



Clinical trial results:

A prospective double-blind randomized Phase III study of 300 mg vs. 150 mg erlotinib in current smokers with locally advanced or metastatic NSCLC in second-line setting after failure on chemotherapy

Summary

| | |
|--------------------------|------------------|
| EudraCT number | 2010-018476-24 |
| Trial protocol | NL ES DE DK |
| Global end of trial date | 07 February 2014 |

Results information

| | |
|--------------------------------|----------------|
| Result version number | v1 (current) |
| This version publication date | 25 April 2016 |
| First version publication date | 08 August 2015 |

Trial information

Trial identification

| | |
|-----------------------|---------|
| Sponsor protocol code | MO22162 |
|-----------------------|---------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01183858 |
| 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 | 29 October 2014 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 28 October 2013 |
| Global end of trial reached? | Yes |
| Global end of trial date | 07 February 2014 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To compare the efficacy of two dose levels of erlotinib (150 mg and 300 mg) on progression-free survival (PFS) in current smokers with stage IIIB/IV NSCLC after failure of first-line platinum-based chemotherapy.

Protection of trial subjects:

All study participants were required to read and sign an Informed Consent Form.

Patients received full supportive care throughout the study, including transfusion of blood products, treatment with antibiotics, anti-emetics, anti-diarrheals, and analgesics as appropriate.

Background therapy: -

Evidence for comparator: -

| | |
|---|-----------------|
| Actual start date of recruitment | 14 October 2010 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-----------------|
| Country: Number of subjects enrolled | Netherlands: 11 |
| Country: Number of subjects enrolled | Spain: 29 |
| Country: Number of subjects enrolled | Denmark: 12 |
| Country: Number of subjects enrolled | France: 19 |
| Country: Number of subjects enrolled | Germany: 97 |
| Country: Number of subjects enrolled | China: 95 |
| Country: Number of subjects enrolled | Egypt: 11 |
| Country: Number of subjects enrolled | Switzerland: 5 |
| Country: Number of subjects enrolled | Turkey: 34 |
| Worldwide total number of subjects | 313 |
| EEA total number of subjects | 168 |

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) | 217 |
| From 65 to 84 years | 96 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

315 participants were randomized. 313 participants were included in the Intent-to -treat (ITT) population. The ITT population excluded 2 randomized participants: 1 participant randomized in error and 1 participant with missing source data.

Pre-assignment period milestones

| | |
|------------------------------|--------------------|
| Number of subjects started | 315 ^[1] |
| Number of subjects completed | 313 |

Pre-assignment subject non-completion reasons

| | |
|----------------------------|---------------------------------|
| Reason: Number of subjects | Randomized in error: 1 |
| Reason: Number of subjects | Missing Source Documentation: 1 |

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same. Justification: The worldwide number of 313 participants is based on the Intent-to -treat (ITT) population. The ITT population excluded 2 randomized participants: 1 participant randomized in error and 1 participant with missing source data who are included in the Pre-Assignment period.

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, Monitor, Data analyst, Assessor |

Arms

| | |
|------------------------------|------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Erlotinib 150 mg |

Arm description:

Erlotinib 150 mg single daily oral dose until disease progression.

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

Dosage and administration details:

Single daily oral dose.

| | |
|------------------|------------------|
| Arm title | Erlotinib 300 mg |
|------------------|------------------|

Arm description:

Erlotinib 300 mg single daily oral dose until disease progression.

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

| | |
|--|-----------|
| Investigational medicinal product name | Erlotinib |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Single daily oral dose.

| Number of subjects in period 1 | Erlotinib 150 mg | Erlotinib 300 mg |
|---|------------------|------------------|
| Started | 154 | 159 |
| Intent-to-treat Population | 154 | 159 |
| Safety Population | 154 | 158 |
| Completed | 1 | 3 |
| Not completed | 153 | 156 |
| Discontinued Smoking | 3 | 1 |
| Withdrew Consent | 4 | 4 |
| Death not related to PD | 5 | 6 |
| Investigator's Decision | - | 3 |
| Refused Treatment | 1 | 4 |
| Progressive Disease | 112 | 115 |
| Other Protocol Violation | 1 | - |
| Death related to Progressive Disease (PD) | 4 | 5 |
| Adverse Event(s) | 14 | 11 |
| Administrative/Other | 6 | 6 |
| Lost to follow-up | 1 | 1 |
| Insufficient Therapeutic Response | 2 | - |

Baseline characteristics

Reporting groups

| | |
|-----------------------|------------------|
| Reporting group title | Erlotinib 150 mg |
|-----------------------|------------------|

Reporting group description:

Erlotinib 150 mg single daily oral dose until disease progression.

| | |
|-----------------------|------------------|
| Reporting group title | Erlotinib 300 mg |
|-----------------------|------------------|

Reporting group description:

Erlotinib 300 mg single daily oral dose until disease progression.

| Reporting group values | Erlotinib 150 mg | Erlotinib 300 mg | Total |
|---|------------------|------------------|-------|
| Number of subjects | 154 | 159 | 313 |
| Age categorical Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 106 | 111 | 217 |
| From 65-84 years | 48 | 48 | 96 |
| 85 years and over | 0 | 0 | 0 |
| Age continuous Units: years | | | |
| arithmetic mean | 59.7 | 59.2 | |
| standard deviation | ± 9.25 | ± 9.14 | - |
| Gender categorical Units: Subjects | | | |
| Female | 34 | 35 | 69 |
| Male | 120 | 124 | 244 |

End points

End points reporting groups

| | |
|--|------------------|
| Reporting group title | Erlotinib 150 mg |
| Reporting group description: Erlotinib 150 mg single daily oral dose until disease progression. | |
| Reporting group title | Erlotinib 300 mg |
| Reporting group description: Erlotinib 300 mg single daily oral dose until disease progression. | |

Primary: Progression-Free Survival (PFS)

| | |
|--|---------------------------------|
| End point title | Progression-Free Survival (PFS) |
| End point description: PFS is defined as the time from randomization to the date of first occurrence of disease progression or death. For target lesions, Progressive Disease (PD) was defined as at least a 20% increase in the sum of the longest diameter of target lesions, taking as reference the smallest sum of the longest diameter recorded since treatment started or the appearance of 1 or more new lesions. For non-target lesions, PD was defined as the appearance of 1 or more new lesions and/or unequivocal progression of existing non-target lesions Intent-to-treat Population included all randomized participants. 2 participants were excluded from analysis: 1 participant randomized in error and 1 participant with missing source data. | |
| End point type | Primary |
| End point timeframe: Randomization to Clinical Cutoff: 28 October 2013 (Up to 36.5 months) | |

| End point values | Erlotinib 150 mg | Erlotinib 300 mg | | |
|----------------------------------|-------------------|------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 154 | 159 | | |
| Units: weeks | | | | |
| median (confidence interval 95%) | 6.86 (6.29 to 12) | 7 (6.29 to 11) | | |

Statistical analyses

| | |
|---|-------------------------------------|
| Statistical analysis title | Statistical Analysis 1 |
| Comparison groups | Erlotinib 150 mg v Erlotinib 300 mg |
| Number of subjects included in analysis | 313 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.671 ^[1] |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.05 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.83 |
| upper limit | 1.33 |

Notes:

[1] - Unstratified analysis.

Primary: Progression-Free Survival at the End of Study

| | |
|-----------------|---|
| End point title | Progression-Free Survival at the End of Study |
|-----------------|---|

End point description:

PFS is defined as the time from randomization to the date of first occurrence of disease progression or death. For target lesions, Progressive Disease (PD) was defined as at least a 20% increase in the sum of the longest diameter of target lesions, taking as reference the smallest sum of the longest diameter recorded since treatment started or the appearance of 1 or more new lesions. For non-target lesions, PD was defined as the appearance of 1 or more new lesions and/or unequivocal progression of existing non-target lesions

Intent-to-treat Population included all randomized participants. 2 participants were excluded from analysis: 1 participant randomized in error and 1 participant with missing source data.

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

End point timeframe:

Randomization to End of Study: 14 October 2010 – 7 February 2014 (Up to 39.8 months)

| End point values | Erlotinib 150 mg | Erlotinib 300 mg | | |
|----------------------------------|-------------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 154 | 159 | | |
| Units: weeks | | | | |
| median (confidence interval 95%) | 6.86 (6.29 to 12) | 7 (6.29 to 11.43) | | |

Statistical analyses

| | |
|---|-------------------------------------|
| Statistical analysis title | Statistical Analysis 1 |
| Comparison groups | Erlotinib 300 mg v Erlotinib 150 mg |
| Number of subjects included in analysis | 313 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.625 ^[2] |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.06 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.84 |
| upper limit | 1.33 |

Notes:

[2] - Unstratified Analysis

Secondary: Overall Survival (OS)

| | |
|-----------------|-----------------------|
| End point title | Overall Survival (OS) |
|-----------------|-----------------------|

End point description:

OS defined as the time from randomization to the date of death due to any cause.

Intent-to-treat Population included all randomized participants. 2 participants were excluded from analysis: 1 participant randomized in error and 1 participant with missing source data.

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

End point timeframe:

Randomization to Clinical Cutoff: 28 October 2013 (Up to 36.5 months)

| End point values | Erlotinib 150 mg | Erlotinib 300 mg | | |
|----------------------------------|---------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 154 | 159 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 6.77 (5.65 to 8.77) | 6.83 (5.39 to 8.48) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Response Rate (ORR)

| | |
|-----------------|-----------------------------|
| End point title | Overall Response Rate (ORR) |
|-----------------|-----------------------------|

End point description:

Tumor response was assessed by the investigator using computer tomography (CT) or magnetic resonance imaging (MRI) scans according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. A participant was defined as a responder if they sustained a complete response (CR) or partial response (PR) for at least 4 weeks during randomized treatment (confirmed response). Patients with no tumor assessment after the start of study treatment were to be considered as non-responders. The percentage of participants in each best response category is presented.

Intent-to-treat Population included all randomized participants. 2 participants were excluded from analysis: 1 participant randomized in error and 1 participant with missing source data.

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

End point timeframe:

Randomization to Clinical Cutoff: 28 October 2013 (Up to 36.5 months)

| End point values | Erlotinib 150 mg | Erlotinib 300 mg | | |
|----------------------------------|---------------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 154 | 159 | | |
| Units: participants | | | | |
| number (confidence interval 95%) | | | | |
| Complete Response | 0 (0 to 0) | 0 (0 to 0) | | |
| Partial Response | 7.1 (3.6 to 12.4) | 2.5 (0.7 to 6.3) | | |
| Stable Disease | 33.1 (25.8 to 41.1) | 34 (26.6 to 41.9) | | |
| Progressive Disease | 44.8 (36.8 to 53) | 45.9 (38 to 54) | | |
| Not Evaluable | 14.9 (9.7 to 21.6) | 17.6 (12 to 24.4) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Control Rate (DCR)

| | |
|-----------------|----------------------------|
| End point title | Disease Control Rate (DCR) |
|-----------------|----------------------------|

End point description:

Tumor response was assessed by the investigator using computer tomography (CT) or magnetic resonance imaging (MRI) scans. Disease control rates were measured according to RECIST version 1.1 criteria. A participant was defined as having controlled disease if they sustained a Complete Response (CR) or Partial Response (PR) for at least 4 weeks during randomized treatment (confirmed response), or Stable Disease (SD) for at least 6 weeks. Patients with no tumor assessment after the start of study treatment were considered as having uncontrolled disease. The percentage of participants with Disease Control is presented.

Intent-to-treat Population included all randomized participants. 2 participants were excluded from analysis: 1 participant randomized in error and 1 participant with missing source data.

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

End point timeframe:

Randomization to Clinical Cutoff: 28 October 2013 (Up to 36.5 months)

| End point values | Erlotinib 150 mg | Erlotinib 300 mg | | |
|-----------------------------------|---------------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 154 | 159 | | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | 40.3 (32.4 to 48.5) | 36.5 (29 to 44.5) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Progression (TTP)

| | |
|-----------------|---------------------------|
| End point title | Time to Progression (TTP) |
|-----------------|---------------------------|

End point description:

Tumor response was assessed by the investigator using computer tomography (CT) or magnetic resonance imaging (MRI) scans according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 criteria. Time to progression (TTP) in weeks was defined as the time from randomization to the date of disease progression. Participants without event were censored at the date of the last tumor assessment when the patient was known to be progression free.

Intent-to-treat Population included all randomized participants. 2 participants were excluded from analysis: 1 participant randomized in error and 1 participant with missing source data.

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

End point timeframe:

Randomization to Clinical Cutoff: 28 October 2013 (Up to 36.5 months)

| End point values | Erlotinib 150 mg | Erlotinib 300 mg | | |
|----------------------------------|----------------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 154 | 159 | | |
| Units: weeks | | | | |
| median (confidence interval 95%) | 9.86 (6.43 to 12.14) | 9.14 (6.43 to 12) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Adverse Events (AEs) at the End of the Study

| | |
|-----------------|--|
| End point title | Number of Participants With Adverse Events (AEs) at the End of the Study |
|-----------------|--|

End point description:

An adverse event was considered any unfavorable and unintended sign, symptom, or disease associated with the use of the study drug, whether or not considered related to the study drug. Preexisting conditions that worsened during the study were reported as adverse events.

A serious adverse event is any experience that suggests a significant hazard, contraindication, side effect or precaution that: results in death, is life-threatening, required in-patient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect or is medically significant.

Adverse Events in the following categories are presented: Adverse Events, Serious Adverse Events, AEs leading to withdrawal from treatment and AEs leading to death.

Safety population included all randomized participants who received at least one dose of study drug.

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

End point timeframe:

Randomization to End of Study: 14 October 2010 – 7 February 2014 (Up to 39.8 months)

| End point values | Erlotinib 150 mg | Erlotinib 300 mg | | |
|-----------------------------|------------------|------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 154 | 158 | | |
| Units: participants | | | | |
| Adverse Events (AEs) | 130 | 141 | | |
| Serious Adverse Events | 29 | 35 | | |
| AEs leading to withdrawal | 18 | 15 | | |
| AEs leading to death | 12 | 13 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS) at the End of Study

| | |
|-----------------|---|
| End point title | Overall Survival (OS) at the End of Study |
|-----------------|---|

End point description:

OS defined as the time from randomization to the date of death due to any cause.
Intent-to-treat Population included all randomized participants. 2 participants were excluded from analysis: 1 participant randomized in error and 1 participant with missing source data.

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

End point timeframe:

Randomization to End of Study: 14 October 2010 – 7 February 2014 (Up to 39.8 months)

| End point values | Erlotinib 150 mg | Erlotinib 300 mg | | |
|----------------------------------|------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 154 | 159 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 7 (5.65 to 8.84) | 6.9 (5.62 to 8.64) | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Randomization to End of Study: 14 October 2010 – 7 February 2014 (Up to 39.8 months)

Adverse event reporting additional description:

Safety population: All participants who received at least 1 dose of study drug.

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 16.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|------------------|
| Reporting group title | Erlotinib 150 mg |
|-----------------------|------------------|

Reporting group description:

Erlotinib 150 mg single daily oral dose until disease progression.

| | |
|-----------------------|------------------|
| Reporting group title | Erlotinib 300 mg |
|-----------------------|------------------|

Reporting group description:

Erlotinib 300 mg single daily oral dose until disease progression.

| Serious adverse events | Erlotinib 150 mg | Erlotinib 300 mg | |
|---|-------------------|-------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 29 / 154 (18.83%) | 35 / 158 (22.15%) | |
| number of deaths (all causes) | 123 | 125 | |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Gastric cancer | | | |
| subjects affected / exposed | 1 / 154 (0.65%) | 0 / 158 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pericardial effusion malignant | | | |
| subjects affected / exposed | 1 / 154 (0.65%) | 0 / 158 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders | | | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 0 / 154 (0.00%) | 1 / 158 (0.63%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|--|-----------------|-----------------|--|
| Peripheral ischaemia | | | |
| subjects affected / exposed | 0 / 154 (0.00%) | 1 / 158 (0.63%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| General physical health deterioration | | | |
| subjects affected / exposed | 1 / 154 (0.65%) | 3 / 158 (1.90%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Fatigue | | | |
| subjects affected / exposed | 1 / 154 (0.65%) | 1 / 158 (0.63%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Death | | | |
| subjects affected / exposed | 1 / 154 (0.65%) | 0 / 158 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Mucosal inflammation | | | |
| subjects affected / exposed | 1 / 154 (0.65%) | 0 / 158 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sudden death | | | |
| subjects affected / exposed | 0 / 154 (0.00%) | 1 / 158 (0.63%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Dyspnoea | | | |
| subjects affected / exposed | 3 / 154 (1.95%) | 1 / 158 (0.63%) | |
| occurrences causally related to treatment / all | 1 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Respiratory failure | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 154 (0.00%) | 2 / 158 (1.27%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Acute respiratory failure | | | |
| subjects affected / exposed | 1 / 154 (0.65%) | 0 / 158 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Chronic obstructive pulmonary disease | | | |
| subjects affected / exposed | 1 / 154 (0.65%) | 0 / 158 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemoptysis | | | |
| subjects affected / exposed | 0 / 154 (0.00%) | 1 / 158 (0.63%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Hydropneumothorax | | | |
| subjects affected / exposed | 1 / 154 (0.65%) | 0 / 158 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonitis | | | |
| subjects affected / exposed | 0 / 154 (0.00%) | 1 / 158 (0.63%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumothorax | | | |
| subjects affected / exposed | 0 / 154 (0.00%) | 1 / 158 (0.63%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Pulmonary haemorrhage | | | |
| subjects affected / exposed | 0 / 154 (0.00%) | 1 / 158 (0.63%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Injury, poisoning and procedural complications | | | |

| | | | |
|---|-----------------|-----------------|--|
| Femur fracture | | | |
| subjects affected / exposed | 0 / 154 (0.00%) | 1 / 158 (0.63%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hip fracture | | | |
| subjects affected / exposed | 0 / 154 (0.00%) | 1 / 158 (0.63%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Overdose | | | |
| subjects affected / exposed | 1 / 154 (0.65%) | 0 / 158 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Myocardial infarction | | | |
| subjects affected / exposed | 1 / 154 (0.65%) | 3 / 158 (1.90%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 2 | |
| Arteriospasm coronary | | | |
| subjects affected / exposed | 0 / 154 (0.00%) | 1 / 158 (0.63%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac failure | | | |
| subjects affected / exposed | 1 / 154 (0.65%) | 0 / 158 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Intracardiac thrombus | | | |
| subjects affected / exposed | 0 / 154 (0.00%) | 1 / 158 (0.63%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Right ventricular failure | | | |
| subjects affected / exposed | 1 / 154 (0.65%) | 0 / 158 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Nervous system disorders | | | |

| | | | |
|---|-----------------|-----------------|--|
| Cerebral infarction | | | |
| subjects affected / exposed | 1 / 154 (0.65%) | 0 / 158 (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 | 0 / 154 (0.00%) | 1 / 158 (0.63%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Hypoxic-ischaemic encephalopathy | | | |
| subjects affected / exposed | 0 / 154 (0.00%) | 1 / 158 (0.63%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Ischaemic stroke | | | |
| subjects affected / exposed | 0 / 154 (0.00%) | 1 / 158 (0.63%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Neuralgia | | | |
| subjects affected / exposed | 0 / 154 (0.00%) | 1 / 158 (0.63%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Somnolence | | | |
| subjects affected / exposed | 1 / 154 (0.65%) | 0 / 158 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| Febrile neutropenia | | | |
| subjects affected / exposed | 1 / 154 (0.65%) | 0 / 158 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 1 / 154 (0.65%) | 2 / 158 (1.27%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| Haematemesis | | | |
| subjects affected / exposed | 1 / 154 (0.65%) | 1 / 158 (0.63%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Vomiting | | | |
| subjects affected / exposed | 0 / 154 (0.00%) | 2 / 158 (1.27%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Duodenal ulcer | | | |
| subjects affected / exposed | 0 / 154 (0.00%) | 1 / 158 (0.63%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Inguinal hernia | | | |
| subjects affected / exposed | 0 / 154 (0.00%) | 1 / 158 (0.63%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nausea | | | |
| subjects affected / exposed | 0 / 154 (0.00%) | 1 / 158 (0.63%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Stomatitis | | | |
| subjects affected / exposed | 0 / 154 (0.00%) | 1 / 158 (0.63%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Upper gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 0 / 154 (0.00%) | 1 / 158 (0.63%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Hepatic failure | | | |
| subjects affected / exposed | 1 / 154 (0.65%) | 0 / 158 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Renal and urinary disorders | | | |

| | | | |
|---|-----------------|-----------------|--|
| Renal failure | | | |
| subjects affected / exposed | 1 / 154 (0.65%) | 0 / 158 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Renal failure acute | | | |
| subjects affected / exposed | 1 / 154 (0.65%) | 0 / 158 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal failure chronic | | | |
| subjects affected / exposed | 1 / 154 (0.65%) | 0 / 158 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 1 / 154 (0.65%) | 1 / 158 (0.63%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Pneumonia | | | |
| subjects affected / exposed | 6 / 154 (3.90%) | 3 / 158 (1.90%) | |
| occurrences causally related to treatment / all | 0 / 7 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 3 | 0 / 0 | |
| Respiratory tract infection | | | |
| subjects affected / exposed | 0 / 154 (0.00%) | 3 / 158 (1.90%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Anal abscess | | | |
| subjects affected / exposed | 0 / 154 (0.00%) | 1 / 158 (0.63%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lower respiratory tract infection bacterial | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 154 (0.00%) | 1 / 158 (0.63%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lung infection | | | |
| subjects affected / exposed | 1 / 154 (0.65%) | 0 / 158 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Septic shock | | | |
| subjects affected / exposed | 1 / 154 (0.65%) | 0 / 158 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Dehydration | | | |
| subjects affected / exposed | 2 / 154 (1.30%) | 1 / 158 (0.63%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| Non-serious adverse events | Erlotinib 150 mg | Erlotinib 300 mg | |
|---|--------------------|--------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 115 / 154 (74.68%) | 128 / 158 (81.01%) | |
| Investigations | | | |
| Weight decreased | | | |
| subjects affected / exposed | 7 / 154 (4.55%) | 15 / 158 (9.49%) | |
| occurrences (all) | 7 | 16 | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 9 / 154 (5.84%) | 2 / 158 (1.27%) | |
| occurrences (all) | 9 | 2 | |
| General disorders and administration site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed | 21 / 154 (13.64%) | 26 / 158 (16.46%) | |
| occurrences (all) | 28 | 30 | |
| Chest pain | | | |

| | | | |
|---|-------------------------|-------------------------|--|
| subjects affected / exposed occurrences (all) | 7 / 154 (4.55%) 7 | 14 / 158 (8.86%) 18 | |
| Asthenia subjects affected / exposed occurrences (all) | 9 / 154 (5.84%) 10 | 12 / 158 (7.59%) 14 | |
| Pain subjects affected / exposed occurrences (all) | 8 / 154 (5.19%) 8 | 5 / 158 (3.16%) 5 | |
| Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all) | 6 / 154 (3.90%) 6 | 8 / 158 (5.06%) 8 | |
| Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all) | 29 / 154 (18.83%) 36 | 46 / 158 (29.11%) 56 | |
| Nausea subjects affected / exposed occurrences (all) | 20 / 154 (12.99%) 21 | 17 / 158 (10.76%) 19 | |
| Vomiting subjects affected / exposed occurrences (all) | 13 / 154 (8.44%) 14 | 14 / 158 (8.86%) 15 | |
| Constipation subjects affected / exposed occurrences (all) | 9 / 154 (5.84%) 9 | 11 / 158 (6.96%) 11 | |
| Dyspepsia subjects affected / exposed occurrences (all) | 3 / 154 (1.95%) 5 | 8 / 158 (5.06%) 8 | |
| Abdominal pain upper subjects affected / exposed occurrences (all) | 1 / 154 (0.65%) 1 | 8 / 158 (5.06%) 8 | |
| Respiratory, thoracic and mediastinal disorders Dyspnoea subjects affected / exposed occurrences (all) | 26 / 154 (16.88%) 29 | 19 / 158 (12.03%) 19 | |
| Cough | | | |

| | | | |
|--|-------------------------|-------------------------|--|
| subjects affected / exposed occurrences (all) | 23 / 154 (14.94%) 25 | 19 / 158 (12.03%) 25 | |
| Skin and subcutaneous tissue disorders | | | |
| Rash | | | |
| subjects affected / exposed | 43 / 154 (27.92%) | 75 / 158 (47.47%) | |
| occurrences (all) | 53 | 101 | |
| Dry skin | | | |
| subjects affected / exposed | 13 / 154 (8.44%) | 17 / 158 (10.76%) | |
| occurrences (all) | 14 | 19 | |
| Pruritus | | | |
| subjects affected / exposed | 8 / 154 (5.19%) | 16 / 158 (10.13%) | |
| occurrences (all) | 9 | 17 | |
| Dermatitis acneiform | | | |
| subjects affected / exposed | 11 / 154 (7.14%) | 9 / 158 (5.70%) | |
| occurrences (all) | 11 | 9 | |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 8 / 154 (5.19%) | 6 / 158 (3.80%) | |
| occurrences (all) | 11 | 6 | |
| Pain in extremity | | | |
| subjects affected / exposed | 3 / 154 (1.95%) | 8 / 158 (5.06%) | |
| occurrences (all) | 3 | 8 | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 26 / 154 (16.88%) | 32 / 158 (20.25%) | |
| occurrences (all) | 28 | 33 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|--------------|---|
| 05 May 2011 | <ul style="list-style-type: none">•Clarified exclusion criteria to allow the prior use of bevacizumab as standard first-line treatment for Non-small cell lung cancer (NSCLC).•Clarified exclusion criteria to exclude patients with previously diagnosed and treated brain metastases with symptomatic evidence.•Allowed screening evaluations to be performed on the same day as the patient's inclusion provided all the results were obtained prior to inclusion and visit descriptions were aligned for consistency with the laboratory manual, Interactive web response system (IWRS) Electronic case report form (eCRF).•Allowed the results of screening laboratory assessments done within 3 days prior to inclusion to be used for the Baseline laboratory assessment. |
| 09 July 2013 | <ul style="list-style-type: none">•The primary endpoint of Progression-free survival (PFS), as well as response, was updated to be solely based on the investigator-assessed response evaluation; an independent review committee was no longer used due to accumulating evidence pointing to limited value of independent reviews in double-blind, randomized clinical studies.•The protocol originally specified a randomized stratification by geographical region (Eastern Europe, Western Europe and Asia). However during the study only two strata were used (Europe and Asia) for randomization.•The original recruitment period was estimated to be approximately 18 months. Due to slower than expected recruitment, the recruitment period was changed so that it would be closed when approximately 300 patients had been randomized into the study.•This study was event-driven. The primary analysis was scheduled to be undertaken once approximately 277 PFS events (corresponding to the needed number of PFS events for the primary analysis) had occurred. Data were collected and queries answered until database lock, following the receipt of the 277th PFS event. Originally it was thought that this required number of events would be achieved approximately 6 months after the last patient was recruited; however as timing could not be predicted, this reference to the 6-month time frame was removed. Study treatment continued until disease progression, death, unacceptable toxicity or clinician/patient decision to stop study treatment. It was deemed to be likely that some patients would still be on study drug at the end of the study (upon database lock). Patients still receiving treatment were unblinded and patients who were receiving the experimental dose of erlotinib at the end of the study continued to be provided with erlotinib on an ongoing basis through clinical study supply, until disease progression, death, unacceptable toxicity or clinician/patient decision to stop this therapy. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported