# Clinical trial results:
# LUX-Breast 1: An open-label, randomised phase III trial of BIBW 2992 and vinorelbine versus trastuzumab and vinorelbine in patients with metastatic Human Epidermal Growth Factor Receptor 2 (HER2)-overexpressing breast cancer failing one prior trastuzumab teatment

## Summary

| | |
|---|---|
| EudraCT number | 2009-015476-98 |
| Trial protocol | NL BE DE SK PT CZ FR AT IT ES FI LT LV SI GB IE NO |
| Global end of trial date | 06 July 2018 |

**Results information**

| | |
|---|---|
| Result version number | v1 |
| This version publication date | 20 July 2019 |
| First version publication date | 20 July 2019 |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | 1200.75 |

**Additional study identifiers**

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01125566 |
| WHO universal trial number (UTN) | - |

Notes:

**Sponsors**

| | |
|---|---|
| Sponsor organisation name | Boehringer Ingelheim |
| Sponsor organisation address | Binger Strasse 173, Ingelheim am Rhein, Germany, 55612 |
| Public contact | QRPE Processes and Systems Coordination, Clinical Trial Information Disclosure, Boehringer Ingelheim, 001 8002430127, clintriage.rdg@boehringer-ingelheim.com |
| Scientific contact | QRPE Processes and Systems Coordination, Clinical Trial Information Disclosure, Boehringer Ingelheim, 001 8002430127, clintriage.rdg@boehringer-ingelheim.com |

Notes:

**Paediatric regulatory details**

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

Notes:

## Results analysis stage

| | |
|---|---|
| Analysis stage | Final |
| Date of interim/final analysis | 30 July 2018 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 08 June 2013 |
| Global end of trial reached? | Yes |
| Global end of trial date | 06 July 2018 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

To investigate the efficacy and safety of afatinib in combination with vinorelbine with trastuzumab in combination with vinorelbine as treatment in patients with metastatic Human Epidermal Growth Factor Receptor 2 (HER2)-overexpressing breast cancer failing 1 prior trastuzumab treatment.

Protection of trial subjects:

Only participants that met all the study inclusion and none of the exclusion criteria were to be entered in the study. All participants were free to withdraw from the clinical trial at any time for any reason given. Close monitoring of all participants was adhered to throughout the trial conduct. Rescue medication was allowed for all participants as required.

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 22 June 2010 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | Japan: 3 |
| Country: Number of subjects enrolled | China: 141 |
| Country: Number of subjects enrolled | Taiwan: 74 |
| Country: Number of subjects enrolled | Korea, Republic of: 82 |
| Country: Number of subjects enrolled | Austria: 3 |
| Country: Number of subjects enrolled | Belgium: 11 |
| Country: Number of subjects enrolled | Belarus: 13 |
| Country: Number of subjects enrolled | Czech Republic: 10 |
| Country: Number of subjects enrolled | Germany: 26 |
| Country: Number of subjects enrolled | Spain: 22 |
| Country: Number of subjects enrolled | France: 19 |
| Country: Number of subjects enrolled | Italy: 6 |
| Country: Number of subjects enrolled | Ireland: 14 |
| Country: Number of subjects enrolled | Lithuania: 8 |
| Country: Number of subjects enrolled | Latvia: 3 |
| Country: Number of subjects enrolled | Netherlands: 8 |
| Country: Number of subjects enrolled | Portugal: 8 |
| Country: Number of subjects enrolled | Poland: 51 |
| Country: Number of subjects enrolled | Russian Federation: 21 |

| | |
|---|---|
| Country: Number of subjects enrolled | Slovakia: 6 |
| Country: Number of subjects enrolled | Slovenia: 3 |
| Country: Number of subjects enrolled | United Kingdom: 6 |
| Country: Number of subjects enrolled | Canada: 16 |
| Country: Number of subjects enrolled | United States: 27 |
| Country: Number of subjects enrolled | Australia: 16 |
| Country: Number of subjects enrolled | Brazil: 20 |
| Country: Number of subjects enrolled | Egypt: 2 |
| Country: Number of subjects enrolled | Israel: 13 |
| Country: Number of subjects enrolled | India: 53 |
| Country: Number of subjects enrolled | Mexico: 1 |
| Country: Number of subjects enrolled | Peru: 6 |
| Country: Number of subjects enrolled | Argentina: 5 |
| Country: Number of subjects enrolled | Chile: 17 |
| Country: Number of subjects enrolled | Lebanon: 3 |
| Country: Number of subjects enrolled | Singapore: 9 |
| Country: Number of subjects enrolled | Turkey: 2 |
| Country: Number of subjects enrolled | South Africa: 17 |
| Worldwide total number of subjects | 745 |
| EEA total number of subjects | 204 |

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) | 628 |
| From 65 to 84 years | 107 |
| 85 years and over | 10 |

## Subject disposition

### Recruitment

Recruitment details:

Randomised, active-controlled, open-label, parallel-group trial in participants with metastatic human epidermal growth factor receptor2(HER2)-overexpressing breast cancer failing one prior trastuzumab treatment. 508 randomized, 2 were not treated. 75 were switched treatment in which 1 was wrongly classified as discontinued prior to the switch.

### Pre-assignment

Screening details:

Participants were treated in the study until disease progression, undue toxicity, or withdrawal of consent. The cut-off date for RECIST-based efficacy was 08 June 2013; a second analysis (primarily for assessing Overall Survival (OS)) contains all data until final database lock (30 July 2018).

### Period 1

| | |
|---|---|
| Period 1 title | Patients before the switch (26Apr2013) |
| Is this the baseline period? | Yes |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

Blinding implementation details:

This was an open label trial. Blinding was not performed.

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Afatinib + Vinorelbine (AV) |

Arm description:

Participants received oral treatment of film-coated Afatinib tablet at a starting dose of 40 milligram (mg) once daily and weekly 10 minutes intravenous infusion of Vinorelbine 25 mg/meter^2 (meter=m) on days 1, 8, 15, and 22 of each course. The treatment was administered in treatment courses of 28 days. For Afatinib, a protocol-defined dose-reduction scheme was to be followed if a participant experienced certain pre-specified adverse events. From 26 April 2013, any participant who had been randomised to the AV arm stopped treatment, had the option to switch to Trastuzamb + Vinorelbine. 339 participants were randomised to the AV arm, however 2 were not treated and 1 center with 5 participants was excluded from the analysis. Consequently, number of subjects that started is 339 but only 332 reported to ensure consistent reporting with baseline characteristics.

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

Dosage and administration details:

Participants received oral treatment of film-coated Afatinib tablet at a starting dose of 40 milligram (mg) once daily and weekly 10 minutes intravenous infusion of Vinorelbine 25 mg/meter^2 (meter=m) on days 1, 8, 15, and 22 of each course. The treatment was administered in treatment courses of 28 days. For Afatinib, a protocol-defined dosereduction scheme was to be followed if a participant experienced certain pre-specified adverse events. From 26 April 2013, any participant who had been randomised to the AV arm stopped treatment, had the option to switch to Trastuzamb + Vinorelbine.

| | |
|---|---|
| Investigational medicinal product name | Vinorelbine |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Participants received oral treatment of film-coated Afatinib tablet at a starting dose of 40 milligram (mg) once daily and weekly 10 minutes intravenous infusion of Vinorelbine 25 mg/meter^2 (meter=m) on

days 1, 8, 15, and 22 of each course. The treatment was administered in treatment courses of 28 days. For Afatinib, a protocol-defined dosereduction scheme was to be followed if a participant experienced certain pre-specified adverse events. From 26 April 2013, any participant who had been randomised to the AV arm stopped treatment, had the option to switch to Trastuzamb + Vinorelbine.

| **Arm title** | Trastuzumab + Vinorelbine (TV) |
|---|---|

Arm description:

Participants received an intravenous infusion of Trastuzumab 2 mg/kilogram (kg) weekly, following an initial loading dose of 4 mg/kg and weekly 10 minutes intravenous infusion of Vinorelbine 25 mg/m^2 on days 1, 8, 15, and 22 of each course. The treatment was administered in treatment courses of 28 days. 169 participants were randomised to the TV arm, however 1 center with 1 participants was excluded from the analysis. Consequently, number of subjects that started is 169 but only 168 reported to ensure consistent reporting with baseline characteristics.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Trastuzumab |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Powder for concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Participants received an intravenous infusion of Trastuzumab 2 mg/kilogram (kg) weekly, following an initial loading dose of 4 mg/kg and weekly 10 minutes intravenous infusion of Vinorelbine 25 mg/m^2 on days 1, 8, 15, and 22 of each course. The treatment was administered in treatment courses of 28 days.

| | |
|---|---|
| Investigational medicinal product name | Vinorelbine |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Participants received an intravenous infusion of Trastuzumab 2 mg/kilogram (kg) weekly, following an initial loading dose of 4 mg/kg and weekly 10 minutes intravenous infusion of Vinorelbine 25 mg/m^2 on days 1, 8, 15, and 22 of each course. The treatment was administered in treatment courses of 28 days.

| **Number of subjects in period 1[1]** | Afatinib + Vinorelbine (AV) | Trastuzumab + Vinorelbine (TV) |
|---|---|---|
| Started | 332 | 168 |
| Completed | 75 | 0 |
| Not completed | 257 | 168 |
| Adverse event, non-fatal | 24 | 5 |
| Refused to continue taking medication | 24 | 23 |
| Other than listed above | 23 | 13 |
| Lost to follow-up | - | 1 |
| Progressive disease according to RECIST | 180 | 118 |
| Worsening of underlying cancer disease | 6 | 6 |
| Protocol deviation | - | 2 |

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Baseline characteristics are based on patients who were randomised after successfully completing the screening period and received at least one dose of the trial medication.

## Period 2

| | |
|---|---|
| Period 2 title | Patients who switched from AV to TV |
| Is this the baseline period? | No |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

Blinding implementation details:

This was an open label trial. Blinding was not performed.

## Arms

| | |
|---|---|
| **Arm title** | AV switched to TV |

Arm description:

This group describes participants who discontinued AV treatment and switched to TV, provided they were without disease progression on AV, following data monitoring committee (DMC) recommendation to terminate recruitment on 26 April 2013.

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

Dosage and administration details:

Participants received oral treatment of film-coated Afatinib tablet at a starting dose of 40 milligram (mg) once daily and weekly 10 minutes intravenous infusion of Vinorelbine 25 mg/meter^2 (meter=m) on days 1, 8, 15, and 22 of each course. The treatment was administered in treatment courses of 28 days. For Afatinib, a protocol-defined dosereduction scheme was to be followed if a participant experienced certain pre-specified adverse events. From 26 April 2013, any participant who had been randomised to the AV arm stopped treatment, had the option to switch to Trastuzamb + Vinorelbine.

| | |
|---|---|
| Investigational medicinal product name | Vinorelbine |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Intracavernous use |

Dosage and administration details:

Participants received oral treatment of film-coated Afatinib tablet at a starting dose of 40 milligram (mg) once daily and weekly 10 minutes intravenous infusion of Vinorelbine 25 mg/meter^2 (meter=m) on days 1, 8, 15, and 22 of each course. The treatment was administered in treatment courses of 28 days. For Afatinib, a protocol-defined dosereduction scheme was to be followed if a participant experienced certain pre-specified adverse events. From 26 April 2013, any participant who had been randomised to the AV arm stopped treatment, had the option to switch to Trastuzamb + Vinorelbine.

| | |
|---|---|
| Investigational medicinal product name | Trastuzumab |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Participants received an intravenous infusion of Trastuzumab 2 mg/kilogram (kg) weekly, following an initial loading dose of 4 mg/kg and weekly 10 minutes intravenous infusion of Vinorelbine 25 mg/m^2 on days 1, 8, 15, and 22 of each course. The treatment was administered in treatment courses of 28 days.

| | |
|---|---|
| Investigational medicinal product name | Vinorelbine |
| Investigational medicinal product code | |
| Other name | |

| | |
|---|---|
| Pharmaceutical forms | Powder for concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Participants received an intravenous infusion of Trastuzumab 2 mg/kilogram (kg) weekly, following an initial loading dose of 4 mg/kg and weekly 10 minutes intravenous infusion of Vinorelbine 25 mg/m^2 on days 1, 8, 15, and 22 of each course. The treatment was administered in treatment courses of 28 days.

| **Number of subjects in period 2** | AV switched to TV |
|---|---|
| Started | 75 |
| Completed | 2 |
| Not completed | 73 |
| Refused to continue taking medication | 7 |
| Other than listed above | 4 |
| Progressive disease according to RECIST | 59 |
| Worsening of underlying cancer disease | 3 |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Afatinib + Vinorelbine (AV) |

Reporting group description:

Participants received oral treatment of film-coated Afatinib tablet at a starting dose of 40 milligram (mg) once daily and weekly 10 minutes intravenous infusion of Vinorelbine 25 mg/meter^2 (meter=m) on days 1, 8, 15, and 22 of each course. The treatment was administered in treatment courses of 28 days. For Afatinib, a protocol-defined dose-reduction scheme was to be followed if a participant experienced certain pre-specified adverse events. From 26 April 2013, any participant who had been randomised to the AV arm stopped treatment, had the option to switch to Trastuzamb + Vinorelbine. 339 participants were randomised to the AV arm, however 2 were not treated and 1 center with 5 participants was excluded from the analysis. Consequently, number of subjects that started is 339 but only 332 reported to ensure consistent reporting with baseline characteristics.

| Reporting group title | Trastuzumab + Vinorelbine (TV) |
|---|---|

Reporting group description:

Participants received an intravenous infusion of Trastuzumab 2 mg/kilogram (kg) weekly, following an initial loading dose of 4 mg/kg and weekly 10 minutes intravenous infusion of Vinorelbine 25 mg/m^2 on days 1, 8, 15, and 22 of each course. The treatment was administered in treatment courses of 28 days. 169 participants were randomised to the TV arm, however 1 center with 1 participants was excluded from the analysis. Consequently, number of subjects that started is 169 but only 168 reported to ensure consistent reporting with baseline characteristics.

| Reporting group values | Afatinib + Vinorelbine (AV) | Trastuzumab + Vinorelbine (TV) | Total |
|---|---|---|---|
| Number of subjects | 332 | 168 | 500 |
| Age categorical | | | |
| Units: Subjects | | | |
| Age Continuous | | | |
| Treated Set (TS): The TS included all randomised participantsbwho were documented to have taken at least 1 dose of study medication (i.e. afatinib, trastuzumab, or vinorelbine). One centre with 6 subjects was excluded from analysis. | | | |
| Units: years | | | |
| arithmetic mean | 51.8 | 53.1 | |
| standard deviation | ± 11.3 | ± 12.3 | - |
| Sex: Female, Male | | | |
| TS | | | |
| Units: Subjects | | | |
| Female | 332 | 168 | 500 |
| Male | 0 | 0 | 0 |
| Race (NIH/OMB) | | | |
| TS. Ethnicity data was not reported for the trial. | | | |
| Units: Subjects | | | |
| American Indian or Alaska Native | 1 | 1 | 2 |
| Asian | 172 | 81 | 253 |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | 0 |
| Black or African American | 6 | 3 | 9 |
| White | 136 | 72 | 208 |
| More than one race | 0 | 0 | 0 |
| Unknown or Not Reported | 17 | 11 | 28 |

## End points

### End points reporting groups

| Reporting group title | Afatinib + Vinorelbine (AV) |
|---|---|

Reporting group description:

Participants received oral treatment of film-coated Afatinib tablet at a starting dose of 40 milligram (mg) once daily and weekly 10 minutes intravenous infusion of Vinorelbine 25 mg/meter^2 (meter=m) on days 1, 8, 15, and 22 of each course. The treatment was administered in treatment courses of 28 days. For Afatinib, a protocol-defined dose-reduction scheme was to be followed if a participant experienced certain pre-specified adverse events. From 26 April 2013, any participant who had been randomised to the AV arm stopped treatment, had the option to switch to Trastuzamb + Vinorelbine. 339 participants were randomised to the AV arm, however 2 were not treated and 1 center with 5 participants was excluded from the analysis. Consequently, number of subjects that started is 339 but only 332 reported to ensure consistent reporting with baseline characteristics.

| Reporting group title | Trastuzumab + Vinorelbine (TV) |
|---|---|

Reporting group description:

Participants received an intravenous infusion of Trastuzumab 2 mg/kilogram (kg) weekly, following an initial loading dose of 4 mg/kg and weekly 10 minutes intravenous infusion of Vinorelbine 25 mg/m^2 on days 1, 8, 15, and 22 of each course. The treatment was administered in treatment courses of 28 days. 169 participants were randomised to the TV arm, however 1 center with 1 participants was excluded from the analysis. Consequently, number of subjects that started is 169 but only 168 reported to ensure consistent reporting with baseline characteristics.

| Reporting group title | AV switched to TV |
|---|---|

Reporting group description:

This group describes participants who discontinued AV treatment and switched to TV, provided they were without disease progression on AV, following data monitoring committee (DMC) recommendation to terminate recruitment on 26 April 2013.

| Subject analysis set title | Afatinib + Vinorelbine (AV) |
|---|---|
| Subject analysis set type | Per protocol |

Subject analysis set description:

Participants received oral treatment of film-coated Afatinib tablet at a starting dose of 40 milligram (mg) once daily and weekly 10 minutes intravenous infusion of Vinorelbine 25 mg/meter^2 (meter=m) on days 1, 8, 15, and 22 of each course. The treatment was administered in treatment courses of 28 days. For Afatinib, a protocol-defined dose-reduction scheme was to be followed if a participant experienced certain pre-specified adverse events. From 26 April 2013, any participant who had been randomised to the AV arm stopped treatment, had the option to switch to Trastuzamb + Vinorelbine. 339 participants were randomised to the AV arm, however 2 were not treated and 1 center with 5 participants was excluded from the analysis. Consequently, number of subjects that started is 339 but only 332 reported to ensure consistent reporting with baseline characteristics.

| Subject analysis set title | Trastuzumab + Vinorelbine (TV) |
|---|---|
| Subject analysis set type | Per protocol |

Subject analysis set description:

Participants received an intravenous infusion of Trastuzumab 2 mg/kilogram (kg) weekly, following an initial loading dose of 4 mg/kg and weekly 10 minutes intravenous infusion of Vinorelbine 25 mg/m^2 on days 1, 8, 15, and 22 of each course. The treatment was administered in treatment courses of 28 days. 169 participants were randomised to the TV arm, however 1 center with 1 participants was excluded from the analysis. Consequently, number of subjects that started is 169 but only 168 reported to ensure consistent reporting with baseline characteristics.

### Primary: Progression-free Survival (PFS)

| End point title | Progression-free Survival (PFS) |
|---|---|

End point description:

PFS is defined as time from randomisation to disease progression or death whichever occurs first. Assessed by investigator according to the Response Evaluation Criteria in Solid Tumours (RECIST 1.1). RECIST is a set of published rules that define when tumors in cancer patients improve ("respond"), stay the same ("stabilize") or worsen ("progress") during treatment. Only data collected until the cut-off date for RECIST 1.1 based endpoints (08Jun2013) were considered. Progression of disease was determined if at least 1 of the following criteria applied: - At least a 20% increase in the sum of the diameters (SoD) of target lesions taking as reference the smallest SoD recorded since the treatment started, together with an absolute increase in the SoD of at least 5 mm - Appearance of 1 or more new lesions -

Unequivocal progression of existing non-target lesions. Randomised set (RS): The RS included all participants who were randomised to receive treatment, whether treated or not.

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

End point timeframe:

From randomization (07Sep2010) until disease progression, death or data cut-off (08Jun2013); Up to 34 months

| **End point values** | Afatinib + Vinorelbine (AV) | Trastuzumab + Vinorelbine (TV) | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 339[1] | 169[2] | | |
| Units: Months | | | | |
| median (inter-quartile range (Q1-Q3)) | 5.49 (3.55 to 9.07) | 5.55 (3.55 to 10.84) | | |

Notes:

[1] - RS

[2] - RS

## Statistical analyses

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

Statistical analysis description:

Two sided p-value was derived from a log rank test stratified by the setting of prior Trastuzumab failure, hormone receptors status and region of the investigational site.

| Comparison groups | Afatinib + Vinorelbine (AV) v Trastuzumab + Vinorelbine (TV) |
|---|---|
| Number of subjects included in analysis | 508 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[3] |
| P-value | = 0.4224 [4] |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.87 |
| upper limit | 1.41 |

Notes:

[3] - Hazard ratio is derived from Cox proportional hazard model stratified by prior Trastuzumab failure, hormone receptors status and region of the investigational site.

[4] - Two sided p-value was derived from a log rank test stratified by the setting of prior Trastuzumab failure, hormone receptors status and region of the investigational site.

## Secondary: Overall Survival (OS)

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

End point description:

OS is defined as time from randomisation to death irrespective of the cause of the death. For patients who had not died up to the cut-off date (03Sep2013), the date they were last known to be alive was derived from the patient status records, the trial completion record, radiological imaging assessments, the study treatment termination record, and the randomisation date.

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

End point timeframe:

From randomisation (07Sep2010) to database lock (30Jul2018), up to 95 months.

| End point values | Afatinib + Vinorelbine (AV) | Trastuzumab + Vinorelbine (TV) | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 339[5] | 169[6] | | |
| Units: Months | | | | |
| median (inter-quartile range (Q1-Q3)) | 20.17 (10.74 to 39.52) | 29.60 (13.34 to 43.99) | | |

Notes:

[5] - RS including participants with available data for OS

[6] - RS including participants with available data for OS

### Statistical analyses

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

Statistical analysis description:

Results of presented analyses are to be seen as exploratory (no confirmatory testing was performed). Two sided p-value from a log rank test stratified by the setting of prior Trastuzumab failure, hormone receptors status and region of the investigational site.

| | |
|---|---|
| Comparison groups | Afatinib + Vinorelbine (AV) v Trastuzumab + Vinorelbine (TV) |
| Number of subjects included in analysis | 508 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[7] |
| P-value | = 0.024 [8] |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.03 |
| upper limit | 1.63 |

Notes:

[7] - Hazard ratio is derived from Cox proportional hazard model stratified by prior Trastuzumab failure, hormone receptors status and region of the investigational site.

[8] - Two sided p-value from a log rank test stratified by the setting of prior Trastuzumab failure, hormone receptors status and region of the investigational site.

### Secondary: Best RECIST assessment

| End point title | Best RECIST assessment |
|---|---|

End point description:

Best RECIST assessment is defined as CR, PR, stable disease (SD), PD or not evaluable by investigator (RECIST version 1.1). CR for target lesions (TL): Disappearance of all target lesions. CR for non-target lesions (NTL): Disappearance of all non-target lesions and normalization of tumour marker level. All lymph nodes must be non-pathological in size (<10mm short axis). PR: At least a 30% decrease in the sum of diameters (SoD) of target lesions taking as reference the baseline sum diameters. SD: Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as references the smallest SoD while on study. PD: At least a 20% increase in the SoD of target lesions, taking as references the smallest sum on study (this includes the baseline sum if that is the smallest on study). Also, the sum must also demonstrate an absolute increase of a least 5mm. Appearance of one or more new lesions.

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

End point timeframe:

From randomization (07Sep2010) until disease progression, death or data cut-off (08Jun2013); Up to 34 months

| **End point values** | Afatinib + Vinorelbine (AV) | Trastuzumab + Vinorelbine (TV) | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 334[9] | 168[10] | | |
| Units: Percentage of participants | | | | |
| number (not applicable) | | | | |
| Complete response (CR) | 3.3 | 3.0 | | |
| Partial response (PR) | 43.1 | 41.0 | | |
| Stable disease (SD) | 31.7 | 26.8 | | |
| Progressive Disease (PD) | 12.6 | 17.9 | | |
| Missing | 9.3 | 8.3 | | |

Notes:

[9] - RS including participants with available data for best RECIST assessment

[10] - RS including participants with available data for best RECIST assessment

## Statistical analyses

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

Statistical analysis description:

Results of presented analyses are to be seen as exploratory (no confirmatory testing was performed). Logistic regression stratified by prior Trastuzumab failure, hormone receptors status and region of the investigational site.

| Comparison groups | Afatinib + Vinorelbine (AV) v Trastuzumab + Vinorelbine (TV) |
|---|---|
| Number of subjects included in analysis | 502 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[11] |
| P-value | = 0.6431 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.09 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.756 |
| upper limit | 1.572 |

Notes:

[11] - The odds ratio for the comparison afatinib + vinorelbine vs. trastuzumab + vinorelbine below 1 favours Afatinib.

## Secondary: Objective Response (OR)

| End point title | Objective Response (OR) |
|---|---|

End point description:

OR is defined as complete response (CR) and partial response (PR). Assessed by investigator according to Response Evaluation Criteria in Solid Tumours (RECIST) 1.1. Complete Response (CR) for target lesions (TL): Disappearance of all target lesions. Complete Response (CR) for non-target lesions (NTL): Disappearance of all non-target lesions and normalization of tumour marker level. All lymph nodes must

be non-pathological in size (<10mm short axis) Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions taking as reference the baseline sum diameters. Other factors which add to the overall response of an imaging timepoint as PR are as below:- - CR in TL, but non-CR/Non-PD in NTL leads to PR - CR in TL, but not evaluated NTL leads to PR - PR in TL, but non-PD NTL or not all evaluated NTL leads to PR

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

End point timeframe:

Post baseline tumour-imaging was performed at Week 8, 16, 24, 32, 40, 48, 56 and then every 12 weeks (Until final data-base lock on 30 Jul 2018; Up to 95 months)

| **End point values** | Afatinib + Vinorelbine (AV) | Trastuzumab + Vinorelbine (TV) | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 334[12] | 168[13] | | |
| Units: Percentage of participants (%) | | | | |
| number (not applicable) | 46.4 | 47.0 | | |

Notes:

[12] - RS including participants with available data for OR

[13] - RS including participants with available data for OR

## Statistical analyses

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

Statistical analysis description:

Results of presented analyses are to be seen as exploratory (no confirmatory testing was performed). Logistic regression stratified by prior Trastuzumab failure, hormone receptors status and region of the investigational site.

| | |
|---|---|
| Comparison groups | Afatinib + Vinorelbine (AV) v Trastuzumab + Vinorelbine (TV) |
| Number of subjects included in analysis | 502 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[14] |
| P-value | = 0.8829 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.029 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.707 |
| upper limit | 1.496 |

Notes:

[14] - The odds ratio for the comparison afatinib + vinorelbine vs. trastuzumab + vinorelbine below 1 favours AV.

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From first administration of treatment within the trial until last administration of treatment within the trial, up to 76 months.

Adverse event reporting additional description:

Treated set was used for reporting the other adverse event and serious adverse event.

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

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 21.0 |

### Reporting groups

| | |
|---|---|
| Reporting group title | Afatinib + Vinorelbine (AV) |

Reporting group description:

Participants received oral treatment of film-coated Afatinib tablet at a starting dose of 40 milligram (mg) once daily and weekly 10 minutes intravenous infusion of Vinorelbine 25 mg/meter^2 (meter=m) on days 1, 8, 15, and 22 of each course. The treatment was administered in treatment courses of 28 days. For Afatinib, a protocol-defined dose-reduction scheme was to be followed if a participant experienced certain pre-specified adverse events. From 26 April 2013, any participant who had been randomised to the AV arm stopped treatment, had the option to switch to Trastuzamb + Vinorelbine.

| | |
|---|---|
| Reporting group title | AV switched to TV |

Reporting group description:

This group describes participants who discontinued AV treatment and switched to TV, provided they were without disease progression on AV, following data monitoring committee (DMC) recommendation to terminate recruitment on 26 April 2013.

| | |
|---|---|
| Reporting group title | Trastuzumab + Vinorelbine (TV) |

Reporting group description:

Participants received an intravenous infusion of Trastuzumab 2 mg/kilogram (kg) weekly, following an initial loading dose of 4 mg/kg and weekly 10 minutes intravenous infusion of Vinorelbine 25 mg/m^2 on days 1, 8, 15, and 22 of each course. The treatment was administered in treatment courses of 28 days.

| **Serious adverse events** | Afatinib + Vinorelbine (AV) | AV switched to TV | Trastuzumab + Vinorelbine (TV) |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 123 / 337 (36.50%) | 15 / 75 (20.00%) | 45 / 169 (26.63%) |
| number of deaths (all causes) | 235 | 3 | 111 |
| number of deaths resulting from adverse events | 3 | 0 | 0 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Brain cancer metastatic | | | |
| subjects affected / exposed | 1 / 337 (0.30%) | 0 / 75 (0.00%) | 0 / 169 (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 |
| Brain neoplasm | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 2 / 337 (0.59%) | 0 / 75 (0.00%) | 0 / 169 (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 |
| Breast cancer | | | |
| subjects affected / exposed | 3 / 337 (0.89%) | 0 / 75 (0.00%) | 0 / 169 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 3 | 0 / 0 | 0 / 0 |
| Breast cancer metastatic | | | |
| subjects affected / exposed | 2 / 337 (0.59%) | 1 / 75 (1.33%) | 0 / 169 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| Breast cancer recurrent | | | |
| subjects affected / exposed | 1 / 337 (0.30%) | 0 / 75 (0.00%) | 0 / 169 (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 |
| Infected neoplasm | | | |
| subjects affected / exposed | 1 / 337 (0.30%) | 0 / 75 (0.00%) | 0 / 169 (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 |
| Malignant neoplasm progression | | | |
| subjects affected / exposed | 2 / 337 (0.59%) | 1 / 75 (1.33%) | 0 / 169 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| Malignant pleural effusion | | | |
| subjects affected / exposed | 2 / 337 (0.59%) | 0 / 75 (0.00%) | 0 / 169 (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 |
| Metastases to bone | | | |
| subjects affected / exposed | 1 / 337 (0.30%) | 0 / 75 (0.00%) | 0 / 169 (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 |
| Metastases to central nervous system | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 10 / 337 (2.97%) | 3 / 75 (4.00%) | 5 / 169 (2.96%) |
| occurrences causally related to treatment / all | 0 / 10 | 0 / 3 | 0 / 5 |
| deaths causally related to treatment / all | 0 / 4 | 0 / 2 | 0 / 1 |
| Metastases to liver | | | |
| subjects affected / exposed | 3 / 337 (0.89%) | 0 / 75 (0.00%) | 0 / 169 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| Metastases to lung | | | |
| subjects affected / exposed | 1 / 337 (0.30%) | 0 / 75 (0.00%) | 0 / 169 (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 |
| Metastases to meninges | | | |
| subjects affected / exposed | 0 / 337 (0.00%) | 1 / 75 (1.33%) | 0 / 169 (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 |
| Metastatic neoplasm | | | |
| subjects affected / exposed | 1 / 337 (0.30%) | 0 / 75 (0.00%) | 0 / 169 (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 |
| Neoplasm progression | | | |
| subjects affected / exposed | 2 / 337 (0.59%) | 0 / 75 (0.00%) | 0 / 169 (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 |
| Pericardial effusion malignant | | | |
| subjects affected / exposed | 1 / 337 (0.30%) | 0 / 75 (0.00%) | 0 / 169 (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 |
| Tumour necrosis | | | |
| subjects affected / exposed | 1 / 337 (0.30%) | 0 / 75 (0.00%) | 0 / 169 (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 |
| Basal cell carcinoma | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 337 (0.00%) | 0 / 75 (0.00%) | 1 / 169 (0.59%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fibroadenoma of breast | | | |
| subjects affected / exposed | 0 / 337 (0.00%) | 0 / 75 (0.00%) | 1 / 169 (0.59%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ovarian cancer | | | |
| subjects affected / exposed | 1 / 337 (0.30%) | 0 / 75 (0.00%) | 0 / 169 (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 |
| Squamous cell carcinoma | | | |
| subjects affected / exposed | 0 / 337 (0.00%) | 0 / 75 (0.00%) | 1 / 169 (0.59%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 1 / 337 (0.30%) | 0 / 75 (0.00%) | 0 / 169 (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 |
| Hypotension | | | |
| subjects affected / exposed | 1 / 337 (0.30%) | 0 / 75 (0.00%) | 0 / 169 (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 |
| Phlebitis | | | |
| subjects affected / exposed | 1 / 337 (0.30%) | 0 / 75 (0.00%) | 0 / 169 (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 |
| Shock | | | |
| subjects affected / exposed | 1 / 337 (0.30%) | 0 / 75 (0.00%) | 0 / 169 (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 |
| Thrombosis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 337 (0.30%) | 0 / 75 (0.00%) | 1 / 169 (0.59%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Venous thrombosis | | | |
| subjects affected / exposed | 1 / 337 (0.30%) | 0 / 75 (0.00%) | 0 / 169 (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 |
| Aortic stenosis | | | |
| subjects affected / exposed | 0 / 337 (0.00%) | 0 / 75 (0.00%) | 1 / 169 (0.59%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Surgical and medical procedures | | | |
| Breast operation | | | |
| subjects affected / exposed | 1 / 337 (0.30%) | 0 / 75 (0.00%) | 0 / 169 (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 |
| Central venous catheterisation | | | |
| subjects affected / exposed | 0 / 337 (0.00%) | 0 / 75 (0.00%) | 1 / 169 (0.59%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Adverse drug reaction | | | |
| subjects affected / exposed | 0 / 337 (0.00%) | 0 / 75 (0.00%) | 1 / 169 (0.59%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Asthenia | | | |
| subjects affected / exposed | 2 / 337 (0.59%) | 0 / 75 (0.00%) | 1 / 169 (0.59%) |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Chest pain | | | |
| subjects affected / exposed | 1 / 337 (0.30%) | 0 / 75 (0.00%) | 0 / 169 (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 |

| | | | |
|---|---|---|---|
| Condition aggravated | | | |
| subjects affected / exposed | 0 / 337 (0.00%) | 0 / 75 (0.00%) | 1 / 169 (0.59%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Disease progression | | | |
| subjects affected / exposed | 1 / 337 (0.30%) | 0 / 75 (0.00%) | 0 / 169 (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 |
| Facial pain | | | |
| subjects affected / exposed | 0 / 337 (0.00%) | 0 / 75 (0.00%) | 1 / 169 (0.59%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fatigue | | | |
| subjects affected / exposed | 2 / 337 (0.59%) | 0 / 75 (0.00%) | 1 / 169 (0.59%) |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gait disturbance | | | |
| subjects affected / exposed | 0 / 337 (0.00%) | 0 / 75 (0.00%) | 1 / 169 (0.59%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General physical health deterioration | | | |
| subjects affected / exposed | 2 / 337 (0.59%) | 0 / 75 (0.00%) | 1 / 169 (0.59%) |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Mucosal inflammation | | | |
| subjects affected / exposed | 5 / 337 (1.48%) | 0 / 75 (0.00%) | 0 / 169 (0.00%) |
| occurrences causally related to treatment / all | 5 / 5 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 0 / 337 (0.00%) | 0 / 75 (0.00%) | 1 / 169 (0.59%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pyrexia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 15 / 337 (4.45%) | 2 / 75 (2.67%) | 5 / 169 (2.96%) |
| occurrences causally related to treatment / all | 9 / 16 | 0 / 2 | 3 / 5 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Catheter site inflammation | | | |
| subjects affected / exposed | 1 / 337 (0.30%) | 0 / 75 (0.00%) | 0 / 169 (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 |
| Device related thrombosis | | | |
| subjects affected / exposed | 1 / 337 (0.30%) | 0 / 75 (0.00%) | 0 / 169 (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 |
| Multiple organ dysfunction syndrome | | | |
| subjects affected / exposed | 2 / 337 (0.59%) | 0 / 75 (0.00%) | 0 / 169 (0.00%) |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 1 / 2 | 0 / 0 | 0 / 0 |
| Immune system disorders | | | |
| Anaphylactic reaction | | | |
| subjects affected / exposed | 1 / 337 (0.30%) | 0 / 75 (0.00%) | 0 / 169 (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 |
| Reproductive system and breast disorders | | | |
| Breast mass | | | |
| subjects affected / exposed | 0 / 337 (0.00%) | 0 / 75 (0.00%) | 1 / 169 (0.59%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Breast pain | | | |
| subjects affected / exposed | 0 / 337 (0.00%) | 0 / 75 (0.00%) | 1 / 169 (0.59%) |
| 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 haemorrhage | | | |
| subjects affected / exposed | 1 / 337 (0.30%) | 0 / 75 (0.00%) | 0 / 169 (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, thoracic and mediastinal disorders | | | |
| Dyspnoea | | | |
| subjects affected / exposed | 2 / 337 (0.59%) | 0 / 75 (0.00%) | 1 / 169 (0.59%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Interstitial lung disease | | | |
| subjects affected / exposed | 1 / 337 (0.30%) | 0 / 75 (0.00%) | 0 / 169 (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 |
| Pulmonary embolism | | | |
| subjects affected / exposed | 0 / 337 (0.00%) | 1 / 75 (1.33%) | 4 / 169 (2.37%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 1 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Pulmonary fibrosis | | | |
| subjects affected / exposed | 1 / 337 (0.30%) | 0 / 75 (0.00%) | 0 / 169 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| Respiratory failure | | | |
| subjects affected / exposed | 1 / 337 (0.30%) | 0 / 75 (0.00%) | 1 / 169 (0.59%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lung consolidation | | | |
| subjects affected / exposed | 0 / 337 (0.00%) | 1 / 75 (1.33%) | 0 / 169 (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 |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 0 / 337 (0.00%) | 0 / 75 (0.00%) | 1 / 169 (0.59%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sinus disorder | | | |
| subjects affected / exposed | 1 / 337 (0.30%) | 0 / 75 (0.00%) | 0 / 169 (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 |

| | | | |
|---|---|---|---|
| Psychiatric disorders | | | |
| Mood altered | | | |
| subjects affected / exposed | 1 / 337 (0.30%) | 0 / 75 (0.00%) | 0 / 169 (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 | | | |
| Blood creatinine increased | | | |
| subjects affected / exposed | 3 / 337 (0.89%) | 0 / 75 (0.00%) | 0 / 169 (0.00%) |
| occurrences causally related to treatment / all | 4 / 4 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood urea increased | | | |
| subjects affected / exposed | 1 / 337 (0.30%) | 0 / 75 (0.00%) | 0 / 169 (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 |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 1 / 337 (0.30%) | 0 / 75 (0.00%) | 1 / 169 (0.59%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Platelet count decreased | | | |
| subjects affected / exposed | 1 / 337 (0.30%) | 0 / 75 (0.00%) | 0 / 169 (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 | | | |
| Arthropod sting | | | |
| subjects affected / exposed | 1 / 337 (0.30%) | 0 / 75 (0.00%) | 0 / 169 (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 | 0 / 337 (0.00%) | 1 / 75 (1.33%) | 0 / 169 (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 |
| Toxicity to various agents | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 337 (0.00%) | 1 / 75 (1.33%) | 0 / 169 (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 |
| Cardiac disorders | | | |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 0 / 337 (0.00%) | 0 / 75 (0.00%) | 1 / 169 (0.59%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Palpitations | | | |
| subjects affected / exposed | 0 / 337 (0.00%) | 0 / 75 (0.00%) | 2 / 169 (1.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pericardial effusion | | | |
| subjects affected / exposed | 0 / 337 (0.00%) | 0 / 75 (0.00%) | 1 / 169 (0.59%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Left ventricular failure | | | |
| subjects affected / exposed | 0 / 337 (0.00%) | 0 / 75 (0.00%) | 1 / 169 (0.59%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Myocardial ischaemia | | | |
| subjects affected / exposed | 0 / 337 (0.00%) | 0 / 75 (0.00%) | 1 / 169 (0.59%) |
| 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 disorders | | | |
| Altered state of consciousness | | | |
| subjects affected / exposed | 1 / 337 (0.30%) | 0 / 75 (0.00%) | 0 / 169 (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 |
| Central nervous system lesion | | | |
| subjects affected / exposed | 1 / 337 (0.30%) | 0 / 75 (0.00%) | 0 / 169 (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 |
| Depressed level of consciousness | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 337 (0.30%) | 0 / 75 (0.00%) | 1 / 169 (0.59%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Dizziness | | | |
| subjects affected / exposed | 1 / 337 (0.30%) | 0 / 75 (0.00%) | 0 / 169 (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 |
| Dysarthria | | | |
| subjects affected / exposed | 0 / 337 (0.00%) | 0 / 75 (0.00%) | 1 / 169 (0.59%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Epilepsy | | | |
| subjects affected / exposed | 2 / 337 (0.59%) | 0 / 75 (0.00%) | 0 / 169 (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 |
| Gliosis | | | |
| subjects affected / exposed | 1 / 337 (0.30%) | 0 / 75 (0.00%) | 0 / 169 (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 |
| Headache | | | |
| subjects affected / exposed | 2 / 337 (0.59%) | 1 / 75 (1.33%) | 3 / 169 (1.78%) |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 1 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatic encephalopathy | | | |
| subjects affected / exposed | 1 / 337 (0.30%) | 0 / 75 (0.00%) | 0 / 169 (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 |
| Intracranial pressure increased | | | |
| subjects affected / exposed | 1 / 337 (0.30%) | 1 / 75 (1.33%) | 0 / 169 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Lethargy | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 337 (0.00%) | 0 / 75 (0.00%) | 1 / 169 (0.59%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Migraine | | | |
| subjects affected / exposed | 0 / 337 (0.00%) | 0 / 75 (0.00%) | 1 / 169 (0.59%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Paraparesis | | | |
| subjects affected / exposed | 0 / 337 (0.00%) | 0 / 75 (0.00%) | 1 / 169 (0.59%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Peripheral sensory neuropathy | | | |
| subjects affected / exposed | 1 / 337 (0.30%) | 0 / 75 (0.00%) | 0 / 169 (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 |
| Radiculopathy | | | |
| subjects affected / exposed | 0 / 337 (0.00%) | 0 / 75 (0.00%) | 1 / 169 (0.59%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Syncope | | | |
| subjects affected / exposed | 1 / 337 (0.30%) | 0 / 75 (0.00%) | 0 / 169 (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 |
| Transient ischaemic attack | | | |
| subjects affected / exposed | 1 / 337 (0.30%) | 0 / 75 (0.00%) | 0 / 169 (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 |
| Generalised tonic-clonic seizure | | | |
| subjects affected / exposed | 0 / 337 (0.00%) | 0 / 75 (0.00%) | 1 / 169 (0.59%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Seizure | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 337 (0.00%) | 0 / 75 (0.00%) | 2 / 169 (1.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| Blood and lymphatic system disorders | | | |
| Agranulocytosis | | | |
| subjects affected / exposed | 1 / 337 (0.30%) | 0 / 75 (0.00%) | 0 / 169 (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 |
| Anaemia | | | |
| subjects affected / exposed | 2 / 337 (0.59%) | 0 / 75 (0.00%) | 2 / 169 (1.18%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bone marrow failure | | | |
| subjects affected / exposed | 1 / 337 (0.30%) | 0 / 75 (0.00%) | 0 / 169 (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 |
| Febrile neutropenia | | | |
| subjects affected / exposed | 21 / 337 (6.23%) | 2 / 75 (2.67%) | 7 / 169 (4.14%) |
| occurrences causally related to treatment / all | 24 / 25 | 2 / 2 | 6 / 7 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Leukopenia | | | |
| subjects affected / exposed | 2 / 337 (0.59%) | 0 / 75 (0.00%) | 0 / 169 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Neutropenia | | | |
| subjects affected / exposed | 18 / 337 (5.34%) | 2 / 75 (2.67%) | 4 / 169 (2.37%) |
| occurrences causally related to treatment / all | 22 / 25 | 4 / 4 | 9 / 9 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Thrombocytopenia | | | |
| subjects affected / exposed | 0 / 337 (0.00%) | 0 / 75 (0.00%) | 2 / 169 (1.18%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Disseminated intravascular coagulation | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 337 (0.00%) | 1 / 75 (1.33%) | 0 / 169 (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 |
| Eye disorders | | | |
| Diplopia | | | |
| subjects affected / exposed | 0 / 337 (0.00%) | 1 / 75 (1.33%) | 0 / 169 (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 |
| Keratitis | | | |
| subjects affected / exposed | 1 / 337 (0.30%) | 0 / 75 (0.00%) | 0 / 169 (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 disorders | | | |
| Abdominal distension | | | |
| subjects affected / exposed | 1 / 337 (0.30%) | 0 / 75 (0.00%) | 0 / 169 (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 |
| Abdominal pain | | | |
| subjects affected / exposed | 2 / 337 (0.59%) | 0 / 75 (0.00%) | 2 / 169 (1.18%) |
| occurrences causally related to treatment / all | 2 / 3 | 0 / 0 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Constipation | | | |
| subjects affected / exposed | 1 / 337 (0.30%) | 0 / 75 (0.00%) | 0 / 169 (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 |
| Diarrhoea | | | |
| subjects affected / exposed | 21 / 337 (6.23%) | 0 / 75 (0.00%) | 0 / 169 (0.00%) |
| occurrences causally related to treatment / all | 20 / 21 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastritis | | | |
| subjects affected / exposed | 2 / 337 (0.59%) | 0 / 75 (0.00%) | 0 / 169 (0.00%) |
| occurrences causally related to treatment / all | 1 / 4 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastroduodenitis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 337 (0.30%) | 0 / 75 (0.00%) | 0 / 169 (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 |
| Haemorrhagic ascites | | | |
| subjects affected / exposed | 1 / 337 (0.30%) | 0 / 75 (0.00%) | 0 / 169 (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 |
| Ileus | | | |
| subjects affected / exposed | 1 / 337 (0.30%) | 0 / 75 (0.00%) | 1 / 169 (0.59%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intestinal obstruction | | | |
| subjects affected / exposed | 2 / 337 (0.59%) | 0 / 75 (0.00%) | 0 / 169 (0.00%) |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nausea | | | |
| subjects affected / exposed | 3 / 337 (0.89%) | 0 / 75 (0.00%) | 1 / 169 (0.59%) |
| occurrences causally related to treatment / all | 4 / 4 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pancreatitis acute | | | |
| subjects affected / exposed | 1 / 337 (0.30%) | 0 / 75 (0.00%) | 0 / 169 (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 |
| Small intestinal obstruction | | | |
| subjects affected / exposed | 1 / 337 (0.30%) | 0 / 75 (0.00%) | 0 / 169 (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 | 1 / 337 (0.30%) | 0 / 75 (0.00%) | 0 / 169 (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 |
| Vomiting | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 10 / 337 (2.97%) | 0 / 75 (0.00%) | 3 / 169 (1.78%) |
| occurrences causally related to treatment / all | 7 / 12 | 0 / 0 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Abdominal pain upper | | | |
| subjects affected / exposed | 0 / 337 (0.00%) | 0 / 75 (0.00%) | 1 / 169 (0.59%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| Hepatic cirrhosis | | | |
| subjects affected / exposed | 1 / 337 (0.30%) | 0 / 75 (0.00%) | 0 / 169 (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 |
| Hepatic function abnormal | | | |
| subjects affected / exposed | 1 / 337 (0.30%) | 0 / 75 (0.00%) | 0 / 169 (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 |
| Skin and subcutaneous tissue disorders | | | |
| Erythema | | | |
| subjects affected / exposed | 1 / 337 (0.30%) | 0 / 75 (0.00%) | 0 / 169 (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 |
| Rash | | | |
| subjects affected / exposed | 2 / 337 (0.59%) | 0 / 75 (0.00%) | 0 / 169 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Dysuria | | | |
| subjects affected / exposed | 1 / 337 (0.30%) | 0 / 75 (0.00%) | 0 / 169 (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 |
| Neurogenic bladder | | | |
| subjects affected / exposed | 0 / 337 (0.00%) | 0 / 75 (0.00%) | 1 / 169 (0.59%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---|---|---|
| Proteinuria | | | |
| subjects affected / exposed | 1 / 337 (0.30%) | 0 / 75 (0.00%) | 0 / 169 (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 |
| Acute kidney injury | | | |
| subjects affected / exposed | 2 / 337 (0.59%) | 0 / 75 (0.00%) | 0 / 169 (0.00%) |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 2 / 337 (0.59%) | 0 / 75 (0.00%) | 0 / 169 (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 |
| Flank pain | | | |
| subjects affected / exposed | 0 / 337 (0.00%) | 0 / 75 (0.00%) | 1 / 169 (0.59%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intervertebral disc disorder | | | |
| subjects affected / exposed | 0 / 337 (0.00%) | 0 / 75 (0.00%) | 1 / 169 (0.59%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Muscular weakness | | | |
| subjects affected / exposed | 1 / 337 (0.30%) | 0 / 75 (0.00%) | 0 / 169 (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 |
| Neck pain | | | |
| subjects affected / exposed | 0 / 337 (0.00%) | 0 / 75 (0.00%) | 1 / 169 (0.59%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Muscle disorder | | | |
| subjects affected / exposed | 0 / 337 (0.00%) | 0 / 75 (0.00%) | 1 / 169 (0.59%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---|---|---|
| Osteonecrosis of jaw | | | |
| subjects affected / exposed | 0 / 337 (0.00%) | 1 / 75 (1.33%) | 0 / 169 (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 |
| Pain in extremity | | | |
| subjects affected / exposed | 2 / 337 (0.59%) | 0 / 75 (0.00%) | 0 / 169 (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 |
| Infections and infestations | | | |
| Abscess intestinal | | | |
| subjects affected / exposed | 0 / 337 (0.00%) | 0 / 75 (0.00%) | 1 / 169 (0.59%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Atypical pneumonia | | | |
| subjects affected / exposed | 1 / 337 (0.30%) | 0 / 75 (0.00%) | 0 / 169 (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 |
| Cardiac infection | | | |
| subjects affected / exposed | 0 / 337 (0.00%) | 0 / 75 (0.00%) | 1 / 169 (0.59%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Catheter site infection | | | |
| subjects affected / exposed | 0 / 337 (0.00%) | 0 / 75 (0.00%) | 1 / 169 (0.59%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cellulitis | | | |
| subjects affected / exposed | 4 / 337 (1.19%) | 0 / 75 (0.00%) | 2 / 169 (1.18%) |
| occurrences causally related to treatment / all | 2 / 5 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cystitis | | | |
| subjects affected / exposed | 1 / 337 (0.30%) | 0 / 75 (0.00%) | 0 / 169 (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 |
| Device related infection | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 337 (0.30%) | 0 / 75 (0.00%) | 1 / 169 (0.59%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastroenteritis | | | |
| subjects affected / exposed | 1 / 337 (0.30%) | 0 / 75 (0.00%) | 1 / 169 (0.59%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Genital infection | | | |
| subjects affected / exposed | 1 / 337 (0.30%) | 0 / 75 (0.00%) | 0 / 169 (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 |
| Hepatitis B | | | |
| subjects affected / exposed | 1 / 337 (0.30%) | 0 / 75 (0.00%) | 0 / 169 (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 |
| Herpes zoster | | | |
| subjects affected / exposed | 1 / 337 (0.30%) | 0 / 75 (0.00%) | 0 / 169 (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 |
| Infection | | | |
| subjects affected / exposed | 2 / 337 (0.59%) | 0 / 75 (0.00%) | 0 / 169 (0.00%) |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Influenza | | | |
| subjects affected / exposed | 1 / 337 (0.30%) | 0 / 75 (0.00%) | 0 / 169 (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 |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 0 / 337 (0.00%) | 0 / 75 (0.00%) | 1 / 169 (0.59%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lung infection | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 337 (0.30%) | 0 / 75 (0.00%) | 0 / 169 (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 |
| Lymphangitis | | | |
| subjects affected / exposed | 1 / 337 (0.30%) | 0 / 75 (0.00%) | 0 / 169 (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 |
| Pharyngitis | | | |
| subjects affected / exposed | 1 / 337 (0.30%) | 0 / 75 (0.00%) | 0 / 169 (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 |
| Pneumonia | | | |
| subjects affected / exposed | 3 / 337 (0.89%) | 2 / 75 (2.67%) | 1 / 169 (0.59%) |
| occurrences causally related to treatment / all | 1 / 3 | 2 / 3 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| Pulmonary sepsis | | | |
| subjects affected / exposed | 0 / 337 (0.00%) | 1 / 75 (1.33%) | 0 / 169 (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 |
| Sepsis | | | |
| subjects affected / exposed | 4 / 337 (1.19%) | 0 / 75 (0.00%) | 2 / 169 (1.18%) |
| occurrences causally related to treatment / all | 2 / 4 | 0 / 0 | 2 / 2 |
| deaths causally related to treatment / all | 1 / 3 | 0 / 0 | 0 / 0 |
| Septic shock | | | |
| subjects affected / exposed | 1 / 337 (0.30%) | 0 / 75 (0.00%) | 0 / 169 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 337 (0.00%) | 1 / 75 (1.33%) | 1 / 169 (0.59%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary tract infection | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 3 / 337 (0.89%) | 0 / 75 (0.00%) | 1 / 169 (0.59%) |
| occurrences causally related to treatment / all | 3 / 3 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Viraemia | | | |
| subjects affected / exposed | 0 / 337 (0.00%) | 0 / 75 (0.00%) | 1 / 169 (0.59%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Viral infection | | | |
| subjects affected / exposed | 1 / 337 (0.30%) | 0 / 75 (0.00%) | 0 / 169 (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 |
| Wound infection | | | |
| subjects affected / exposed | 1 / 337 (0.30%) | 0 / 75 (0.00%) | 0 / 169 (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 |
| Candida infection | | | |
| subjects affected / exposed | 1 / 337 (0.30%) | 0 / 75 (0.00%) | 0 / 169 (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 | | | |
| Dehydration | | | |
| subjects affected / exposed | 4 / 337 (1.19%) | 1 / 75 (1.33%) | 0 / 169 (0.00%) |
| occurrences causally related to treatment / all | 4 / 4 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypokalaemia | | | |
| subjects affected / exposed | 4 / 337 (1.19%) | 0 / 75 (0.00%) | 0 / 169 (0.00%) |
| occurrences causally related to treatment / all | 3 / 4 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyponatraemia | | | |
| subjects affected / exposed | 0 / 337 (0.00%) | 0 / 75 (0.00%) | 1 / 169 (0.59%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

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

| **Non-serious adverse events** | Afatinib + Vinorelbine (AV) | AV switched to TV | Trastuzumab + Vinorelbine (TV) |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 331 / 337 (98.22%) | 64 / 75 (85.33%) | 163 / 169 (96.45%) |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 24 / 337 (7.12%) | 7 / 75 (9.33%) | 16 / 169 (9.47%) |
| occurrences (all) | 33 | 11 | 26 |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 22 / 337 (6.53%) | 8 / 75 (10.67%) | 11 / 169 (6.51%) |
| occurrences (all) | 27 | 9 | 18 |
| Haemoglobin decreased | | | |
| subjects affected / exposed | 28 / 337 (8.31%) | 5 / 75 (6.67%) | 6 / 169 (3.55%) |
| occurrences (all) | 45 | 6 | 13 |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 16 / 337 (4.75%) | 6 / 75 (8.00%) | 13 / 169 (7.69%) |
| occurrences (all) | 73 | 18 | 57 |
| Weight decreased | | | |
| subjects affected / exposed | 48 / 337 (14.24%) | 6 / 75 (8.00%) | 10 / 169 (5.92%) |
| occurrences (all) | 55 | 13 | 12 |
| White blood cell count decreased | | | |
| subjects affected / exposed | 23 / 337 (6.82%) | 5 / 75 (6.67%) | 3 / 169 (1.78%) |
| occurrences (all) | 107 | 12 | 33 |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 34 / 337 (10.09%) | 5 / 75 (6.67%) | 18 / 169 (10.65%) |
| occurrences (all) | 51 | 5 | 25 |
| Headache | | | |
| subjects affected / exposed | 47 / 337 (13.95%) | 10 / 75 (13.33%) | 25 / 169 (14.79%) |
| occurrences (all) | 73 | 14 | 39 |
| Hypoaesthesia | | | |
| subjects affected / exposed | 9 / 337 (2.67%) | 2 / 75 (2.67%) | 11 / 169 (6.51%) |
| occurrences (all) | 10 | 2 | 12 |
| Neuropathy peripheral | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 15 / 337 (4.45%) | 3 / 75 (4.00%) | 16 / 169 (9.47%) |
| occurrences (all) | 16 | 3 | 18 |
| Peripheral sensory neuropathy | | | |
| subjects affected / exposed | 15 / 337 (4.45%) | 2 / 75 (2.67%) | 11 / 169 (6.51%) |
| occurrences (all) | 16 | 2 | 13 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 103 / 337 (30.56%) | 25 / 75 (33.33%) | 62 / 169 (36.69%) |
| occurrences (all) | 206 | 86 | 161 |
| Leukopenia | | | |
| subjects affected / exposed | 115 / 337 (34.12%) | 28 / 75 (37.33%) | 68 / 169 (40.24%) |
| occurrences (all) | 467 | 136 | 401 |
| Neutropenia | | | |
| subjects affected / exposed | 256 / 337 (75.96%) | 46 / 75 (61.33%) | 139 / 169 (82.25%) |
| occurrences (all) | 1164 | 340 | 1022 |
| Bone marrow failure | | | |
| subjects affected / exposed | 18 / 337 (5.34%) | 5 / 75 (6.67%) | 11 / 169 (6.51%) |
| occurrences (all) | 75 | 22 | 39 |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 63 / 337 (18.69%) | 5 / 75 (6.67%) | 25 / 169 (14.79%) |
| occurrences (all) | 103 | 9 | 38 |
| Fatigue | | | |
| subjects affected / exposed | 106 / 337 (31.45%) | 10 / 75 (13.33%) | 51 / 169 (30.18%) |
| occurrences (all) | 197 | 23 | 106 |
| Mucosal inflammation | | | |
| subjects affected / exposed | 82 / 337 (24.33%) | 4 / 75 (5.33%) | 15 / 169 (8.88%) |
| occurrences (all) | 119 | 5 | 27 |
| Oedema peripheral | | | |
| subjects affected / exposed | 11 / 337 (3.26%) | 1 / 75 (1.33%) | 11 / 169 (6.51%) |
| occurrences (all) | 12 | 1 | 15 |
| Pain | | | |
| subjects affected / exposed | 23 / 337 (6.82%) | 2 / 75 (2.67%) | 7 / 169 (4.14%) |
| occurrences (all) | 31 | 2 | 8 |
| Pyrexia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 74 / 337 (21.96%) | 11 / 75 (14.67%) | 32 / 169 (18.93%) |
| occurrences (all) | 127 | 21 | 53 |
| Chills | | | |
| subjects affected / exposed | 10 / 337 (2.97%) | 3 / 75 (4.00%) | 9 / 169 (5.33%) |
| occurrences (all) | 10 | 6 | 19 |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 40 / 337 (11.87%) | 1 / 75 (1.33%) | 16 / 169 (9.47%) |
| occurrences (all) | 53 | 4 | 23 |
| Abdominal pain upper | | | |
| subjects affected / exposed | 34 / 337 (10.09%) | 5 / 75 (6.67%) | 14 / 169 (8.28%) |
| occurrences (all) | 37 | 7 | 17 |
| Constipation | | | |
| subjects affected / exposed | 35 / 337 (10.39%) | 6 / 75 (8.00%) | 27 / 169 (15.98%) |
| occurrences (all) | 50 | 8 | 42 |
| Diarrhoea | | | |
| subjects affected / exposed | 270 / 337 (80.12%) | 7 / 75 (9.33%) | 45 / 169 (26.63%) |
| occurrences (all) | 786 | 18 | 67 |
| Dyspepsia | | | |
| subjects affected / exposed | 16 / 337 (4.75%) | 3 / 75 (4.00%) | 12 / 169 (7.10%) |
| occurrences (all) | 18 | 3 | 14 |
| Mouth ulceration | | | |
| subjects affected / exposed | 40 / 337 (11.87%) | 1 / 75 (1.33%) | 5 / 169 (2.96%) |
| occurrences (all) | 61 | 1 | 7 |
| Nausea | | | |
| subjects affected / exposed | 102 / 337 (30.27%) | 6 / 75 (8.00%) | 47 / 169 (27.81%) |
| occurrences (all) | 169 | 14 | 77 |
| Stomatitis | | | |
| subjects affected / exposed | 87 / 337 (25.82%) | 4 / 75 (5.33%) | 19 / 169 (11.24%) |
| occurrences (all) | 136 | 4 | 31 |
| Vomiting | | | |
| subjects affected / exposed | 85 / 337 (25.22%) | 5 / 75 (6.67%) | 22 / 169 (13.02%) |
| occurrences (all) | 204 | 9 | 35 |
| Respiratory, thoracic and mediastinal disorders | | | |

| | | | |
|---|---|---|---|
| Cough | | | |
| subjects affected / exposed | 39 / 337 (11.57%) | 10 / 75 (13.33%) | 27 / 169 (15.98%) |
| occurrences (all) | 51 | 12 | 36 |
| Dyspnoea | | | |
| subjects affected / exposed | 27 / 337 (8.01%) | 4 / 75 (5.33%) | 15 / 169 (8.88%) |
| occurrences (all) | 41 | 5 | 23 |
| Epistaxis | | | |
| subjects affected / exposed | 58 / 337 (17.21%) | 3 / 75 (4.00%) | 6 / 169 (3.55%) |
| occurrences (all) | 95 | 5 | 7 |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 30 / 337 (8.90%) | 5 / 75 (6.67%) | 9 / 169 (5.33%) |
| occurrences (all) | 36 | 6 | 12 |
| Rhinorrhoea | | | |
| subjects affected / exposed | 20 / 337 (5.93%) | 5 / 75 (6.67%) | 10 / 169 (5.92%) |
| occurrences (all) | 24 | 7 | 10 |
| Productive cough | | | |
| subjects affected / exposed | 6 / 337 (1.78%) | 4 / 75 (5.33%) | 3 / 169 (1.78%) |
| occurrences (all) | 7 | 7 | 3 |
| Skin and subcutaneous tissue disorders | | | |
| Acne | | | |
| subjects affected / exposed | 22 / 337 (6.53%) | 0 / 75 (0.00%) | 0 / 169 (0.00%) |
| occurrences (all) | 26 | 0 | 0 |
| Alopecia | | | |
| subjects affected / exposed | 34 / 337 (10.09%) | 0 / 75 (0.00%) | 13 / 169 (7.69%) |
| occurrences (all) | 34 | 0 | 15 |
| Dermatitis acneiform | | | |
| subjects affected / exposed | 45 / 337 (13.35%) | 0 / 75 (0.00%) | 0 / 169 (0.00%) |
| occurrences (all) | 59 | 0 | 0 |
| Dry skin | | | |
| subjects affected / exposed | 20 / 337 (5.93%) | 1 / 75 (1.33%) | 1 / 169 (0.59%) |
| occurrences (all) | 22 | 1 | 1 |
| Palmar-plantar erythrodysaesthesia syndrome | | | |
| subjects affected / exposed | 42 / 337 (12.46%) | 0 / 75 (0.00%) | 2 / 169 (1.18%) |
| occurrences (all) | 55 | 0 | 2 |
| Pruritus | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 31 / 337 (9.20%) | 2 / 75 (2.67%) | 8 / 169 (4.73%) |
| occurrences (all) | 41 | 2 | 10 |
| Rash | | | |
| subjects affected / exposed | 160 / 337 (47.48%) | 8 / 75 (10.67%) | 19 / 169 (11.24%) |
| occurrences (all) | 213 | 12 | 22 |
| Psychiatric disorders | | | |
| Insomnia | | | |
| subjects affected / exposed | 26 / 337 (7.72%) | 3 / 75 (4.00%) | 28 / 169 (16.57%) |
| occurrences (all) | 34 | 4 | 32 |
| Renal and urinary disorders | | | |
| Dysuria | | | |
| subjects affected / exposed | 21 / 337 (6.23%) | 1 / 75 (1.33%) | 3 / 169 (1.78%) |
| occurrences (all) | 25 | 1 | 4 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 18 / 337 (5.34%) | 4 / 75 (5.33%) | 8 / 169 (4.73%) |
| occurrences (all) | 26 | 4 | 10 |
| Back pain | | | |
| subjects affected / exposed | 24 / 337 (7.12%) | 7 / 75 (9.33%) | 15 / 169 (8.88%) |
| occurrences (all) | 33 | 10 | 25 |
| Muscle spasms | | | |
| subjects affected / exposed | 27 / 337 (8.01%) | 5 / 75 (6.67%) | 16 / 169 (9.47%) |
| occurrences (all) | 38 | 5 | 21 |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 12 / 337 (3.56%) | 4 / 75 (5.33%) | 12 / 169 (7.10%) |
| occurrences (all) | 15 | 5 | 14 |
| Myalgia | | | |
| subjects affected / exposed | 34 / 337 (10.09%) | 5 / 75 (6.67%) | 18 / 169 (10.65%) |
| occurrences (all) | 39 | 9 | 26 |
| Pain in extremity | | | |
| subjects affected / exposed | 21 / 337 (6.23%) | 3 / 75 (4.00%) | 20 / 169 (11.83%) |
| occurrences (all) | 27 | 3 | 26 |
| Bone pain | | | |
| subjects affected / exposed | 11 / 337 (3.26%) | 0 / 75 (0.00%) | 10 / 169 (5.92%) |
| occurrences (all) | 14 | 0 | 12 |
| Infections and infestations | | | |

| | | | |
|---|---|---|---|
| Nasopharyngitis | | | |
| subjects affected / exposed | 30 / 337 (8.90%) | 2 / 75 (2.67%) | 11 / 169 (6.51%) |
| occurrences (all) | 41 | 6 | 17 |
| Paronychia | | | |
| subjects affected / exposed | 63 / 337 (18.69%) | 2 / 75 (2.67%) | 2 / 169 (1.18%) |
| occurrences (all) | 81 | 2 | 2 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 32 / 337 (9.50%) | 8 / 75 (10.67%) | 27 / 169 (15.98%) |
| occurrences (all) | 33 | 21 | 52 |
| Urinary tract infection | | | |
| subjects affected / exposed | 35 / 337 (10.39%) | 4 / 75 (5.33%) | 15 / 169 (8.88%) |
| occurrences (all) | 50 | 4 | 25 |
| Conjunctivitis | | | |
| subjects affected / exposed | 12 / 337 (3.56%) | 4 / 75 (5.33%) | 4 / 169 (2.37%) |
| occurrences (all) | 13 | 4 | 4 |
| Influenza | | | |
| subjects affected / exposed | 7 / 337 (2.08%) | 4 / 75 (5.33%) | 0 / 169 (0.00%) |
| occurrences (all) | 10 | 4 | 0 |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 98 / 337 (29.08%) | 5 / 75 (6.67%) | 31 / 169 (18.34%) |
| occurrences (all) | 122 | 6 | 51 |
| Hypokalaemia | | | |
| subjects affected / exposed | 43 / 337 (12.76%) | 2 / 75 (2.67%) | 7 / 169 (4.14%) |
| occurrences (all) | 53 | 2 | 32 |

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 19 May 2010 | The restricted medications during treatment with afatinib were changed. An additional explanatory paragraph was added that the concomitant use of potent P-glycoprotein (P-gp) inhibitors and inducers was to be avoided during treatment with afatinib. The background was that a trial (1200.79) in healthy volunteers indicated that co-administration of these drugs affected the harmacokinetics of afatinib. Note: This restriction was loosened again with protocol amendment 4. |
| 02 September 2010 | Several changes and corrections were introduced with the second amendment to the protocol; major changes are presented below. In line with the requirements by the Health Canada's Food and Drug regulations, the source of trastuzumab for Canada was changed from the EU source to the US source. Statistical information was adjusted regarding the early benefit-risk assessment by the DMC. The ranking of the secondary endpoints was changed to reflect their importance. A reduced timeframe between prior trastuzumab treatment and study entry was allowed (changed from 4 weeks to 3 weeks); this resulted in a modified wording of exclusion criterion 4. The visit and vinorelbine-administration process in case of vinorelbine-related AEs was clarified. Corticosteroids were added to the allowed concomitant medications. Further recommendations regarding interstitial lung disease were added, including instructions for the assessment of pulmonary symptoms and actions to be taken with the study medication. A paragraph about the status of patients after discontinuation of study medication was clarified. |
| 28 October 2011 | The third amendment to the protocol again introduced several changes and corrections; major changes are presented below. It was clarified that the left ventricular ejection fraction (LVEF) assessment was not to be repeated at the screening visit if a valid result was available from an assessment performed as part of routine clinical practice within 28 days prior to start of treatment. The dose reduction scheme for afatinib in case of drug-related diarrhoea and the instructions for the treatment of afatinib-related diarrhoea were clarified. The introduction of the requirement for a TMA repository for potential retrospective analyses was added. The definition of the completion of the trial was clarified. New scientific methodologies were implemented to investigate the potential effect of subsequent anti-cancer therapies on OS. The requirements regarding contraception were changed based on new information in the trastuzumab Summary of Product Characteristics (SPC). |
| 12 October 2012 | Keratitis and ulcerative keratitis was observed in 0.8% of patients exposed to afatinib and they were reported after treatment with approved epidermal growth factor receptor (EGFR) inhibitors for cancer was added. European Medicines Agency requested a class labelling. Restriction that patients randomised to treatment with afatinib were not to receive treatment with potent P-gp inhibitors or inducers was removed. Based on new data, it was clarified that caution is warranted in concomitant use of P-glycoprotein (P-gp) inhibitors or inducers with afatinib, but their use in patients need such therapies is no longer prohibited. Exclusion criterion 6 was modified. Based on the current SPC for vinorelbine, exclusion criterion 12 was modified. In exclusion criterion 13 the MDRD formula was then accepted for the estimation of the glomerular filtration rate (GFR). Denosumab treatment for patients with bone metastasis was allowed. AE reporting guidance was changed. It was specified that worsening of the underlying disease or of other pre-existing conditions was to be recorded as an (S)AE in the electronic case report form ((e)CRF). Changes in vital signs, electrocardiogram (ECG), physical examination and laboratory test results were to be recorded as an (S)AE in the eCRF, if they were judged clinically relevant by the investigator. Drug-induced liver injury (DILI) was defined as a significant AE and a list of always serious AEs was defined; the reporting obligations of the investigator were specified. Further details about the planned second analysis of overall survival (OS) were added. Several new documents were added to the appendix. The rationale behind this were the modification of exclusion criterion 13. |

| | |
|---|---|
| 14 May 2013 | An independent DMC monitored the safety of patients who participated in the trial and benefit-risk assessment that was pre-defined in the clinical trial protocol. The DMC concluded that there was a low likelihood of the study meeting the pre-defined criteria for increased efficacy in terms of PFS. In addition, a high rate of treatment discontinuations and dose reductions as well as a higher rate of SAEs and deaths were observed in the afatinib + vinorelbine arm. The DMC recommended stopping recruitment of patients. Further recruitment into this study was therefore stopped as of 26 Apr 2013. |
| 23 August 2013 | Amendment 6 specified which procedures were no longer needed due to the premature discontinuation of the trial (e.g. additional FU visits, collection of health-related quality of life questionnaires, information about healthcare-resource use, biomarker sub-study, central independent review of images). In addition, the handling of unscheduled pharmacokinetic samples was specified. In addition, it was clarified that the primary endpoint changed from PFS based on central independent review to PFS based on investigator assessment. A list clearly defining the primary, secondary, and other endpoints of the trial was added. The sections about statistical methods were updated and several analyses were cancelled. Amendment 6 also defined that on trial level, the trial was considered complete when the last patient had completed the EOT visit and the FU visit 28 days after EOT. |
| 12 June 2014 | Several clarifications and updated information were introduced with the seventh amendment to the protocol; major changes are presented below. Based on the current SPC for trastuzumab, the instructions for management of trastuzumab cardiotoxicity were modified. Following the request by regulatory authorities, further recommendations for the assessment of keratitis were added to the section about rescue medication, emergency procedures, and additional treatments. The period for the collection of OS data was prolonged to ensure an adequate follow-up of patients and appropriate reporting of OS data: the observation period could have proceeded until at least 50% of patients per arm, or up to 75% of patients overall had died. |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

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

The Data Monitoring Committee recommended termination of recruitment due to low likelihood of the study meeting its primary objectives.

Notes: