjects affected / exposed | 0 / 319 (0.00%) | 0 / 248 (0.00%) | 1 / 162 (0.62%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac failure | | | |
| subjects affected / exposed | 0 / 319 (0.00%) | 1 / 248 (0.40%) | 0 / 162 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| Cardio-respiratory arrest | | | |
| subjects affected / exposed | 0 / 319 (0.00%) | 0 / 248 (0.00%) | 0 / 162 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiopulmonary failure | | | |
| subjects affected / exposed | 0 / 319 (0.00%) | 0 / 248 (0.00%) | 0 / 162 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Myocardial infarction | | | |
| subjects affected / exposed | 0 / 319 (0.00%) | 0 / 248 (0.00%) | 0 / 162 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pericardial effusion | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 319 (0.31%) | 0 / 248 (0.00%) | 0 / 162 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ventricular extrasystoles | | | |
| subjects affected / exposed | 0 / 319 (0.00%) | 0 / 248 (0.00%) | 0 / 162 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Cerebral ischaemia | | | |
| subjects affected / exposed | 1 / 319 (0.31%) | 0 / 248 (0.00%) | 0 / 162 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 0 / 319 (0.00%) | 0 / 248 (0.00%) | 0 / 162 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dizziness | | | |
| subjects affected / exposed | 0 / 319 (0.00%) | 0 / 248 (0.00%) | 0 / 162 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hydrocephalus | | | |
| subjects affected / exposed | 1 / 319 (0.31%) | 0 / 248 (0.00%) | 0 / 162 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Hypoglycaemic coma | | | |
| subjects affected / exposed | 0 / 319 (0.00%) | 0 / 248 (0.00%) | 0 / 162 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Paraparesis | | | |
| subjects affected / exposed | 1 / 319 (0.31%) | 0 / 248 (0.00%) | 0 / 162 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Syncope | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 319 (0.00%) | 0 / 248 (0.00%) | 0 / 162 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 1 / 319 (0.31%) | 1 / 248 (0.40%) | 0 / 162 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Leukopenia | | | |
| subjects affected / exposed | 0 / 319 (0.00%) | 0 / 248 (0.00%) | 1 / 162 (0.62%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Neutropenia | | | |
| subjects affected / exposed | 0 / 319 (0.00%) | 0 / 248 (0.00%) | 1 / 162 (0.62%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Eye disorders | | | |
| Retinal artery occlusion | | | |
| subjects affected / exposed | 0 / 319 (0.00%) | 1 / 248 (0.40%) | 0 / 162 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Gastric ulcer | | | |
| subjects affected / exposed | 0 / 319 (0.00%) | 2 / 248 (0.81%) | 0 / 162 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastritis erosive | | | |
| subjects affected / exposed | 0 / 319 (0.00%) | 0 / 248 (0.00%) | 0 / 162 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemorrhoids thrombosed | | | |
| subjects affected / exposed | 1 / 319 (0.31%) | 0 / 248 (0.00%) | 0 / 162 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|-----------------|-----------------|-----------------|
| Nausea | | | |
| subjects affected / exposed | 0 / 319 (0.00%) | 0 / 248 (0.00%) | 0 / 162 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vomiting | | | |
| subjects affected / exposed | 0 / 319 (0.00%) | 0 / 248 (0.00%) | 0 / 162 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diarrhoea | | | |
| subjects affected / exposed | 0 / 319 (0.00%) | 1 / 248 (0.40%) | 0 / 162 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| Jaundice | | | |
| subjects affected / exposed | 0 / 319 (0.00%) | 1 / 248 (0.40%) | 0 / 162 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| Liver injury | | | |
| subjects affected / exposed | 0 / 319 (0.00%) | 1 / 248 (0.40%) | 0 / 162 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skin and subcutaneous tissue disorders | | | |
| Rash | | | |
| subjects affected / exposed | 0 / 319 (0.00%) | 1 / 248 (0.40%) | 0 / 162 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skin mass | | | |
| subjects affected / exposed | 0 / 319 (0.00%) | 0 / 248 (0.00%) | 0 / 162 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 319 (0.31%) | 0 / 248 (0.00%) | 1 / 162 (0.62%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary retention | | | |
| subjects affected / exposed | 1 / 319 (0.31%) | 0 / 248 (0.00%) | 0 / 162 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 0 / 319 (0.00%) | 1 / 248 (0.40%) | 0 / 162 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Osteonecrosis of jaw | | | |
| subjects affected / exposed | 0 / 319 (0.00%) | 0 / 248 (0.00%) | 0 / 162 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Abscess oral | | | |
| subjects affected / exposed | 1 / 319 (0.31%) | 0 / 248 (0.00%) | 0 / 162 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Impetigo | | | |
| subjects affected / exposed | 0 / 319 (0.00%) | 1 / 248 (0.40%) | 0 / 162 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lobar pneumonia | | | |
| subjects affected / exposed | 1 / 319 (0.31%) | 0 / 248 (0.00%) | 0 / 162 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Peritonitis | | | |
| subjects affected / exposed | 0 / 319 (0.00%) | 0 / 248 (0.00%) | 0 / 162 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|-----------------|-----------------|-----------------|
| Pharyngitis | | | |
| subjects affected / exposed | 0 / 319 (0.00%) | 0 / 248 (0.00%) | 0 / 162 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia | | | |
| subjects affected / exposed | 3 / 319 (0.94%) | 2 / 248 (0.81%) | 1 / 162 (0.62%) |
| occurrences causally related to treatment / all | 0 / 3 | 1 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 1 |
| Respiratory tract infection | | | |
| subjects affected / exposed | 0 / 319 (0.00%) | 0 / 248 (0.00%) | 0 / 162 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sepsis | | | |
| subjects affected / exposed | 0 / 319 (0.00%) | 0 / 248 (0.00%) | 1 / 162 (0.62%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Septic shock | | | |
| subjects affected / exposed | 1 / 319 (0.31%) | 0 / 248 (0.00%) | 0 / 162 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary tract infection | | | |
| subjects affected / exposed | 1 / 319 (0.31%) | 1 / 248 (0.40%) | 0 / 162 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Dehydration | | | |
| subjects affected / exposed | 1 / 319 (0.31%) | 1 / 248 (0.40%) | 0 / 162 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diabetes mellitus | | | |
| subjects affected / exposed | 1 / 319 (0.31%) | 0 / 248 (0.00%) | 0 / 162 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypokalaemia | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 319 (0.00%) | 0 / 248 (0.00%) | 1 / 162 (0.62%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolic acidosis | | | |
| subjects affected / exposed | 0 / 319 (0.00%) | 0 / 248 (0.00%) | 0 / 162 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| Serious adverse events | Erlotinib (Early Erlotinib) | | |
|---|-----------------------------|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 36 / 322 (11.18%) | | |
| number of deaths (all causes) | 25 | | |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Meningeal neoplasm | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vascular disorders | | | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypotension | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Peripheral ischaemia | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Superior vena cava syndrome | | | |

| | | | |
|--|-----------------|--|--|
| subjects affected / exposed | 0 / 322 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Thrombosis | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Surgical and medical procedures | | | |
| Finger amputation | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Death | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Fatigue | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hyperthermia | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Impaired healing | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | | |
|---|-----------------|--|--|--|
| Perforated ulcer | | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pyrexia | | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Respiratory, thoracic and mediastinal disorders | | | | |
| Pneumonia aspiration | | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| Chronic obstructive pulmonary disease | | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Dyspnoea | | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Haemoptysis | | | | |
| subjects affected / exposed | 2 / 322 (0.62%) | | | |
| occurrences causally related to treatment / all | 1 / 2 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| Interstitial lung disease | | | | |
| subjects affected / exposed | 2 / 322 (0.62%) | | | |
| occurrences causally related to treatment / all | 2 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pleural effusion | | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |

| | | | |
|---|-----------------|--|--|
| Pleuritic pain | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 4 / 322 (1.24%) | | |
| occurrences causally related to treatment / all | 0 / 4 | | |
| deaths causally related to treatment / all | 0 / 3 | | |
| Respiratory failure | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Psychiatric disorders | | | |
| Confusional state | | | |
| subjects affected / exposed | 2 / 322 (0.62%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Depression | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Injury, poisoning and procedural complications | | | |
| Spinal compression fracture | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Subdural haematoma | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Tracheal obstruction | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|---|-----------------|--|--|
| Femur fracture | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Fracture | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hip fracture | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ilium fracture | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Limb injury | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac disorders | | | |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Arrhythmia | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac failure | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 0 / 322 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardio-respiratory arrest | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Cardiopulmonary failure | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Myocardial infarction | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pericardial effusion | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ventricular extrasystoles | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nervous system disorders | | | |
| Cerebral ischaemia | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 2 / 322 (0.62%) | | |
| occurrences causally related to treatment / all | 1 / 2 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Dizziness | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 322 (0.31%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hydrocephalus | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypoglycaemic coma | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Paraparesis | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Syncope | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 2 / 322 (0.62%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Leukopenia | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Neutropenia | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Eye disorders | | | |

| | | | |
|---|-----------------|--|--|
| Retinal artery occlusion | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |
| Gastric ulcer | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastritis erosive | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Haemorrhoids thrombosed | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nausea | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vomiting | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Diarrhoea | | | |
| subjects affected / exposed | 2 / 322 (0.62%) | | |
| occurrences causally related to treatment / all | 1 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatobiliary disorders | | | |
| Jaundice | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|---|-----------------|--|--|
| Liver injury | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Skin and subcutaneous tissue disorders | | | |
| Rash | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Skin mass | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Urinary retention | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Osteonecrosis of jaw | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| Abscess oral | | | |

| | | | | |
|---|-----------------|--|--|--|
| subjects affected / exposed | 0 / 322 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Impetigo | | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Lobar pneumonia | | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Peritonitis | | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pharyngitis | | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pneumonia | | | | |
| subjects affected / exposed | 4 / 322 (1.24%) | | | |
| occurrences causally related to treatment / all | 1 / 6 | | | |
| deaths causally related to treatment / all | 0 / 2 | | | |
| Respiratory tract infection | | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Sepsis | | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Septic shock | | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 0 / 322 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Metabolism and nutrition disorders | | | |
| Dehydration | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Diabetes mellitus | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypokalaemia | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Metabolic acidosis | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |

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

| Non-serious adverse events | Placebo (Late Erlotinib) | Second-Line Erlotinib (Late Erlotinib) | Second-Line Chemotherapy (Early Erlotinib) |
|---|--------------------------|--|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 107 / 319 (33.54%) | 1 / 248 (0.40%) | 0 / 162 (0.00%) |
| General disorders and administration site conditions | | | |
| Chest pain | | | |

| | | | |
|---|--|-----------------|-----------------|
| subjects affected / exposed | 11 / 319 (3.45%) | 0 / 248 (0.00%) | 0 / 162 (0.00%) |
| occurrences (all) | 12 | 0 | 0 |
| Fatigue | | | |
| subjects affected / exposed | 20 / 319 (6.27%) | 0 / 248 (0.00%) | 0 / 162 (0.00%) |
| occurrences (all) | 21 | 0 | 0 |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 14 / 319 (4.39%) | 0 / 248 (0.00%) | 0 / 162 (0.00%) |
| occurrences (all) | 20 | 0 | 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 37 / 319 (11.60%) | 0 / 248 (0.00%) | 0 / 162 (0.00%) |
| occurrences (all) | 40 | 0 | 0 |
| Dyspnoea | | | |
| subjects affected / exposed | 23 / 319 (7.21%) | 0 / 248 (0.00%) | 0 / 162 (0.00%) |
| occurrences (all) | 25 | 0 | 0 |
| Skin and subcutaneous tissue disorders | | | |
| Pruritus | | | |
| subjects affected / exposed | 3 / 319 (0.94%) | 0 / 248 (0.00%) | 0 / 162 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| Rash | Additional description: Per protocol, only serious AEs were to be reported during the OLP. However, one non-serious AE was reported for a participant in the Second-Line Erlotinib (Late Erlotinib) arm and was therefore included in the analysis and coded with MedDRA (18.1). | | |
| subjects affected / exposed | 32 / 319 (10.03%) | 1 / 248 (0.40%) | 0 / 162 (0.00%) |
| occurrences (all) | 33 | 1 | 0 |
| Rash maculo-papular | | | |
| subjects affected / exposed | 3 / 319 (0.94%) | 0 / 248 (0.00%) | 0 / 162 (0.00%) |
| occurrences (all) | 4 | 0 | 0 |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 11 / 319 (3.45%) | 0 / 248 (0.00%) | 0 / 162 (0.00%) |
| occurrences (all) | 11 | 0 | 0 |

| | | | |
|---|-----------------------------|--|--|
| Non-serious adverse events | Erlotinib (Early Erlotinib) | | |
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 206 / 322 (63.98%) | | |
| General disorders and administration site conditions | | | |

| | | | |
|--|--|--|--|
| Chest pain subjects affected / exposed occurrences (all) | 17 / 322 (5.28%) 20 | | |
| Fatigue subjects affected / exposed occurrences (all) | 21 / 322 (6.52%) 21 | | |
| Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all) | 78 / 322 (24.22%) 102 | | |
| Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) Dyspnoea subjects affected / exposed occurrences (all) | 31 / 322 (9.63%) 33 27 / 322 (8.39%) 28 | | |
| Skin and subcutaneous tissue disorders Pruritus subjects affected / exposed occurrences (all) | 17 / 322 (5.28%) 20 | | |
| Rash | Additional description: Per protocol, only serious AEs were to be reported during the OLP. However, one non-serious AE was reported for a participant in the Second-Line Erlotinib (Late Erlotinib) arm and was therefore included in the analysis and coded with MedDRA (18.1). | | |
| subjects affected / exposed occurrences (all) | 127 / 322 (39.44%) 148 | | |
| Rash maculo-papular subjects affected / exposed occurrences (all) | 17 / 322 (5.28%) 21 | | |
| Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all) | 21 / 322 (6.52%) 24 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|---|
| 25 February 2013 | The protocol was amended primarily to allow a lower dose of carboplatin in combination with pemetrexed during the screening phase. Additional minor updates/clarifications were provided for several aspects of the protocol including adverse event reporting, dose modification, administration and unblinding, data collection, and recruitment. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

Following the final analysis, the study was closed and all remaining participants were withdrawn from the study and considered "Not Completed" (as presented under Subject Disposition). However, the overall status of study was confirmed as completed.

Notes: