



Clinical trial results:

A randomised, phase II trial to evaluate a treatment with Tyrosine Kinase Inhibitor of Epidermal Growth Factor (EGFR-TKI) versus EGFR-TKI associated with an anti-estrogen treatment (fulvestrant) in women with an advanced stage of non squamous non small cell lung cancer

Summary

| | |
|--------------------------|------------------|
| EudraCT number | 2011-003571-11 |
| Trial protocol | FR |
| Global end of trial date | 30 November 2018 |

Results information

| | |
|--------------------------------|------------------|
| Result version number | v1 (current) |
| This version publication date | 02 February 2023 |
| First version publication date | 02 February 2023 |

Trial information

Trial identification

| | |
|-----------------------|-----------|
| Sponsor protocol code | IFCT-1003 |
|-----------------------|-----------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01556191 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | IFCT |
| Sponsor organisation address | 10 rue de la Grange Batelière, Paris, France, 75009 |
| Public contact | IFCT, IFCT, 33 156811045, contact@ifct.fr |
| Scientific contact | IFCT, IFCT, 33 156811045, contact@ifct.fr |

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 | 01 May 2018 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 30 November 2018 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

3-months progression free survival for patient with EGFR mutation

9-months progression free survival for patient with EGFR wild type

Protection of trial subjects:

Algorithms for management of adverse events were provided in the protocol.

Background therapy: -

Evidence for comparator: -

| | |
|---|-------------|
| Actual start date of recruitment | 15 May 2012 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-------------|
| Country: Number of subjects enrolled | France: 379 |
| Worldwide total number of subjects | 379 |
| EEA total number of subjects | 379 |

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) | 177 |
| From 65 to 84 years | 196 |
| 85 years and over | 6 |

Subject disposition

Recruitment

Recruitment details:

379 patients included.

204 patients (gefitinib 104 and G+Fulvestrant 100) and 175 patients (erlotinib 87 and E+Fulvestrant 88) were enrolled in the EGFR mutated and EGFR-WT cohorts respectively.

Pre-assignment

Screening details:

Main inclusion criteria were histologically confirmed inoperable stage III or stage IV nonsquamous NSCLCs, the presence of at least one lesion that could be measured by a CT scan (RECIST v1.1), postmenopausal female (either >60 year or amenorrhea >12 months), with a World Health Organization performance index of 0, 1, or 2.

Period 1

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

Arms

| | |
|------------------------------|-------------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | A1 - EGFR mut Gefitinib |

Arm description:

EGFR mutated patients receiving Gefitinib.

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

Dosage and administration details:

Gefitinib is administered orally in a 250 mg tablet (single dose) / day

| | |
|------------------|-------------------------------------|
| Arm title | B1 - EGFR mut Gefitinib Fulvestrant |
|------------------|-------------------------------------|

Arm description:

EGFR mutated patients receiving Gefitinib + Fulvestrant

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

Dosage and administration details:

Gefitinib is administered orally in a 250 mg tablet (single dose) / day

| | |
|--|------------------------|
| Investigational medicinal product name | Fulvestrant |
| Investigational medicinal product code | |
| Other name | Faslodex |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Intramuscular use |

Dosage and administration details:

Prefilled syringe of 5 ml (250 mg of fulvestrant) :

Two slow, intramuscular injections (2 x 250 mg) by month with an additional 500 mg dose two weeks after the initial dose. 5 ml in each buttock with prefilled syringes.

| | |
|---|------------------------|
| Arm title | A2 - EGFR WT Erlotinib |
| Arm description: EGFR WT patients receiving Erlotinib. | |
| Arm type | Experimental |
| Investigational medicinal product name | Erlotinib |
| Investigational medicinal product code | |
| Other name | Tarceva |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Erlotinib is administered orally in a 150 mg tablet (also available in 25 and 100 mg), to be taken on an empty stomach (one hour before or two hours after eating) by day.

| | |
|--|------------------------------------|
| Arm title | B2 - EGFR WT Erlotinib Fulvestrant |
| Arm description: EGFR WT patients receiving Erlotinib + Fulvestrant | |
| Arm type | Experimental |
| Investigational medicinal product name | Erlotinib |
| Investigational medicinal product code | |
| Other name | Tarceva |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Erlotinib is administered orally in a 150 mg tablet (also available in 25 and 100 mg), to be taken on an empty stomach (one hour before or two hours after eating) by day.

| | |
|--|------------------------|
| Investigational medicinal product name | Fulvestrant |
| Investigational medicinal product code | |
| Other name | Faslodex |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Intramuscular use |

Dosage and administration details:

Prefilled syringe of 5 ml (250 mg of fulvestrant) :

Two slow, intramuscular injections (2 x 250 mg) by month with an additional 500 mg dose two weeks after the initial dose. 5 ml in each buttock with prefilled syringes.

| Number of subjects in period 1 | A1 - EGFR mut Gefitinib | B1 - EGFR mut Gefitinib Fulvestrant | A2 - EGFR WT Erlotinib |
|---------------------------------------|----------------------------|--|---------------------------|
| Started | 104 | 100 | 87 |
| Completed | 9 | 3 | 1 |
| Not completed | 95 | 97 | 86 |
| Patient's choice | 1 | 3 | 2 |
| Adverse event, non-fatal | 8 | 9 | 3 |
| Death | 3 | 3 | 5 |

| | | | |
|----------------------|----|----|----|
| Other | 7 | 5 | 3 |
| Intercurrent disease | - | - | - |
| Complication | - | 1 | - |
| Second cancer | - | 1 | - |
| Lack of efficacy | 76 | 75 | 73 |

| Number of subjects in period 1 | B2 - EGFR WT Erlotinib Fulvestrant |
|---------------------------------------|---------------------------------------|
| Started | 88 |
| Completed | 0 |
| Not completed | 88 |
| Patient's choice | - |
| Adverse event, non-fatal | 2 |
| Death | 4 |
| Other | 4 |
| Intercurrent disease | 1 |
| Complication | - |
| Second cancer | - |
| Lack of efficacy | 77 |

Baseline characteristics

Reporting groups

| | |
|---|-------------------------------------|
| Reporting group title | A1 - EGFR mut Gefitinib |
| Reporting group description: EGFR mutated patients receiving Gefitinib. | |
| Reporting group title | B1 - EGFR mut Gefitinib Fulvestrant |
| Reporting group description: EGFR mutated patients receiving Gefitinib + Fulvestrant | |
| Reporting group title | A2 - EGFR WT Erlotinib |
| Reporting group description: EGFR WT patients receiving Erlotinib. | |
| Reporting group title | B2 - EGFR WT Erlotinib Fulvestrant |
| Reporting group description: EGFR WT patients receiving Erlotinib + Fulvestrant | |

| Reporting group values | A1 - EGFR mut Gefitinib | B1 - EGFR mut Gefitinib Fulvestrant | A2 - EGFR WT Erlotinib |
|---|-------------------------|-------------------------------------|------------------------|
| Number of subjects | 104 | 100 | 87 |
| Age categorical | | | |
| Age distribution | | | |
| Units: Subjects | | | |
| Adults (18-64 years) | 34 | 38 | 47 |
| From 65-84 years | 69 | 58 | 39 |
| 85 years and over | 1 | 4 | 1 |
| Age continuous | | | |
| Units: years | | | |
| median | 67.71 | 68.30 | 64.56 |
| full range (min-max) | 49.5 to 89.1 | 50.1 to 90.9 | 43.6 to 85.4 |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 104 | 100 | 87 |
| Smoking population | | | |
| Number of smoking and non smoking patients | | | |
| Units: Subjects | | | |
| Smoker | 24 | 31 | 62 |
| Non smoker | 80 | 69 | 25 |
| ECOG Performance Status | | | |
| Patient's ECOG PS during the screening/inclusion visit. | | | |
| Units: Subjects | | | |
| ECOG 0 | 42 | 42 | 27 |
| ECOG 1 | 53 | 49 | 46 |
| ECOG 2 | 9 | 9 | 14 |
| Histology subtype | | | |
| Histology subtype of patients' cancer | | | |
| Units: Subjects | | | |
| Adenocarcinoma | 99 | 95 | 82 |
| Non adenocarcinoma | 5 | 5 | 5 |
| EGFR mutation | | | |

| | | | |
|---|---------|---------|---------|
| Patient with an EGFR mutation and patients with a WT EGFR gene. | | | |
| Units: Subjects | | | |
| EGFR WT | 0 | 0 | 85 |
| EGFR muted | 104 | 100 | 0 |
| MISSING | | | 2 |
| Previous line of treatment | | | |
| Number of patients' previous line of treatment. | | | |
| Units: Subjects | | | |
| 1 previous line of treatment | 104 | 100 | 61 |
| 2 or more previous lines of treatment | 0 | 0 | 26 |
| Menopausal status | | | |
| Menopausal status of the patients | | | |
| Units: Subjects | | | |
| Premenopausal patient | 0 | 0 | 0 |
| Postmenopausal patient | 104 | 100 | 87 |
| Estrogen Receptor Alpha (ERa) | | | |
| Results of the Estrogen Receptor Alpha positivity test | | | |
| Units: Subjects | | | |
| Negative | 34 | 41 | 26 |
| Positive | 10 | 9 | 7 |
| Unknown | 60 | 50 | 54 |
| Pack-years for smokers | | | |
| Number of pack-years for the smokers. | | | |
| Units: Pack-years | | | |
| median | 12 | 11.5 | 37.5 |
| full range (min-max) | 1 to 54 | 1 to 50 | 1 to 92 |

| | | | |
|---|---------------------------------------|-------|--|
| Reporting group values | B2 - EGFR WT Erlotinib Fulvestrant | Total | |
| Number of subjects | 88 | 379 | |
| Age categorical | | | |
| Age distribution | | | |
| Units: Subjects | | | |
| Adults (18-64 years) | 58 | 177 | |
| From 65-84 years | 30 | 196 | |
| 85 years and over | 0 | 6 | |
| Age continuous | | | |
| Units: years | | | |
| median | 61.03 | | |
| full range (min-max) | 43.7 to 80.5 | - | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 88 | 379 | |
| Smoking population | | | |
| Number of smoking and non smoking patients | | | |
| Units: Subjects | | | |
| Smoker | 70 | 187 | |
| Non smoker | 18 | 192 | |
| ECOG Performance Status | | | |
| Patient's ECOG PS during the screening/inclusion visit. | | | |
| Units: Subjects | | | |

| | | | |
|---|----------|-----|--|
| ECOG 0 | 41 | 152 | |
| ECOG 1 | 33 | 181 | |
| ECOG 2 | 14 | 46 | |
| Histology subtype | | | |
| Histology subtype of patients' cancer | | | |
| Units: Subjects | | | |
| Adenocarcinoma | 82 | 358 | |
| Non adenocarcinoma | 6 | 21 | |
| EGFR mutation | | | |
| Patient with an EGFR mutation and patients with a WT EGFR gene. | | | |
| Units: Subjects | | | |
| EGFR WT | 88 | 173 | |
| EGFR muted | 0 | 204 | |
| MISSING | | 2 | |
| Previous line of treatment | | | |
| Number of patients' previous line of treatment. | | | |
| Units: Subjects | | | |
| 1 previous line of treatment | 59 | 324 | |
| 2 or more previous lines of treatment | 29 | 55 | |
| Menopausal status | | | |
| Menopausal status of the patients | | | |
| Units: Subjects | | | |
| Premenopausal patient | 0 | 0 | |
| Postmenopausal patient | 88 | 379 | |
| Estrogen Receptor Alpha (ERa) | | | |
| Results of the Estrogen Receptor Alpha positivity test | | | |
| Units: Subjects | | | |
| Negative | 25 | 126 | |
| Positive | 8 | 34 | |
| Unknown | 55 | 219 | |
| Pack-years for smokers | | | |
| Number of pack-years for the smokers. | | | |
| Units: Pack-years | | | |
| median | 35 | | |
| full range (min-max) | 1 to 120 | - | |

Subject analysis sets

| | |
|---|--------------------|
| Subject analysis set title | Intent-to-treat |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: | |
| All patients who were included are counted into this subject analysis set | |

| | | | |
|-------------------------------|-----------------|--|--|
| Reporting group values | Intent-to-treat | | |
| Number of subjects | 379 | | |
| Age categorical | | | |
| Age distribution | | | |
| Units: Subjects | | | |
| Adults (18-64 years) | 177 | | |
| From 65-84 years | 196 | | |

| | | | |
|-------------------|---|--|--|
| 85 years and over | 6 | | |
|-------------------|---|--|--|

| | | | |
|---|--------------|--|--|
| Age continuous | | | |
| Units: years | | | |
| median | 66.18 | | |
| full range (min-max) | 43.6 to 90.9 | | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 379 | | |
| Smoking population | | | |
| Number of smoking and non smoking patients | | | |
| Units: Subjects | | | |
| Smoker | 187 | | |
| Non smoker | 192 | | |
| ECOG Performance Status | | | |
| Patient's ECOG PS during the screening/inclusion visit. | | | |
| Units: Subjects | | | |
| ECOG 0 | 152 | | |
| ECOG 1 | 181 | | |
| ECOG 2 | 46 | | |
| Histology subtype | | | |
| Histology subtype of patients' cancer | | | |
| Units: Subjects | | | |
| Adenocarcinoma | 358 | | |
| Non adenocarcinoma | 21 | | |
| EGFR mutation | | | |
| Patient with an EGFR mutation and patients with a WT EGFR gene. | | | |
| Units: Subjects | | | |
| EGFR WT | 173 | | |
| EGFR muted | 204 | | |
| MISSING | 2 | | |
| Previous line of treatment | | | |
| Number of patients' previous line of treatment. | | | |
| Units: Subjects | | | |
| 1 previous line of treatment | 324 | | |
| 2 or more previous lines of treatment | 55 | | |
| Menopausal status | | | |
| Menopausal status of the patients | | | |
| Units: Subjects | | | |
| Premenopausal patient | 0 | | |
| Postmenopausal patient | 379 | | |
| Estrogen Receptor Alpha (ERa) | | | |
| Results of the Estrogen Receptor Alpha positivity test | | | |
| Units: Subjects | | | |
| Negative | 126 | | |
| Positive | 34 | | |
| Unknown | 219 | | |

| | | | |
|---------------------------------------|----------|--|--|
| Pack-years for smokers | | | |
| Number of pack-years for the smokers. | | | |
| Units: Pack-years | | | |
| median | 29 | | |
| full range (min-max) | 1 to 120 | | |

End points

End points reporting groups

| | |
|--|-------------------------------------|
| Reporting group title | A1 - EGFR mut Gefitinib |
| Reporting group description: EGFR mutated patients receiving Gefitinib. | |
| Reporting group title | B1 - EGFR mut Gefitinib Fulvestrant |
| Reporting group description: EGFR mutated patients receiving Gefitinib + Fulvestrant | |
| Reporting group title | A2 - EGFR WT Erlotinib |
| Reporting group description: EGFR WT patients receiving Erlotinib. | |
| Reporting group title | B2 - EGFR WT Erlotinib Fulvestrant |
| Reporting group description: EGFR WT patients receiving Erlotinib + Fulvestrant | |
| Subject analysis set title | Intent-to-treat |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: All patients who were included are counted into this subject analysis set | |

Primary: Progression free survival at 9 months

| | |
|---|--|
| End point title | Progression free survival at 9 months ^[1] |
| End point description: Progression free survival (PFS) at 9 months for EGFR mutated patients. PFS : The length of time between randomisation and tumour progression or death (any cause). | |
| End point type | Primary |
| End point timeframe: From inclusion to 9 months post inclusion. | |

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This end point : Progression free survival at 9 month is specific to 2 arms (A1 and B1).

| End point values | A1 - EGFR mut Gefitinib | B1 - EGFR mut Gefitinib Fulvestrant | | |
|--|----------------------------|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 93 ^[2] | 93 ^[3] | | |
| Units: Patients | | | | |
| Number of patient without progression at 9 months | 50 | 54 | | |

Notes:

[2] - Intent to treat patients restricted to the number of necessary subjects calculated in the protocole

[3] - Intent to treat patients restricted to the number of necessary subjects calculated in the protocole

Statistical analyses

| | |
|---|--------------------------------------|
| Statistical analysis title | Progression free survival at 9 month |
| Statistical analysis description: EGFR mutated patients: The statistical hypotheses in mutated patients are as follows: H0: p0 (9-month progression-free survival rate) ≤ 45% H1: p1 (9-month progression-free survival rate) ≥ 60% | |

Under these assumptions, 102 patients (93 + 10% non-evaluable) are needed in each arm, i.e. 204 patients.

| | |
|---|---|
| Comparison groups | A1 - EGFR mut Gefitinib v B1 - EGFR mut Gefitinib Fulvestrant |
| Number of subjects included in analysis | 186 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[4] |
| P-value | = 0.05 |
| Method | Binomial test |
| Parameter estimate | Difference of proportion |

Notes:

[4] - No comment

Primary: Progression free survival at 3 months

| | |
|---|--|
| End point title | Progression free survival at 3 months ^[5] |
| End point description: | |
| Progression free survival at 3 months for EGFR wild type patients. | |
| PFS : The length of time between randomisation and tumour progression or death (any cause). | |
| End point type | Primary |
| End point timeframe: | |
| From inclusion to 3 months post inclusion | |

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This end point : Progression free survival at 9 month is specific to 2 arms (A2 and B2).

| End point values | A2 - EGFR WT Erlotinib | B2 - EGFR WT Erlotinib Fulvestrant | | |
|--|------------------------|------------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 83 ^[6] | 86 ^[7] | | |
| Units: Patients | | | | |
| Number of patients without progression at 3 months | 29 | 29 | | |

Notes:

[6] - Intent to treat patients restricted to the number of necessary subjects calculated in the protocole

[7] - Intent to treat patients restricted to the number of necessary subjects calculated in the protocole

Statistical analyses

| | |
|--|---|
| Statistical analysis title | Progression free survival at 3 month |
| Statistical analysis description: | |
| EGFR-unmutated patients : | |
| The statistical hypotheses in non-mutated patients are as follows: | |
| H0: p0 (Progression-free survival rate at 3 months) ≤ 30% | |
| H1: p1 (3-month progression-free survival rate) ≥ 45% | |
| Under these assumptions, 95 patients (86 + 10% non-evaluable) are needed in each arm, i.e. 190 patients. | |
| Comparison groups | A2 - EGFR WT Erlotinib v B2 - EGFR WT Erlotinib Fulvestrant |
| Number of subjects included in analysis | 169 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[8] |
| P-value | = 0.05 |
| Method | Binomial test |
| Parameter estimate | Difference of proportion |

Notes:

[8] - No comment

Secondary: Response at 2 months at intent to treat population

End point title Response at 2 months at intent to treat population

End point description:

Response at 2 months at intent to treat population

End point type Secondary

End point timeframe:

From inclusion to 2 months post inclusion

| End point values | A1 - EGFR mut Gefitinib | B1 - EGFR mut Gefitinib Fulvestrant | A2 - EGFR WT Erlotinib | B2 - EGFR WT Erlotinib Fulvestrant |
|-----------------------------|----------------------------|---|---------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 104 | 100 | 87 | 88 |
| Units: Patients | | | | |
| Complete response | 1 | 0 | 0 | 0 |
| Partial response | 56 | 52 | 3 | 2 |
| Stable disease | 35 | 34 | 25 | 24 |
| Disease progression | 12 | 14 | 59 | 62 |

Statistical analyses

No statistical analyses for this end point

Secondary: Best response in intent to treat population

End point title Best response in intent to treat population

End point description:

Best response in intent to treat population

End point type Secondary

End point timeframe:

From inclusion to the end of treatment

| End point values | A1 - EGFR mut Gefitinib | B1 - EGFR mut Gefitinib Fulvestrant | A2 - EGFR WT Erlotinib | B2 - EGFR WT Erlotinib Fulvestrant |
|-----------------------------|----------------------------|---|---------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 104 | 100 | 87 | 88 |
| Units: Patients | | | | |
| Complete response | 1 | 2 | 1 | 0 |
| Partial response | 71 | 62 | 3 | 3 |
| Stable disease | 23 | 23 | 26 | 24 |
| Disease progression | 9 | 13 | 57 | 61 |

Statistical analyses

No statistical analyses for this end point

Secondary: Progression free survival

| | |
|-----------------|---------------------------|
| End point title | Progression free survival |
|-----------------|---------------------------|

End point description:

Progression free survival.

PFS : The length of time between randomisation and tumour progression or death (any cause).

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

End point timeframe:

From inclusion to the first observed progression (RECIST 1.1)

| End point values | A1 - EGFR mut Gefitinib | B1 - EGFR mut Gefitinib Fulvestrant | A2 - EGFR WT Erlotinib | B2 - EGFR WT Erlotinib Fulvestrant |
|----------------------------------|----------------------------|---|---------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 93 ^[9] | 93 ^[10] | 83 ^[11] | 86 ^[12] |
| Units: month | | | | |
| median (confidence interval 95%) | | | | |
| PFS | 9.4 (8.0 to 12.7) | 9.9 (7.7 to 11.2) | 2.0 (1.8 to 2.6) | 1.8 (1.7 to 2.1) |

Notes:

[9] - Intent to treat patients restricted to the number of necessary subjects calculated in the protocole

[10] - Intent to treat patients restricted to the number of necessary subjects calculated in the protocole

[11] - Intent to treat patients restricted to the number of necessary subjects calculated in the protocole

[12] - Intent to treat patients restricted to the number of necessary subjects calculated in the protocole

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival

| | |
|-----------------|------------------|
| End point title | Overall survival |
|-----------------|------------------|

End point description:

Overall survival (in months)

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

End point timeframe:

From inclusion to death.

| End point values | A1 - EGFR mut Gefitinib | B1 - EGFR mut Gefitinib Fulvestrant | A2 - EGFR WT Erlotinib | B2 - EGFR WT Erlotinib Fulvestrant |
|----------------------------------|----------------------------|---|---------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 104 | 98 | 83 | 88 |
| Units: month | | | | |
| median (confidence interval 95%) | | | | |
| Overall survival in months | 29.9 (23.2 to 43.8) | 22.1 (18.6 to 25.7) | 7.3 (5.4 to 9.3) | 10.0 (6.6 to 14.6) |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse event monitoring was performed at day 15 of the first cycle, before each cycle (i.e., every 4 weeks until the end of protocol treatment), and for 30 days after drug discontinuation for each patient

Adverse event reporting additional description:

The maximal grade of adverse events was collected by cycle of treatment.

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

Dictionary used

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

| | |
|--------------------|----|
| Dictionary version | 21 |
|--------------------|----|

Reporting groups

| | |
|-----------------------|-------------------------|
| Reporting group title | A1 - EGFR mut Gefitinib |
|-----------------------|-------------------------|

Reporting group description:

Patients with an EGFR mutation who received gefitinib only

| | |
|-----------------------|-------------------------------------|
| Reporting group title | B1 - EGFR mut Gefitinib Fulvestrant |
|-----------------------|-------------------------------------|

Reporting group description:

Patients with an EGFR mutation who received gefitinib and fulvestrant

| | |
|-----------------------|------------------------|
| Reporting group title | A2 - EGFR WT Erlotinib |
|-----------------------|------------------------|

Reporting group description:

Patients with a WT EGFR who received erlotinib only

| | |
|-----------------------|------------------------------------|
| Reporting group title | B2 - EGFR WT Erlotinib Fulvestrant |
|-----------------------|------------------------------------|

Reporting group description:

Patients with a WT EGFR who received erlotinib and fulvestrant

| Serious adverse events | A1 - EGFR mut Gefitinib | B1 - EGFR mut Gefitinib Fulvestrant | A2 - EGFR WT Erlotinib |
|---|-------------------------|-------------------------------------|------------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 33 / 103 (32.04%) | 26 / 99 (26.26%) | 46 / 87 (52.87%) |
| number of deaths (all causes) | 3 | 3 | 7 |
| number of deaths resulting from adverse events | 0 | 1 | 5 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Bronchial carcinoma | | | |
| subjects affected / exposed | 0 / 103 (0.00%) | 2 / 99 (2.02%) | 5 / 87 (5.75%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 5 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 3 |
| Colon cancer stage 0 | | | |
| subjects affected / exposed | 1 / 103 (0.97%) | 0 / 99 (0.00%) | 0 / 87 (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 |
| Metastases to meninges | | | |

| | | | |
|---|-----------------|----------------|----------------|
| subjects affected / exposed | 1 / 103 (0.97%) | 0 / 99 (0.00%) | 1 / 87 (1.15%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Pericarditis malignant | | | |
| subjects affected / exposed | 0 / 103 (0.00%) | 1 / 99 (1.01%) | 0 / 87 (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 |
| Second primary malignancy | | | |
| subjects affected / exposed | 0 / 103 (0.00%) | 1 / 99 (1.01%) | 0 / 87 (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 |
| Vascular disorders | | | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 0 / 103 (0.00%) | 0 / 99 (0.00%) | 0 / 87 (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 |
| Haemorrhage | | | |
| subjects affected / exposed | 0 / 103 (0.00%) | 1 / 99 (1.01%) | 0 / 87 (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 |
| Phlebitis superficial | | | |
| subjects affected / exposed | 1 / 103 (0.97%) | 0 / 99 (0.00%) | 0 / 87 (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 | 5 / 103 (4.85%) | 2 / 99 (2.02%) | 3 / 87 (3.45%) |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 2 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| Superior vena cava syndrome | | | |
| subjects affected / exposed | 0 / 103 (0.00%) | 0 / 99 (0.00%) | 2 / 87 (2.30%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Thrombophlebitis superficial | | | |

| | | | |
|--|-----------------|----------------|------------------|
| subjects affected / exposed | 0 / 103 (0.00%) | 1 / 99 (1.01%) | 0 / 87 (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 |
| Venous thrombosis | | | |
| subjects affected / exposed | 0 / 103 (0.00%) | 1 / 99 (1.01%) | 0 / 87 (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 |
| Venous thrombosis limb | | | |
| subjects affected / exposed | 0 / 103 (0.00%) | 1 / 99 (1.01%) | 0 / 87 (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 |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 1 / 103 (0.97%) | 0 / 99 (0.00%) | 1 / 87 (1.15%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Chest pain | | | |
| subjects affected / exposed | 1 / 103 (0.97%) | 1 / 99 (1.01%) | 0 / 87 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gait disturbance | | | |
| subjects affected / exposed | 0 / 103 (0.00%) | 1 / 99 (1.01%) | 0 / 87 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| General physical health deterioration | | | |
| subjects affected / exposed | 4 / 103 (3.88%) | 5 / 99 (5.05%) | 16 / 87 (18.39%) |
| occurrences causally related to treatment / all | 1 / 4 | 1 / 6 | 2 / 17 |
| deaths causally related to treatment / all | 0 / 2 | 0 / 2 | 0 / 12 |
| Inflammation | | | |
| subjects affected / exposed | 0 / 103 (0.00%) | 0 / 99 (0.00%) | 0 / 87 (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 |
| Malaise | | | |

| | | | |
|---|-----------------|----------------|----------------|
| subjects affected / exposed | 0 / 103 (0.00%) | 0 / 99 (0.00%) | 0 / 87 (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 |
| Medical device pain | | | |
| subjects affected / exposed | 0 / 103 (0.00%) | 0 / 99 (0.00%) | 0 / 87 (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 |
| Multiple organ dysfunction syndrome | | | |
| subjects affected / exposed | 0 / 103 (0.00%) | 1 / 99 (1.01%) | 0 / 87 (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 |
| Pain | | | |
| subjects affected / exposed | 1 / 103 (0.97%) | 0 / 99 (0.00%) | 0 / 87 (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 |
| Pyrexia | | | |
| subjects affected / exposed | 2 / 103 (1.94%) | 0 / 99 (0.00%) | 0 / 87 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Acute respiratory distress syndrome | | | |
| subjects affected / exposed | 0 / 103 (0.00%) | 1 / 99 (1.01%) | 1 / 87 (1.15%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| Chronic obstructive pulmonary disease | | | |
| subjects affected / exposed | 0 / 103 (0.00%) | 0 / 99 (0.00%) | 0 / 87 (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 |
| Cough | | | |
| subjects affected / exposed | 0 / 103 (0.00%) | 0 / 99 (0.00%) | 0 / 87 (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 |
| Dyspnoea | | | |

| | | | |
|---|-----------------|----------------|----------------|
| subjects affected / exposed | 3 / 103 (2.91%) | 1 / 99 (1.01%) | 4 / 87 (4.60%) |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 1 | 0 / 4 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Haemoptysis | | | |
| subjects affected / exposed | 0 / 103 (0.00%) | 0 / 99 (0.00%) | 2 / 87 (2.30%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lung disorder | | | |
| subjects affected / exposed | 1 / 103 (0.97%) | 1 / 99 (1.01%) | 1 / 87 (1.15%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pleural effusion | | | |
| subjects affected / exposed | 2 / 103 (1.94%) | 1 / 99 (1.01%) | 0 / 87 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Pneumonia aspiration | | | |
| subjects affected / exposed | 0 / 103 (0.00%) | 1 / 99 (1.01%) | 0 / 87 (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 |
| Pneumothorax | | | |
| subjects affected / exposed | 1 / 103 (0.97%) | 0 / 99 (0.00%) | 0 / 87 (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 |
| Respiratory distress | | | |
| subjects affected / exposed | 2 / 103 (1.94%) | 1 / 99 (1.01%) | 2 / 87 (2.30%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| Respiratory failure | | | |
| subjects affected / exposed | 0 / 103 (0.00%) | 0 / 99 (0.00%) | 1 / 87 (1.15%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Psychiatric disorders | | | |
| Depression | | | |

| | | | |
|---|-----------------|----------------|----------------|
| subjects affected / exposed | 1 / 103 (0.97%) | 1 / 99 (1.01%) | 0 / 87 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Mania | | | |
| subjects affected / exposed | 1 / 103 (0.97%) | 0 / 99 (0.00%) | 0 / 87 (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 |
| Suicidal ideation | | | |
| subjects affected / exposed | 0 / 103 (0.00%) | 2 / 99 (2.02%) | 0 / 87 (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 |
| Suicide attempt | | | |
| subjects affected / exposed | 1 / 103 (0.97%) | 0 / 99 (0.00%) | 0 / 87 (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 |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 0 / 103 (0.00%) | 1 / 99 (1.01%) | 0 / 87 (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 |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 0 / 103 (0.00%) | 1 / 99 (1.01%) | 0 / 87 (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 |
| Platelet count decreased | | | |
| subjects affected / exposed | 0 / 103 (0.00%) | 0 / 99 (0.00%) | 0 / 87 (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 |
| Weight decreased | | | |
| subjects affected / exposed | 1 / 103 (0.97%) | 0 / 99 (0.00%) | 0 / 87 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |

| | | | |
|--|-----------------|----------------|----------------|
| Accident at home alternative assessment type: Systematic | | | |
| subjects affected / exposed | 0 / 103 (0.00%) | 0 / 99 (0.00%) | 0 / 87 (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 |
| Fall | | | |
| subjects affected / exposed | 4 / 103 (3.88%) | 1 / 99 (1.01%) | 1 / 87 (1.15%) |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Femur fracture | | | |
| subjects affected / exposed | 1 / 103 (0.97%) | 0 / 99 (0.00%) | 0 / 87 (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 | 1 / 103 (0.97%) | 0 / 99 (0.00%) | 0 / 87 (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 |
| Humerus fracture | | | |
| subjects affected / exposed | 1 / 103 (0.97%) | 0 / 99 (0.00%) | 0 / 87 (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 |
| Radius fracture | | | |
| subjects affected / exposed | 1 / 103 (0.97%) | 0 / 99 (0.00%) | 0 / 87 (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 |
| Wrist fracture | | | |
| subjects affected / exposed | 1 / 103 (0.97%) | 1 / 99 (1.01%) | 0 / 87 (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 |
| Cardiac disorders | | | |
| Arrhythmia supraventricular | | | |
| subjects affected / exposed | 0 / 103 (0.00%) | 0 / 99 (0.00%) | 0 / 87 (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 |

| | | | |
|---|-----------------|----------------|----------------|
| Atrial fibrillation | | | |
| subjects affected / exposed | 0 / 103 (0.00%) | 0 / 99 (0.00%) | 1 / 87 (1.15%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac tamponade | | | |
| subjects affected / exposed | 1 / 103 (0.97%) | 0 / 99 (0.00%) | 0 / 87 (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 |
| Pericardial effusion | | | |
| subjects affected / exposed | 1 / 103 (0.97%) | 0 / 99 (0.00%) | 0 / 87 (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 |
| Tachycardia | | | |
| subjects affected / exposed | 1 / 103 (0.97%) | 0 / 99 (0.00%) | 0 / 87 (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 |
| Nervous system disorders | | | |
| Balance disorder | | | |
| subjects affected / exposed | 2 / 103 (1.94%) | 0 / 99 (0.00%) | 0 / 87 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Brain oedema | | | |
| subjects affected / exposed | 0 / 103 (0.00%) | 2 / 99 (2.02%) | 0 / 87 (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 |
| Cerebral haemorrhage | | | |
| subjects affected / exposed | 0 / 103 (0.00%) | 0 / 99 (0.00%) | 1 / 87 (1.15%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 1 / 103 (0.97%) | 0 / 99 (0.00%) | 0 / 87 (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 |
| Cognitive disorder | | | |

| | | | |
|---|-----------------|----------------|----------------|
| subjects affected / exposed | 0 / 103 (0.00%) | 1 / 99 (1.01%) | 0 / 87 (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 |
| Headache | | | |
| subjects affected / exposed | 1 / 103 (0.97%) | 0 / 99 (0.00%) | 0 / 87 (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 |
| Hemiplegia | | | |
| subjects affected / exposed | 0 / 103 (0.00%) | 0 / 99 (0.00%) | 1 / 87 (1.15%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Hypoaesthesia oral | | | |
| subjects affected / exposed | 1 / 103 (0.97%) | 0 / 99 (0.00%) | 0 / 87 (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 |
| Hypokinesia | | | |
| subjects affected / exposed | 0 / 103 (0.00%) | 0 / 99 (0.00%) | 0 / 87 (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 |
| IIIrd nerve disorder | | | |
| subjects affected / exposed | 0 / 103 (0.00%) | 0 / 99 (0.00%) | 1 / 87 (1.15%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorder | | | |
| subjects affected / exposed | 1 / 103 (0.97%) | 1 / 99 (1.01%) | 0 / 87 (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 |
| Neuralgia | | | |
| subjects affected / exposed | 1 / 103 (0.97%) | 0 / 99 (0.00%) | 0 / 87 (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 |
| Paraesthesia | | | |

| | | | |
|---|-----------------|----------------|----------------|
| subjects affected / exposed | 0 / 103 (0.00%) | 1 / 99 (1.01%) | 0 / 87 (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 |
| Partial seizures | | | |
| subjects affected / exposed | 0 / 103 (0.00%) | 1 / 99 (1.01%) | 0 / 87 (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 |
| Seizure | | | |
| subjects affected / exposed | 1 / 103 (0.97%) | 0 / 99 (0.00%) | 0 / 87 (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 |
| Ear and labyrinth disorders | | | |
| Vertigo | | | |
| subjects affected / exposed | 0 / 103 (0.00%) | 1 / 99 (1.01%) | 0 / 87 (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 |
| Eye disorders | | | |
| Diplopia | | | |
| subjects affected / exposed | 0 / 103 (0.00%) | 0 / 99 (0.00%) | 1 / 87 (1.15%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Retinal detachment | | | |
| subjects affected / exposed | 1 / 103 (0.97%) | 0 / 99 (0.00%) | 0 / 87 (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 |
| Visual acuity reduced | | | |
| subjects affected / exposed | 0 / 103 (0.00%) | 0 / 99 (0.00%) | 1 / 87 (1.15%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 0 / 103 (0.00%) | 0 / 99 (0.00%) | 0 / 87 (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 | 2 / 103 (1.94%) | 1 / 99 (1.01%) | 0 / 87 (0.00%) |
| occurrences causally related to treatment / all | 1 / 2 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dysphagia | | | |
| subjects affected / exposed | 1 / 103 (0.97%) | 0 / 99 (0.00%) | 0 / 87 (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 |
| Gastrointestinal obstruction | | | |
| subjects affected / exposed | 1 / 103 (0.97%) | 0 / 99 (0.00%) | 0 / 87 (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 |
| Intestinal obstruction | | | |
| subjects affected / exposed | 0 / 103 (0.00%) | 0 / 99 (0.00%) | 0 / 87 (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 |
| Nausea | | | |
| subjects affected / exposed | 0 / 103 (0.00%) | 1 / 99 (1.01%) | 1 / 87 (1.15%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Proctitis | | | |
| subjects affected / exposed | 1 / 103 (0.97%) | 0 / 99 (0.00%) | 0 / 87 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Stomatitis | | | |
| subjects affected / exposed | 0 / 103 (0.00%) | 1 / 99 (1.01%) | 0 / 87 (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 |
| Subileus | | | |
| subjects affected / exposed | 0 / 103 (0.00%) | 0 / 99 (0.00%) | 1 / 87 (1.15%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vomiting | | | |

| | | | |
|---|-----------------|----------------|----------------|
| subjects affected / exposed | 1 / 103 (0.97%) | 0 / 99 (0.00%) | 1 / 87 (1.15%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| Cholestasis | | | |
| subjects affected / exposed | 0 / 103 (0.00%) | 0 / 99 (0.00%) | 2 / 87 (2.30%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Hepatic failure | | | |
| subjects affected / exposed | 1 / 103 (0.97%) | 0 / 99 (0.00%) | 0 / 87 (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 |
| Hepatocellular injury | | | |
| subjects affected / exposed | 1 / 103 (0.97%) | 0 / 99 (0.00%) | 0 / 87 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Jaundice | | | |
| subjects affected / exposed | 0 / 103 (0.00%) | 0 / 99 (0.00%) | 1 / 87 (1.15%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Skin and subcutaneous tissue disorders | | | |
| Rash | | | |
| subjects affected / exposed | 0 / 103 (0.00%) | 0 / 99 (0.00%) | 0 / 87 (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 |
| Subacute cutaneous lupus erythematosus | | | |
| subjects affected / exposed | 1 / 103 (0.97%) | 0 / 99 (0.00%) | 0 / 87 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 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 | 0 / 103 (0.00%) | 0 / 99 (0.00%) | 2 / 87 (2.30%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|-----------------|----------------|----------------|
| Renal colic | | | |
| subjects affected / exposed | 1 / 103 (0.97%) | 0 / 99 (0.00%) | 0 / 87 (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 | | | |
| Back pain | | | |
| subjects affected / exposed | 0 / 103 (0.00%) | 1 / 99 (1.01%) | 2 / 87 (2.30%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bone pain | | | |
| subjects affected / exposed | 2 / 103 (1.94%) | 2 / 99 (2.02%) | 3 / 87 (3.45%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 1 |
| Infections and infestations | | | |
| Anal abscess | | | |
| subjects affected / exposed | 0 / 103 (0.00%) | 0 / 99 (0.00%) | 1 / 87 (1.15%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bronchitis | | | |
| subjects affected / exposed | 0 / 103 (0.00%) | 0 / 99 (0.00%) | 2 / 87 (2.30%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Catheter site infection | | | |
| subjects affected / exposed | 0 / 103 (0.00%) | 0 / 99 (0.00%) | 1 / 87 (1.15%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Clostridium colitis | | | |
| subjects affected / exposed | 1 / 103 (0.97%) | 0 / 99 (0.00%) | 0 / 87 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cystitis | | | |
| subjects affected / exposed | 0 / 103 (0.00%) | 0 / 99 (0.00%) | 1 / 87 (1.15%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|-----------------|----------------|----------------|
| Infectious pleural effusion | | | |
| subjects affected / exposed | 0 / 103 (0.00%) | 1 / 99 (1.01%) | 0 / 87 (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 |
| Ophthalmic herpes simplex | | | |
| subjects affected / exposed | 0 / 103 (0.00%) | 0 / 99 (0.00%) | 1 / 87 (1.15%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 103 (0.00%) | 1 / 99 (1.01%) | 1 / 87 (1.15%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Spinal cord infection | | | |
| subjects affected / exposed | 1 / 103 (0.97%) | 0 / 99 (0.00%) | 1 / 87 (1.15%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 103 (0.00%) | 0 / 99 (0.00%) | 1 / 87 (1.15%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vaginal infection | | | |
| subjects affected / exposed | 1 / 103 (0.97%) | 0 / 99 (0.00%) | 0 / 87 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Cell death | | | |
| subjects affected / exposed | 0 / 103 (0.00%) | 0 / 99 (0.00%) | 1 / 87 (1.15%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Decreased appetite | | | |
| subjects affected / exposed | 0 / 103 (0.00%) | 2 / 99 (2.02%) | 2 / 87 (2.30%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |

| Serious adverse events | B2 - EGFR WT Erlotinib Fulvestrant | | |
|---|---------------------------------------|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 33 / 88 (37.50%) | | |
| number of deaths (all causes) | 4 | | |
| number of deaths resulting from adverse events | 4 | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Bronchial carcinoma | | | |
| subjects affected / exposed | 1 / 88 (1.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Colon cancer stage 0 | | | |
| subjects affected / exposed | 0 / 88 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Metastases to meninges | | | |
| subjects affected / exposed | 0 / 88 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pericarditis malignant | | | |
| subjects affected / exposed | 0 / 88 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Second primary malignancy | | | |
| subjects affected / exposed | 0 / 88 (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 | 1 / 88 (1.14%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Haemorrhage | | | |

| | | | |
|--|----------------|--|--|
| subjects affected / exposed | 0 / 88 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Phlebitis superficial | | | |
| subjects affected / exposed | 1 / 88 (1.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 2 / 88 (2.27%) | | |
| occurrences causally related to treatment / all | 1 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Superior vena cava syndrome | | | |
| subjects affected / exposed | 0 / 88 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Thrombophlebitis superficial | | | |
| subjects affected / exposed | 0 / 88 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Venous thrombosis | | | |
| subjects affected / exposed | 0 / 88 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Venous thrombosis limb | | | |
| subjects affected / exposed | 0 / 88 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 1 / 88 (1.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Chest pain | | | |

| | | | | |
|---|------------------|--|--|--|
| subjects affected / exposed | 1 / 88 (1.14%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Gait disturbance | | | | |
| subjects affected / exposed | 0 / 88 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| General physical health deterioration | | | | |
| subjects affected / exposed | 12 / 88 (13.64%) | | | |
| occurrences causally related to treatment / all | 1 / 13 | | | |
| deaths causally related to treatment / all | 0 / 7 | | | |
| Inflammation | | | | |
| subjects affected / exposed | 1 / 88 (1.14%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Malaise | | | | |
| subjects affected / exposed | 1 / 88 (1.14%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Medical device pain | | | | |
| subjects affected / exposed | 1 / 88 (1.14%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Multiple organ dysfunction syndrome | | | | |
| subjects affected / exposed | 0 / 88 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pain | | | | |
| subjects affected / exposed | 0 / 88 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pyrexia | | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 2 / 88 (2.27%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Acute respiratory distress syndrome | | | |
| subjects affected / exposed | 0 / 88 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Chronic obstructive pulmonary disease | | | |
| subjects affected / exposed | 1 / 88 (1.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cough | | | |
| subjects affected / exposed | 1 / 88 (1.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Dyspnoea | | | |
| subjects affected / exposed | 5 / 88 (5.68%) | | |
| occurrences causally related to treatment / all | 0 / 5 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Haemoptysis | | | |
| subjects affected / exposed | 0 / 88 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Lung disorder | | | |
| subjects affected / exposed | 2 / 88 (2.27%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pleural effusion | | | |
| subjects affected / exposed | 1 / 88 (1.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pneumonia aspiration | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 0 / 88 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pneumothorax | | | |
| subjects affected / exposed | 1 / 88 (1.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory distress | | | |
| subjects affected / exposed | 1 / 88 (1.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory failure | | | |
| subjects affected / exposed | 0 / 88 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Psychiatric disorders | | | |
| Depression | | | |
| subjects affected / exposed | 0 / 88 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Mania | | | |
| subjects affected / exposed | 0 / 88 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Suicidal ideation | | | |
| subjects affected / exposed | 0 / 88 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Suicide attempt | | | |
| subjects affected / exposed | 0 / 88 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Investigations | | | |

| | | | | |
|---|----------------|--|--|--|
| Alanine aminotransferase increased | | | | |
| subjects affected / exposed | 0 / 88 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Aspartate aminotransferase increased | | | | |
| subjects affected / exposed | 0 / 88 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Platelet count decreased | | | | |
| subjects affected / exposed | 1 / 88 (1.14%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| Weight decreased | | | | |
| subjects affected / exposed | 0 / 88 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Injury, poisoning and procedural complications | | | | |
| Accident at home | | | | |
| alternative assessment type: Systematic | | | | |
| subjects affected / exposed | 1 / 88 (1.14%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| Fall | | | | |
| subjects affected / exposed | 0 / 88 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Femur fracture | | | | |
| subjects affected / exposed | 0 / 88 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Fracture | | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 0 / 88 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Humerus fracture | | | |
| subjects affected / exposed | 0 / 88 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Radius fracture | | | |
| subjects affected / exposed | 0 / 88 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Wrist fracture | | | |
| subjects affected / exposed | 0 / 88 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac disorders | | | |
| Arrhythmia supraventricular | | | |
| subjects affected / exposed | 1 / 88 (1.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 0 / 88 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac tamponade | | | |
| subjects affected / exposed | 1 / 88 (1.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Pericardial effusion | | | |
| subjects affected / exposed | 0 / 88 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Tachycardia | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 0 / 88 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nervous system disorders | | | |
| Balance disorder | | | |
| subjects affected / exposed | 1 / 88 (1.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Brain oedema | | | |
| subjects affected / exposed | 0 / 88 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cerebral haemorrhage | | | |
| subjects affected / exposed | 0 / 88 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 1 / 88 (1.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Cognitive disorder | | | |
| subjects affected / exposed | 0 / 88 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Headache | | | |
| subjects affected / exposed | 0 / 88 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hemiplegia | | | |
| subjects affected / exposed | 1 / 88 (1.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Hypoaesthesia oral | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 0 / 88 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypokinesia | | | |
| subjects affected / exposed | 1 / 88 (1.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| IIIrd nerve disorder | | | |
| subjects affected / exposed | 0 / 88 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nervous system disorder | | | |
| subjects affected / exposed | 1 / 88 (1.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Neuralgia | | | |
| subjects affected / exposed | 0 / 88 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Paraesthesia | | | |
| subjects affected / exposed | 0 / 88 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Partial seizures | | | |
| subjects affected / exposed | 0 / 88 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Seizure | | | |
| subjects affected / exposed | 0 / 88 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ear and labyrinth disorders | | | |
| Vertigo | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 0 / 88 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Eye disorders | | | |
| Diplopia | | | |
| subjects affected / exposed | 0 / 88 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Retinal detachment | | | |
| subjects affected / exposed | 0 / 88 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Visual acuity reduced | | | |
| subjects affected / exposed | 0 / 88 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 1 / 88 (1.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Diarrhoea | | | |
| subjects affected / exposed | 2 / 88 (2.27%) | | |
| occurrences causally related to treatment / all | 1 / 2 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Dysphagia | | | |
| subjects affected / exposed | 0 / 88 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal obstruction | | | |
| subjects affected / exposed | 0 / 88 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Intestinal obstruction | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 1 / 88 (1.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nausea | | | |
| subjects affected / exposed | 2 / 88 (2.27%) | | |
| occurrences causally related to treatment / all | 1 / 2 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Proctitis | | | |
| subjects affected / exposed | 0 / 88 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Stomatitis | | | |
| subjects affected / exposed | 0 / 88 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Subileus | | | |
| subjects affected / exposed | 0 / 88 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vomiting | | | |
| subjects affected / exposed | 5 / 88 (5.68%) | | |
| occurrences causally related to treatment / all | 1 / 5 | | |
| deaths causally related to treatment / all | 0 / 2 | | |
| Hepatobiliary disorders | | | |
| Cholestasis | | | |
| subjects affected / exposed | 0 / 88 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatic failure | | | |
| subjects affected / exposed | 0 / 88 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatocellular injury | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 1 / 88 (1.14%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Jaundice | | | |
| subjects affected / exposed | 1 / 88 (1.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Skin and subcutaneous tissue disorders | | | |
| Rash | | | |
| subjects affected / exposed | 1 / 88 (1.14%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Subacute cutaneous lupus erythematosus | | | |
| subjects affected / exposed | 0 / 88 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 0 / 88 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal colic | | | |
| subjects affected / exposed | 0 / 88 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 0 / 88 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Bone pain | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 2 / 88 (2.27%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Infections and infestations | | | |
| Anal abscess | | | |
| subjects affected / exposed | 0 / 88 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Bronchitis | | | |
| subjects affected / exposed | 2 / 88 (2.27%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Catheter site infection | | | |
| subjects affected / exposed | 0 / 88 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Clostridium colitis | | | |
| subjects affected / exposed | 0 / 88 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cystitis | | | |
| subjects affected / exposed | 0 / 88 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infectious pleural effusion | | | |
| subjects affected / exposed | 0 / 88 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ophthalmic herpes simplex | | | |
| subjects affected / exposed | 0 / 88 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pneumonia | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 0 / 88 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Spinal cord infection | | | |
| subjects affected / exposed | 0 / 88 (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 / 88 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vaginal infection | | | |
| subjects affected / exposed | 0 / 88 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Metabolism and nutrition disorders | | | |
| Cell death | | | |
| subjects affected / exposed | 0 / 88 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Decreased appetite | | | |
| subjects affected / exposed | 2 / 88 (2.27%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

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

| Non-serious adverse events | A1 - EGFR mut Gefitinib | B1 - EGFR mut Gefitinib Fulvestrant | A2 - EGFR WT Erlotinib |
|---|----------------------------|--|---------------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 101 / 103 (98.06%) | 99 / 99 (100.00%) | 87 / 87 (100.00%) |
| Vascular disorders | | | |
| Hot flush | | | |
| subjects affected / exposed | 3 / 103 (2.91%) | 11 / 99 (11.11%) | 0 / 87 (0.00%) |
| occurrences (all) | 12 | 56 | 0 |

| | | | |
|---|--------------------------|-------------------------|------------------------|
| Epistaxis subjects affected / exposed occurrences (all) | 7 / 103 (6.80%) 12 | 7 / 99 (7.07%) 9 | 2 / 87 (2.30%) 3 |
| General disorders and administration site conditions | | | |
| Asthenia subjects affected / exposed occurrences (all) | 45 / 103 (43.69%) 117 | 56 / 99 (56.57%) 131 | 34 / 87 (39.08%) 82 |
| Chest pain subjects affected / exposed occurrences (all) | 16 / 103 (15.53%) 48 | 12 / 99 (12.12%) 28 | 10 / 87 (11.49%) 18 |
| General physical health deterioration subjects affected / exposed occurrences (all) | 7 / 103 (6.80%) 8 | 9 / 99 (9.09%) 10 | 19 / 87 (21.84%) 25 |
| Fatigue subjects affected / exposed occurrences (all) | 7 / 103 (6.80%) 12 | 11 / 99 (11.11%) 25 | 13 / 87 (14.94%) 18 |
| Oedema peripheral subjects affected / exposed occurrences (all) | 8 / 103 (7.77%) 13 | 10 / 99 (10.10%) 27 | 7 / 87 (8.05%) 7 |
| Xerosis subjects affected / exposed occurrences (all) | 11 / 103 (10.68%) 20 | 6 / 99 (6.06%) 26 | 2 / 87 (2.30%) 3 |
| Pain subjects affected / exposed occurrences (all) | 4 / 103 (3.88%) 6 | 5 / 99 (5.05%) 10 | 6 / 87 (6.90%) 7 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough subjects affected / exposed occurrences (all) | 32 / 103 (31.07%) 109 | 33 / 99 (33.33%) 74 | 20 / 87 (22.99%) 42 |
| Dyspnoea subjects affected / exposed occurrences (all) | 34 / 103 (33.01%) 88 | 25 / 99 (25.25%) 77 | 27 / 87 (31.03%) 57 |
| Chest pain subjects affected / exposed occurrences (all) | 12 / 103 (11.65%) 24 | 10 / 99 (10.10%) 13 | 3 / 87 (3.45%) 3 |
| Productive cough | | | |

| | | | |
|--|--------------------------|-------------------------|------------------------|
| subjects affected / exposed occurrences (all) | 6 / 103 (5.83%) 10 | 2 / 99 (2.02%) 3 | 4 / 87 (4.60%) 4 |
| Psychiatric disorders Depression subjects affected / exposed occurrences (all) | 6 / 103 (5.83%) 21 | 6 / 99 (6.06%) 7 | 1 / 87 (1.15%) 1 |
| Investigations Alanine aminotransferase increased subjects affected / exposed occurrences (all) | 35 / 103 (33.98%) 115 | 29 / 99 (29.29%) 104 | 7 / 87 (8.05%) 12 |
| Aspartate aminotransferase increased subjects affected / exposed occurrences (all) | 29 / 103 (28.16%) 110 | 25 / 99 (25.25%) 102 | 9 / 87 (10.34%) 18 |
| Gamma-glutamyltransferase increased subjects affected / exposed occurrences (all) | 13 / 103 (12.62%) 45 | 15 / 99 (15.15%) 49 | 10 / 87 (11.49%) 18 |
| Weight decreased subjects affected / exposed occurrences (all) | 7 / 103 (6.80%) 16 | 14 / 99 (14.14%) 18 | 17 / 87 (19.54%) 21 |
| Blood alkaline phosphatase increased subjects affected / exposed occurrences (all) | 15 / 103 (14.56%) 42 | 10 / 99 (10.10%) 23 | 6 / 87 (6.90%) 10 |
| Nervous system disorders Headache subjects affected / exposed occurrences (all) | 14 / 103 (13.59%) 26 | 7 / 99 (7.07%) 17 | 4 / 87 (4.60%) 9 |
| Paraesthesia subjects affected / exposed occurrences (all) | 6 / 103 (5.83%) 15 | 7 / 99 (7.07%) 9 | 3 / 87 (3.45%) 38 |
| Dysgeusia subjects affected / exposed occurrences (all) | 3 / 103 (2.91%) 3 | 6 / 99 (6.06%) 7 | 2 / 87 (2.30%) 3 |
| Confusional state subjects affected / exposed occurrences (all) | 0 / 103 (0.00%) 0 | 5 / 99 (5.05%) 6 | 0 / 87 (0.00%) 0 |
| Blood and lymphatic system disorders | | | |

| | | | |
|-----------------------------|-------------------|------------------|------------------|
| Anaemia | | | |
| subjects affected / exposed | 14 / 103 (13.59%) | 20 / 99 (20.20%) | 31 / 87 (35.63%) |
| occurrences (all) | 62 | 51 | 50 |
| Neutropenia | | | |
| subjects affected / exposed | 8 / 103 (7.77%) | 4 / 99 (4.04%) | 3 / 87 (3.45%) |
| occurrences (all) | 44 | 14 | 3 |
| Thrombocytopenia | | | |
| subjects affected / exposed | 4 / 103 (3.88%) | 4 / 99 (4.04%) | 6 / 87 (6.90%) |
| occurrences (all) | 6 | 18 | 8 |
| Lymphopenia | | | |
| subjects affected / exposed | 5 / 103 (4.85%) | 4 / 99 (4.04%) | 6 / 87 (6.90%) |
| occurrences (all) | 13 | 8 | 10 |
| Ear and labyrinth disorders | | | |
| Vertigo | | | |
| subjects affected / exposed | 7 / 103 (6.80%) | 9 / 99 (9.09%) | 3 / 87 (3.45%) |
| occurrences (all) | 13 | 14 | 3 |
| Eye disorders | | | |
| Dry eye | | | |
| subjects affected / exposed | 8 / 103 (7.77%) | 7 / 99 (7.07%) | 8 / 87 (9.20%) |
| occurrences (all) | 18 | 16 | 10 |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 66 / 103 (64.08%) | 60 / 99 (60.61%) | 42 / 87 (48.28%) |
| occurrences (all) | 338 | 287 | 95 |
| Nausea | | | |
| subjects affected / exposed | 21 / 103 (20.39%) | 25 / 99 (25.25%) | 24 / 87 (27.59%) |
| occurrences (all) | 41 | 62 | 34 |
| Vomiting | | | |
| subjects affected / exposed | 14 / 103 (13.59%) | 10 / 99 (10.10%) | 17 / 87 (19.54%) |
| occurrences (all) | 19 | 12 | 20 |
| Constipation | | | |
| subjects affected / exposed | 17 / 103 (16.50%) | 13 / 99 (13.13%) | 6 / 87 (6.90%) |
| occurrences (all) | 34 | 25 | 6 |
| Stomatitis | | | |
| subjects affected / exposed | 12 / 103 (11.65%) | 6 / 99 (6.06%) | 10 / 87 (11.49%) |
| occurrences (all) | 18 | 11 | 16 |
| Abdominal pain | | | |

| | | | |
|--|-------------------|------------------|------------------|
| subjects affected / exposed | 12 / 103 (11.65%) | 8 / 99 (8.08%) | 6 / 87 (6.90%) |
| occurrences (all) | 17 | 11 | 8 |
| Abdominal pain upper | | | |
| subjects affected / exposed | 12 / 103 (11.65%) | 10 / 99 (10.10%) | 3 / 87 (3.45%) |
| occurrences (all) | 17 | 19 | 3 |
| Dry mouth | | | |
| subjects affected / exposed | 6 / 103 (5.83%) | 10 / 99 (10.10%) | 5 / 87 (5.75%) |
| occurrences (all) | 6 | 12 | 6 |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 9 / 103 (8.74%) | 4 / 99 (4.04%) | 1 / 87 (1.15%) |
| occurrences (all) | 25 | 10 | 2 |
| Aphthous stomatitis | | | |
| subjects affected / exposed | 6 / 103 (5.83%) | 2 / 99 (2.02%) | 1 / 87 (1.15%) |
| occurrences (all) | 13 | 3 | 1 |
| Pyrexia | | | |
| subjects affected / exposed | 10 / 103 (9.71%) | 3 / 99 (3.03%) | 1 / 87 (1.15%) |
| occurrences (all) | 11 | 3 | 1 |
| Skin and subcutaneous tissue disorders | | | |
| Dry skin | | | |
| subjects affected / exposed | 50 / 103 (48.54%) | 43 / 99 (43.43%) | 18 / 87 (20.69%) |
| occurrences (all) | 221 | 158 | 54 |
| Rash | | | |
| subjects affected / exposed | 36 / 103 (34.95%) | 31 / 99 (31.31%) | 20 / 87 (22.99%) |
| occurrences (all) | 99 | 91 | 37 |
| Acne | | | |
| subjects affected / exposed | 11 / 103 (10.68%) | 13 / 99 (13.13%) | 15 / 87 (17.24%) |
| occurrences (all) | 30 | 34 | 25 |
| Erythema | | | |
| subjects affected / exposed | 18 / 103 (17.48%) | 16 / 99 (16.16%) | 5 / 87 (5.75%) |
| occurrences (all) | 33 | 30 | 13 |
| Pruritus | | | |
| subjects affected / exposed | 17 / 103 (16.50%) | 14 / 99 (14.14%) | 7 / 87 (8.05%) |
| occurrences (all) | 35 | 30 | 8 |
| Skin fissures | | | |
| subjects affected / exposed | 10 / 103 (9.71%) | 10 / 99 (10.10%) | 4 / 87 (4.60%) |
| occurrences (all) | 43 | 17 | 10 |

| | | | |
|--|-------------------------|------------------------|------------------------|
| Skin toxicity subjects affected / exposed occurrences (all) | 12 / 103 (11.65%) 23 | 6 / 99 (6.06%) 9 | 4 / 87 (4.60%) 5 |
| Nail disorder subjects affected / exposed occurrences (all) | 14 / 103 (13.59%) 27 | 8 / 99 (8.08%) 16 | 1 / 87 (1.15%) 3 |
| Alopecia subjects affected / exposed occurrences (all) | 9 / 103 (8.74%) 17 | 11 / 99 (11.11%) 29 | 1 / 87 (1.15%) 2 |
| Dermatitis acneiform subjects affected / exposed occurrences (all) | 5 / 103 (4.85%) 11 | 5 / 99 (5.05%) 7 | 5 / 87 (5.75%) 27 |
| Renal and urinary disorders Renal failure subjects affected / exposed occurrences (all) | 10 / 103 (9.71%) 35 | 7 / 99 (7.07%) 32 | 12 / 87 (13.79%) 46 |
| Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all) | 21 / 103 (20.39%) 57 | 17 / 99 (17.17%) 42 | 9 / 87 (10.34%) 15 |
| Arthralgia subjects affected / exposed occurrences (all) | 12 / 103 (11.65%) 20 | 18 / 99 (18.18%) 38 | 8 / 87 (9.20%) 11 |
| Bone pain subjects affected / exposed occurrences (all) | 9 / 103 (8.74%) 18 | 10 / 99 (10.10%) 17 | 8 / 87 (9.20%) 19 |
| Musculoskeletal pain subjects affected / exposed occurrences (all) | 5 / 103 (4.85%) 7 | 9 / 99 (9.09%) 13 | 5 / 87 (5.75%) 5 |
| Muscle spasms subjects affected / exposed occurrences (all) | 11 / 103 (10.68%) 28 | 9 / 99 (9.09%) 40 | 2 / 87 (2.30%) 7 |
| Pain in extremity subjects affected / exposed occurrences (all) | 7 / 103 (6.80%) 10 | 7 / 99 (7.07%) 13 | 1 / 87 (1.15%) 2 |
| Myalgia | | | |

| | | | |
|--|-------------------------|------------------------|----------------------|
| subjects affected / exposed occurrences (all) | 6 / 103 (5.83%) 6 | 3 / 99 (3.03%) 4 | 3 / 87 (3.45%) 4 |
| Musculoskeletal chest pain subjects affected / exposed occurrences (all) | 1 / 103 (0.97%) 1 | 6 / 99 (6.06%) 7 | 0 / 87 (0.00%) 0 |
| Infections and infestations | | | |
| Folliculitis subjects affected / exposed occurrences (all) | 10 / 103 (9.71%) 61 | 12 / 99 (12.12%) 40 | 8 / 87 (9.20%) 18 |
| Paronychia subjects affected / exposed occurrences (all) | 15 / 103 (14.56%) 45 | 10 / 99 (10.10%) 26 | 3 / 87 (3.45%) 17 |
| Bronchitis subjects affected / exposed occurrences (all) | 8 / 103 (7.77%) 15 | 8 / 99 (8.08%) 9 | 5 / 87 (5.75%) 6 |
| Urinary tract infection subjects affected / exposed occurrences (all) | 7 / 103 (6.80%) 13 | 9 / 99 (9.09%) 18 | 3 / 87 (3.45%) 3 |
| Conjunctivitis subjects affected / exposed occurrences (all) | 8 / 103 (7.77%) 25 | 8 / 99 (8.08%) 19 | 2 / 87 (2.30%) 3 |
| Rhinitis subjects affected / exposed occurrences (all) | 6 / 103 (5.83%) 12 | 8 / 99 (8.08%) 13 | 3 / 87 (3.45%) 4 |
| Cystitis subjects affected / exposed occurrences (all) | 7 / 103 (6.80%) 10 | 5 / 99 (5.05%) 8 | 1 / 87 (1.15%) 1 |
| Nasopharyngitis subjects affected / exposed occurrences (all) | 6 / 103 (5.83%) 6 | 5 / 99 (5.05%) 5 | 1 / 87 (1.15%) 1 |
| Lung infection subjects affected / exposed occurrences (all) | 1 / 103 (0.97%) 1 | 0 / 99 (0.00%) 0 | 5 / 87 (5.75%) 6 |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |

| | | | |
|-----------------------------|-------------------|------------------|------------------|
| subjects affected / exposed | 20 / 103 (19.42%) | 26 / 99 (26.26%) | 34 / 87 (39.08%) |
| occurrences (all) | 38 | 52 | 54 |
| Hypoalbuminaemia | | | |
| subjects affected / exposed | 5 / 103 (4.85%) | 5 / 99 (5.05%) | 6 / 87 (6.90%) |
| occurrences (all) | 10 | 12 | 10 |

| Non-serious adverse events | B2 - EGFR WT Erlotinib Fulvestrant | | |
|---|---------------------------------------|--|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 86 / 88 (97.73%) | | |
| Vascular disorders | | | |
| Hot flush | | | |
| subjects affected / exposed | 7 / 88 (7.95%) | | |
| occurrences (all) | 11 | | |
| Epistaxis | | | |
| subjects affected / exposed | 4 / 88 (4.55%) | | |
| occurrences (all) | 5 | | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 25 / 88 (28.41%) | | |
| occurrences (all) | 41 | | |
| Chest pain | | | |
| subjects affected / exposed | 10 / 88 (11.36%) | | |
| occurrences (all) | 13 | | |
| General physical health deterioration | | | |
| subjects affected / exposed | 13 / 88 (14.77%) | | |
| occurrences (all) | 15 | | |
| Fatigue | | | |
| subjects affected / exposed | 4 / 88 (4.55%) | | |
| occurrences (all) | 4 | | |
| Oedema peripheral | | | |
| subjects affected / exposed | 2 / 88 (2.27%) | | |
| occurrences (all) | 4 | | |
| Xerosis | | | |
| subjects affected / exposed | 3 / 88 (3.41%) | | |
| occurrences (all) | 6 | | |
| Pain | | | |

| | | | |
|--|---------------------|--|--|
| subjects affected / exposed occurrences (all) | 4 / 88 (4.55%) 5 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 28 / 88 (31.82%) | | |
| occurrences (all) | 44 | | |
| Dyspnoea | | | |
| subjects affected / exposed | 23 / 88 (26.14%) | | |
| occurrences (all) | 36 | | |
| Chest pain | | | |
| subjects affected / exposed | 1 / 88 (1.14%) | | |
| occurrences (all) | 1 | | |
| Productive cough | | | |
| subjects affected / exposed | 2 / 88 (2.27%) | | |
| occurrences (all) | 2 | | |
| Psychiatric disorders | | | |
| Depression | | | |
| subjects affected / exposed | 2 / 88 (2.27%) | | |
| occurrences (all) | 3 | | |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 9 / 88 (10.23%) | | |
| occurrences (all) | 11 | | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 12 / 88 (13.64%) | | |
| occurrences (all) | 19 | | |
| Gamma-glutamyltransferase increased | | | |
| subjects affected / exposed | 14 / 88 (15.91%) | | |
| occurrences (all) | 20 | | |
| Weight decreased | | | |
| subjects affected / exposed | 7 / 88 (7.95%) | | |
| occurrences (all) | 7 | | |
| Blood alkaline phosphatase increased | | | |
| subjects affected / exposed | 12 / 88 (13.64%) | | |
| occurrences (all) | 17 | | |

| | | | |
|--------------------------------------|------------------|--|--|
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 5 / 88 (5.68%) | | |
| occurrences (all) | 5 | | |
| Paraesthesia | | | |
| subjects affected / exposed | 2 / 88 (2.27%) | | |
| occurrences (all) | 2 | | |
| Dysgeusia | | | |
| subjects affected / exposed | 1 / 88 (1.14%) | | |
| occurrences (all) | 1 | | |
| Confusional state | | | |
| subjects affected / exposed | 2 / 88 (2.27%) | | |
| occurrences (all) | 2 | | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 29 / 88 (32.95%) | | |
| occurrences (all) | 48 | | |
| Neutropenia | | | |
| subjects affected / exposed | 6 / 88 (6.82%) | | |
| occurrences (all) | 16 | | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 7 / 88 (7.95%) | | |
| occurrences (all) | 14 | | |
| Lymphopenia | | | |
| subjects affected / exposed | 4 / 88 (4.55%) | | |
| occurrences (all) | 8 | | |
| Ear and labyrinth disorders | | | |
| Vertigo | | | |
| subjects affected / exposed | 1 / 88 (1.14%) | | |
| occurrences (all) | 1 | | |
| Eye disorders | | | |
| Dry eye | | | |
| subjects affected / exposed | 2 / 88 (2.27%) | | |
| occurrences (all) | 2 | | |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |

| | | | |
|--|------------------|--|--|
| subjects affected / exposed | 42 / 88 (47.73%) | | |
| occurrences (all) | 101 | | |
| Nausea | | | |
| subjects affected / exposed | 23 / 88 (26.14%) | | |
| occurrences (all) | 32 | | |
| Vomiting | | | |
| subjects affected / exposed | 17 / 88 (19.32%) | | |
| occurrences (all) | 20 | | |
| Constipation | | | |
| subjects affected / exposed | 9 / 88 (10.23%) | | |
| occurrences (all) | 13 | | |
| Stomatitis | | | |
| subjects affected / exposed | 4 / 88 (4.55%) | | |
| occurrences (all) | 6 | | |
| Abdominal pain | | | |
| subjects affected / exposed | 4 / 88 (4.55%) | | |
| occurrences (all) | 4 | | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 2 / 88 (2.27%) | | |
| occurrences (all) | 3 | | |
| Dry mouth | | | |
| subjects affected / exposed | 2 / 88 (2.27%) | | |
| occurrences (all) | 4 | | |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 3 / 88 (3.41%) | | |
| occurrences (all) | 7 | | |
| Aphthous stomatitis | | | |
| subjects affected / exposed | 1 / 88 (1.14%) | | |
| occurrences (all) | 1 | | |
| Pyrexia | | | |
| subjects affected / exposed | 5 / 88 (5.68%) | | |
| occurrences (all) | 6 | | |
| Skin and subcutaneous tissue disorders | | | |
| Dry skin | | | |
| subjects affected / exposed | 22 / 88 (25.00%) | | |
| occurrences (all) | 42 | | |

| | | | |
|---|------------------|--|--|
| Rash | | | |
| subjects affected / exposed | 28 / 88 (31.82%) | | |
| occurrences (all) | 64 | | |
| Acne | | | |
| subjects affected / exposed | 7 / 88 (7.95%) | | |
| occurrences (all) | 13 | | |
| Erythema | | | |
| subjects affected / exposed | 6 / 88 (6.82%) | | |
| occurrences (all) | 8 | | |
| Pruritus | | | |
| subjects affected / exposed | 5 / 88 (5.68%) | | |
| occurrences (all) | 5 | | |
| Skin fissures | | | |
| subjects affected / exposed | 5 / 88 (5.68%) | | |
| occurrences (all) | 13 | | |
| Skin toxicity | | | |
| subjects affected / exposed | 6 / 88 (6.82%) | | |
| occurrences (all) | 6 | | |
| Nail disorder | | | |
| subjects affected / exposed | 2 / 88 (2.27%) | | |
| occurrences (all) | 2 | | |
| Alopecia | | | |
| subjects affected / exposed | 1 / 88 (1.14%) | | |
| occurrences (all) | 1 | | |
| Dermatitis acneiform | | | |
| subjects affected / exposed | 2 / 88 (2.27%) | | |
| occurrences (all) | 4 | | |
| Renal and urinary disorders | | | |
| Renal failure | | | |
| subjects affected / exposed | 8 / 88 (9.09%) | | |
| occurrences (all) | 13 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 7 / 88 (7.95%) | | |
| occurrences (all) | 13 | | |
| Arthralgia | | | |

| | | | |
|-----------------------------|------------------|--|--|
| subjects affected / exposed | 5 / 88 (5.68%) | | |
| occurrences (all) | 6 | | |
| Bone pain | | | |
| subjects affected / exposed | 10 / 88 (11.36%) | | |
| occurrences (all) | 18 | | |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 7 / 88 (7.95%) | | |
| occurrences (all) | 7 | | |
| Muscle spasms | | | |
| subjects affected / exposed | 1 / 88 (1.14%) | | |
| occurrences (all) | 2 | | |
| Pain in extremity | | | |
| subjects affected / exposed | 5 / 88 (5.68%) | | |
| occurrences (all) | 9 | | |
| Myalgia | | | |
| subjects affected / exposed | 0 / 88 (0.00%) | | |
| occurrences (all) | 0 | | |
| Musculoskeletal chest pain | | | |
| subjects affected / exposed | 2 / 88 (2.27%) | | |
| occurrences (all) | 2 | | |
| Infections and infestations | | | |
| Folliculitis | | | |
| subjects affected / exposed | 4 / 88 (4.55%) | | |
| occurrences (all) | 5 | | |
| Paronychia | | | |
| subjects affected / exposed | 3 / 88 (3.41%) | | |
| occurrences (all) | 6 | | |
| Bronchitis | | | |
| subjects affected / exposed | 3 / 88 (3.41%) | | |
| occurrences (all) | 3 | | |
| Urinary tract infection | | | |
| subjects affected / exposed | 4 / 88 (4.55%) | | |
| occurrences (all) | 5 | | |
| Conjunctivitis | | | |
| subjects affected / exposed | 3 / 88 (3.41%) | | |
| occurrences (all) | 5 | | |

| | | | |
|------------------------------------|------------------|--|--|
| Rhinitis | | | |
| subjects affected / exposed | 1 / 88 (1.14%) | | |
| occurrences (all) | 1 | | |
| Cystitis | | | |
| subjects affected / exposed | 1 / 88 (1.14%) | | |
| occurrences (all) | 1 | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 0 / 88 (0.00%) | | |
| occurrences (all) | 0 | | |
| Lung infection | | | |
| subjects affected / exposed | 4 / 88 (4.55%) | | |
| occurrences (all) | 4 | | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 22 / 88 (25.00%) | | |
| occurrences (all) | 30 | | |
| Hypoalbuminaemia | | | |
| subjects affected / exposed | 4 / 88 (4.55%) | | |
| occurrences (all) | 4 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|--|
| 04 May 2012 | This amendment concerns the addition of 10% additional patients in order to take into account patients who will not be evaluable, the clarification of the inclusion criteria, the addition of the actions to be taken according to the toxicities of gefitinib, the addition of side effects of fulvestrant and various corrections in particular in the statistical part. |
| 10 December 2012 | This amendment concerns: <ul style="list-style-type: none">- the addition of new investigation centers- the removal of three centres: Lille Oscar Lambret, Maubeuge polyclinic and Saint-Omer- the change of address of one center (Toulon CHI)- the elimination of the realization of the partial pressure of oxygen at inclusion- the removal of the QLQ-C30 questionnaire- minor protocol fixes. |
| 07 May 2015 | This amendment concerns: <ul style="list-style-type: none">- extension of the study- the change of investigator for five centres: Le Mans CHG, Dax, Reims CHU, Clamart, Bobigny- the addition in the protocol of a maximum delay in the start of treatment- clarification of the non-inclusion criterion for patients who have already received an experimental drug.- modification of the non-inclusion criterion on anticoagulants- the addition of an additional ancillary study |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/32144133>