

**Clinical trial results:****LUX-Breast 2: An open-label, multinational, phase-II trial of Afatinib (BIBW 2992) in patients with metastatic human epidermal growth factor receptor (HER2) - overexpressing breast cancer failing HER2 - targeted treatment in the neoadjuvant and/or adjuvant treatment setting****Summary**

| | |
|--------------------------|----------------|
| EudraCT number | 2010-021945-29 |
| Trial protocol | GB |
| Global end of trial date | 13 March 2017 |

Results information

| | |
|--------------------------------|---------------|
| Result version number | v1 |
| This version publication date | 24 March 2018 |
| First version publication date | 24 March 2018 |

Trial information**Trial identification**

| | |
|-----------------------|---------|
| Sponsor protocol code | 1200.98 |
|-----------------------|---------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01271725 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

| | |
|--|---------------|
| Analysis stage | Final |
| Date of interim/final analysis | 10 April 2017 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 13 March 2017 |
| Global end of trial reached? | Yes |
| Global end of trial date | 13 March 2017 |
| Was the trial ended prematurely? | Yes |

Notes:

General information about the trial

Main objective of the trial:

To investigate the efficacy and safety of afatinib alone, and of afatinib in combination with weekly paclitaxel or vinorelbine upon progression on afatinib monotherapy, in patients with HER2-overexpressing, metastatic breast cancer, who failed HER2-targeted treatment in the adjuvant and/or neoadjuvant setting.

Protection of trial subjects:

All patients were informed that they were free to withdraw their consent at any time during the study without penalty or prejudice. The patients were informed that their personal trial related data would be considered confidential and used by BI in accordance with the local data protection laws. The level of disclosure was explained to the patients. The patients were also informed that their medical records could be examined by Clinical Quality Assurance auditors appointed by BI, by members of the appropriate IEC/IRB, and by inspectors from regulatory authorities. Confidentiality of patient data was ensured by the use of depersonalised patient identification codes (patient numbers). The terms and conditions of the insurance cover were available to the investigator and the patients in the Investigator Site File.

Background therapy: -

Evidence for comparator: -

| | |
|---|--------------|
| Actual start date of recruitment | 04 July 2011 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | Hong Kong: 4 |
| Country: Number of subjects enrolled | India: 19 |
| Country: Number of subjects enrolled | Poland: 1 |
| Country: Number of subjects enrolled | Russian Federation: 23 |
| Country: Number of subjects enrolled | Taiwan: 32 |
| Country: Number of subjects enrolled | United Kingdom: 8 |
| Worldwide total number of subjects | 87 |
| EEA total number of subjects | 9 |

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) | 77 |
| From 65 to 84 years | 10 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

An open-label, multinational, phase-II trial of Afatinib (BIBW 2992) in patients with metastatic human epidermal growth factor receptor (HER2) - overexpressing breast cancer failing HER2 - targeted treatment in the neoadjuvant and/or adjuvant treatment setting

Pre-assignment

Screening details:

All subjects were screened for eligibility to participate in the trial. Subjects attended a specialist sites which ensured that they met all strictly implemented inclusion/exclusion criteria. Subjects were not to be entered to trial treatment if any one of the specific entry criteria was violated.

Period 1

| | |
|------------------------------|-----------------------------|
| Period 1 title | Part A |
| Is this the baseline period? | Yes |
| Allocation method | Non-randomised - controlled |
| Blinding used | Not blinded |

Blinding implementation details:

An open-label trial

Arms

| | |
|------------------|----------------------|
| Arm title | Afatinib monotherapy |
|------------------|----------------------|

Arm description:

Patient received Afatinib monotherapy orally once daily at a dose of 40 milligram (mg) filmcoated tablets until progression of their disease, unacceptable adverse events or other reason necessitating withdrawal. A dose reduction to 30mg and 20mg was possible if 40mg was not tolerated.

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

Patient received Afatinib monotherapy orally once daily at a dose of 40 milligram (mg) film coated tablets until progression of their disease, unacceptable adverse events or other reason necessitating withdrawal

| Number of subjects in period 1^[1] | Afatinib monotherapy |
|---|----------------------|
| Started | 74 |
| Completed | 39 |
| Not completed | 35 |
| Adverse event, serious fatal | 3 |
| Consent withdrawn by subject | 12 |
| Adverse event, non-fatal | 5 |
| Other than specified | 3 |
| Clinical signs/symptoms of progression | 2 |

| | |
|---|---|
| Lost to follow-up | 1 |
| Progressive disease according to RECIST | 8 |
| Protocol deviation | 1 |

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 the patients who were successfully completed the screening period and received at least one of the trial medication.

Period 2

| | |
|------------------------------|-----------------------------|
| Period 2 title | Part B |
| Is this the baseline period? | No |
| Allocation method | Non-randomised - controlled |
| Blinding used | Not blinded |

Blinding implementation details:

An open-label trial

Arms

| | |
|------------------|--|
| Arm title | Afatinib and Paclitaxel or Vinorelbine combination therapy |
|------------------|--|

Arm description:

Patient received Afatinib monotherapy orally once daily at a dose of 40 mg film-coated tablets until progression of their disease, unacceptable adverse events or other reason necessitating withdrawal (A dose reduction to 30mg and 20mg was possible if 40mg was not tolerated) and 80 mg/square meter (m²) Paclitaxel concentrate for intravenous infusion or 25 mg/m² Vinorelbine concentrate for intravenous infusion once weekly starting after treatment failure on afatinib monotherapy

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

Patient received Afatinib monotherapy orally once daily at a dose of 40 milligram (mg) film coated tablets until progression of their disease, unacceptable adverse events or other reason necessitating withdrawal

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

Patient received 25 mg/m² Vinorelbine concentrate for intravenous infusion once weekly.

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

Dosage and administration details:

Patient received 80 mg/square meter (m²) Paclitaxel concentrate for intravenous infusion once weekly.

| Number of subjects in period 2 | Afatinib and Paclitaxel or Vinorelbine combination therapy |
|--|--|
| Started | 39 |
| Completed | 27 |
| Not completed | 12 |
| Consent withdrawn by subject | 6 |
| Adverse event, non-fatal | 1 |
| Other than specified | 2 |
| Clinical signs/symptoms of progression | 2 |
| Protocol deviation | 1 |

Baseline characteristics

Reporting groups

| | |
|---|----------------------|
| Reporting group title | Afatinib monotherapy |
| Reporting group description: | |
| Patient received Afatinib monotherapy orally once daily at a dose of 40 milligram (mg) filmcoated tablets until progression of their disease, unacceptable adverse events or other reason necessitating withdrawal. A dose reduction to 30mg and 20mg was possible if 40mg was not tolerated. | |

| Reporting group values | Afatinib monotherapy | Total | |
|--|----------------------|-------|--|
| Number of subjects | 74 | 74 | |
| Age categorical | | | |
| The treated set for monotherapy comprised all patients who received at least 1 dose of afatinib. The treated set for combination therapy comprised all patients who received at least 1 dose of each of afatinib and paclitaxel, or of afatinib and vinorelbine. | | | |
| Units: Subjects | | | |

| | | | |
|---|--------|----|--|
| Age Continuous | | | |
| Age at the time of signing informed consent form is presented. The treated set for monotherapy comprised all patients who received at least 1 dose of afatinib. The treated set for combination therapy comprised all patients who received at least 1 dose of each of afatinib and paclitaxel, or of afatinib and vinorelbine. The baseline population analysis set was Treated set. | | | |
| Units: years | | | |
| arithmetic mean | 51.3 | | |
| standard deviation | ± 10.6 | - | |
| Sex: Female, Male | | | |
| Number of subjects is categorized as Male or Female. The treated set for monotherapy comprised all patients who received at least 1 dose of afatinib. The treated set for combination therapy comprised all patients who received at least 1 dose of each of afatinib and paclitaxel, or of afatinib and vinorelbine. | | | |
| Units: Subjects | | | |
| Female | 74 | 74 | |
| Male | 0 | 0 | |
| Race (NIH/OMB) | | | |
| Ethnicity was not captured in this trial. The treated set for monotherapy comprised all patients who received at least 1 dose of afatinib. The treated set for combination therapy comprised all patients who received at least 1 dose of each of afatinib and paclitaxel, or of afatinib and vinorelbine. | | | |
| Units: Subjects | | | |
| American Indian or Alaska Native | 0 | 0 | |
| Asian | 47 | 47 | |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | |
| Black or African American | 0 | 0 | |
| White | 27 | 27 | |
| More than one race | 0 | 0 | |
| Unknown or Not Reported | 0 | 0 | |

End points

End points reporting groups

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

Reporting group description:

Patient received Afatinib monotherapy orally once daily at a dose of 40 milligram (mg) filmcoated tablets until progression of their disease, unacceptable adverse events or other reason necessitating withdrawal. A dose reduction to 30mg and 20mg was possible if 40mg was not tolerated.

| | |
|-----------------------|--|
| Reporting group title | Afatinib and Paclitaxel or Vinorelbine combination therapy |
|-----------------------|--|

Reporting group description:

Patient received Afatinib monotherapy orally once daily at a dose of 40 mg film-coated tablets until progression of their disease, unacceptable adverse events or other reason necessitating withdrawal (A dose reduction to 30mg and 20mg was possible if 40mg was not tolerated) and 80 mg/square meter (m²) Paclitaxel concentrate for intravenous infusion or 25 mg/m² Vinorelbine concentrate for intravenous infusion once weekly starting after treatment failure on afatinib monotherapy

| | |
|----------------------------|--|
| Subject analysis set title | Afatinib and Vinorelbine combination therapy |
|----------------------------|--|

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

Subject analysis set description:

Patient received Afatinib monotherapy orally once daily at a dose of 40 mg film-coated tablets until progression of their disease, unacceptable adverse events or other reason necessitating withdrawal (A dose reduction to 30mg and 20mg was possible if 40mg was not tolerated) and 25 mg/m² Vinorelbine concentrate for intravenous infusion once weekly starting after treatment failure on afatinib monotherapy

| | |
|----------------------------|---|
| Subject analysis set title | Afatinib and Paclitaxel combination therapy |
|----------------------------|---|

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

Subject analysis set description:

Patient received Afatinib monotherapy orally once daily at a dose of 40 mg film-coated tablets until progression of their disease, unacceptable adverse events or other reason necessitating withdrawal (A dose reduction to 30mg and 20mg was possible if 40mg was not tolerated) and 80 mg/square meter (m²) Paclitaxel concentrate for intravenous infusion once weekly starting after treatment failure on afatinib monotherapy

Primary: Objective Response (OR) assessed by Response Evaluation Criteria in Solid Tumours Version (RECIST) 1.1

| | |
|-----------------|---|
| End point title | Objective Response (OR) assessed by Response Evaluation Criteria in Solid Tumours Version (RECIST) 1.1 ^[1] |
|-----------------|---|

End point description:

Objective response according to RECIST v1.1. Best overall response of confirmed complete response (CR) or confirmed partial response (PR) recorded since first administration of trial medication and until the earliest of disease progression, death or start of next treatment in each part separately. Percentage of participants with OR along with exact 95% Confidence Interval by Clopper and Pearson is presented. The treated set for monotherapy comprised all patients who received at least 1 dose of afatinib. The treated set for combination therapy comprised all patients who received at least 1 dose of each of afatinib and paclitaxel, or of afatinib and vinorelbine.

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

End point timeframe:

From the initial dose of study drug until 28 days after end of the treatment period, up to 1562 days

Notes:

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

Justification: This endpoint was evaluated only descriptively. Thus, no statistical hypothesis test was tested.

| End point values | Afatinib monotherapy | Afatinib and Paclitaxel or Vinorelbine combination therapy | | |
|----------------------------------|----------------------|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 74 ^[2] | 39 ^[3] | | |
| Units: Percentage | | | | |
| number (confidence interval 95%) | 18 (10 to 28) | 31 (17 to 48) | | |

Notes:

[2] - Treated Set

[3] - Treated Set

Statistical analyses

No statistical analyses for this end point

Secondary: Best Overall Response According to RECIST v1.1 (With confirmation)

| | |
|-----------------|--|
| End point title | Best Overall Response According to RECIST v1.1 (With confirmation) |
|-----------------|--|

End point description:

Best overall response is the best overall response to trial medication according to RECIST version 1.1 and was calculated relative to the baseline of each respective part. Percentage of participants with best overall response along with exact 95% Confidence Interval by Clopper and Pearson is presented. Best overall response was defined as the best response recorded at any time from the first administration of drug to the End of Treatment (EOT). As Per RECIST v1.1 for target lesions and assessed by Magnetic resonance imaging (MRI): Complete Response (CR), disappearance of all target lesions; Partial Response (PR) & gt;=30% decrease in the sum of the longest diameter of target lesions; progression, as a 20% increase in the sum of the longest diameter of target lesions, or a measurable increase in a non-target lesion, or the appearance of new lesions; Stable Disease (SD), neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for disease progression.

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

End point timeframe:

From the initial dose of study drug until 28 days after end of the treatment period, up to 1562 days

| End point values | Afatinib monotherapy | Afatinib and Paclitaxel or Vinorelbine combination therapy | | |
|----------------------------------|----------------------|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 74 ^[4] | 39 ^[5] | | |
| Units: Percentage | | | | |
| number (confidence interval 95%) | | | | |
| Complete response (CR) | 1 (0 to 7) | 0 (0 to 9) | | |
| Partial response (PR) | 16 (9 to 27) | 31 (17 to 48) | | |
| Stable disease (SD) | 45 (33 to 57) | 46 (30 to 63) | | |
| Progressive disease | 28 (19 to 40) | 10 (3 to 24) | | |
| Not evaluable | 9 (4 to 19) | 13 (4 to 27) | | |

Notes:

[4] - Treated set

[5] - Treated set

Statistical analyses

No statistical analyses for this end point

Secondary: Best Overall Response According to RECIST v1.1 (Regardless of confirmation)

| | |
|-----------------|---|
| End point title | Best Overall Response According to RECIST v1.1 (Regardless of confirmation) |
|-----------------|---|

End point description:

Best overall response is the best overall response to trial medication (without clinical disease assessment) according to RECIST version 1.1 and was calculated relative to the baseline of each respective part. Percentage of participants with best overall response along with exact 95% Confidence Interval by Clopper and Pearson is presented. Best overall response was defined as the best response recorded at any time from the first administration of drug to the End of Treatment (EOT). As Per RECIST v1.1 for target lesions and assessed by MRI: Complete Response (CR), disappearance of all target lesions; Partial Response (PR) & gt;=30% decrease in the sum of the longest diameter of target lesions; progression, as a 20% increase in the sum of the longest diameter of target lesions, or a measurable increase in a non-target lesion, or the appearance of new lesions; Stable Disease (SD), neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for disease progression.

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

End point timeframe:

From the initial dose of study drug until 28 days after end of the treatment period, up to 1562 days

| End point values | Afatinib monotherapy | Afatinib and Paclitaxel or Vinorelbine combination therapy | | |
|----------------------------------|----------------------|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 74 ^[6] | 39 ^[7] | | |
| Units: Percentage | | | | |
| number (confidence interval 95%) | | | | |
| Complete response (CR) | 1 (0 to 7) | 0 (0 to 9) | | |
| Partial response (PR) | 19 (11 to 30) | 44 (28 to 60) | | |
| Stable disease (SD) | 42 (31 to 54) | 33 (19 to 50) | | |
| Progressive disease | 28 (19 to 40) | 10 (3 to 24) | | |
| Not evaluable | 9 (4 to 19) | 13 (4 to 27) | | |

Notes:

[6] - Treated Set

[7] - Treated Set

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival (PFS)

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

End point description:

Progression Free Survival is defined as the time from the drug start date to the date of 1st disease progression or death for monotherapy and 2nd disease progression or death from the drug start date of the combination therapy for combination therapy'. Median is calculated from the Kaplan–Meier curve.

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

End point timeframe:

From drug start date in monotherapy to 1st disease progression and drug start date in combination therapy to 2nd disease progression

| End point values | Afatinib monotherapy | Afatinib and Paclitaxel or Vinorelbine combination therapy | | |
|----------------------------------|----------------------|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 74 ^[8] | 39 ^[9] | | |
| Units: Days | | | | |
| median (confidence interval 95%) | 86.0 (72.0 to 127.0) | 135.0 (95.0 to 224.0) | | |

Notes:

[8] - Treated Set

[9] - Treated Set

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Objective Response according to RECIST v1.1

| | |
|------------------------|---|
| End point title | Duration of Objective Response according to RECIST v1.1 |
| End point description: | Duration of objective response, defined as the time from first objective response to the time of progression or death. (regardless of confirmation) |
| End point type | Secondary |
| End point timeframe: | From the first objective response to the time of progression or death |

| End point values | Afatinib monotherapy | Afatinib and Paclitaxel or Vinorelbine combination therapy | | |
|----------------------------------|-----------------------|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 74 ^[10] | 39 ^[11] | | |
| Units: Days | | | | |
| median (confidence interval 95%) | 168.5 (85.0 to 253.0) | 125.0 (73.0 to 505.0) | | |

Notes:

[10] - Treated Set

[11] - Treated Set

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of patients with highest common terminology criteria for adverse events (CTCAE) version 3.0 Grade of 3 or higher

| | |
|-----------------|---|
| End point title | Percentage of patients with highest common terminology criteria for adverse events (CTCAE) version 3.0 Grade of 3 or higher |
|-----------------|---|

higher

End point description:

Percentage of patients with highest common terminology criteria for adverse events (CTCAE) version 3.0 Grade of 3 or higher.

End point type Secondary

End point timeframe:

From the initial dose of study drug until 28 days after end of the treatment period, up to 1562 days

| End point values | Afatinib monotherapy | Afatinib and Vinorelbine combination therapy | Afatinib and Paclitaxel combination therapy | |
|-----------------------------|----------------------|--|---|--|
| Subject group type | Reporting group | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 74 ^[12] | 13 ^[13] | 26 ^[14] | |
| Units: Percentage | 43 | 62 | 65 | |

Notes:

[12] - Treated Set

[13] - Treated Set

[14] - Treated Set

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline to end of treatment in systolic blood pressure (SBP)

End point title Change from baseline to end of treatment in systolic blood pressure (SBP)

End point description:

Change from baseline to end of treatment in systolic blood pressure (SBP).

End point type Secondary

End point timeframe:

Baseline and End of treatment period

| End point values | Afatinib monotherapy | Afatinib and Vinorelbine combination therapy | Afatinib and Paclitaxel combination therapy | |
|--------------------------------------|----------------------|--|---|--|
| Subject group type | Reporting group | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 74 ^[15] | 13 ^[16] | 26 ^[17] | |
| Units: Millimeter of mercury (mmHg) | | | | |
| arithmetic mean (standard deviation) | -1.2 (± 17.9) | -1.0 (± 15.1) | -3.7 (± 12.1) | |

Notes:

[15] - Treated Set

[16] - Treated Set

[17] - Treated Set

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline to end of treatment in diastolic blood pressure (DBP)

End point title | Change from baseline to end of treatment in diastolic blood pressure (DBP)

End point description:

Change from baseline to end of treatment in diastolic blood pressure (DBP).

End point type | Secondary

End point timeframe:

Baseline and End of treatment period

| End point values | Afatinib monotherapy | Afatinib and Vinorelbine combination therapy | Afatinib and Paclitaxel combination therapy | |
|--------------------------------------|----------------------|--|---|--|
| Subject group type | Reporting group | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 74 ^[18] | 13 ^[19] | 26 ^[20] | |
| Units: Millimeter of mercury (mmHg) | | | | |
| arithmetic mean (standard deviation) | -1.8 (± 12.0) | 1.9 (± 10.7) | -1.6 (± 10.0) | |

Notes:

[18] - Treated Set

[19] - Treated Set

[20] - Treated Set

Statistical analyses

No statistical analyses for this end point

Secondary: Number of patient with possibly clinically significant (PCS) laboratory values

End point title | Number of patient with possibly clinically significant (PCS) laboratory values

End point description:

Number of patient with possibly clinically significant (PCS) laboratory values by functional group (haematology, differentials, coagulation, electrolytes, enzymes, and substrates). These findings were reported as adverse events.

99999: Not Applicable

End point type | Secondary

End point timeframe:

From the initial dose of study drug until 28 days after end of the treatment period, up to 1562 days

| End point values | Afatinib monotherapy | Afatinib and Vinorelbine combination therapy | Afatinib and Paclitaxel combination therapy | |
|-------------------------------|----------------------|--|---|--|
| Subject group type | Reporting group | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 74 ^[21] | 13 ^[22] | 26 ^[23] | |
| Units: Number of Participants | | | | |

| | | | |
|---|-------|-------|-------|
| Weight decreased | 10 | 1 | 4 |
| Alanine aminotransferase increased | 5 | 0 | 4 |
| Neutrophil count decreased | 99999 | 2 | 1 |
| Aspartate aminotransferase increased | 3 | 1 | 3 |
| Alanine aminotransferase | 99999 | 1 | 0 |
| Aspartate aminotransferase | 99999 | 1 | 0 |
| Blood creatinine increased | 2 | 0 | 2 |
| Blood glucose decreased | 99999 | 1 | 0 |
| Blood lactate dehydrogenase increased | 2 | 0 | 2 |
| Blood uric acid increased | 2 | 0 | 2 |
| Blood calcium decreased | 99999 | 0 | 1 |
| Blood sodium decreased | 1 | 0 | 1 |
| Haemoglobin decreased | 3 | 0 | 1 |
| Urine output decreased | 99999 | 0 | 1 |
| White blood cell count decreased | 1 | 0 | 1 |
| Blood alkaline phosphatase increased | 4 | 99999 | 99999 |
| Blood alkaline phosphatase | 1 | 99999 | 99999 |
| Blood creatine phosphokinase increased | 1 | 99999 | 99999 |
| Blood lactic acid increased | 1 | 99999 | 99999 |
| Blood potassium decreased | 1 | 99999 | 99999 |
| Glomerular filtration rate decreased | 1 | 99999 | 99999 |
| Liver function test increased | 1 | 99999 | 99999 |
| Lymphocyte count decreased | 1 | 99999 | 99999 |
| Platelet count decreased | 1 | 99999 | 99999 |
| Red blood cell sedimentation rate increased | 1 | 99999 | 99999 |

Notes:

[21] - Treated Set

[22] - Treated Set

[23] - Treated Set

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the initial dose of study drug until 28 days after end of the treatment period, up to 1562 days

Adverse event reporting additional description:

Safety analyses were performed for monotherapy and combination therapy separately using the respective treated sets. Treated set for monotherapy comprised all patients who received at least 1 dose of afatinib. Treated set for combination therapy comprised all patients who received at least 1 dose of each afatinib/paclitaxel or afatinib/vinorelbine.

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 19.1 |
|--------------------|------|

Reporting groups

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

Reporting group description:

Patient received Afatinib monotherapy orally once daily at a dose of 40 milligram (mg) film-coated tablets until progression of their disease, unacceptable adverse events or other reason necessitating withdrawal. A dose reduction to 30mg and 20mg was possible if 40mg was not tolerated.

| | |
|-----------------------|--|
| Reporting group title | Afatinib and Vinorelbine combination therapy |
|-----------------------|--|

Reporting group description:

Patient received Afatinib monotherapy orally once daily at a dose of 40 mg film-coated tablets until progression of their disease, unacceptable adverse events or other reason necessitating withdrawal (A dose reduction to 30mg and 20mg was possible if 40mg was not tolerated) and 25 mg/m² Vinorelbine concentrate for intravenous infusion once weekly starting after treatment failure on afatinib monotherapy

| | |
|-----------------------|---|
| Reporting group title | Afatinib and Paclitaxel combination therapy |
|-----------------------|---|

Reporting group description:

Patient received Afatinib monotherapy orally once daily at a dose of 40 mg film-coated tablets until progression of their disease, unacceptable adverse events or other reason necessitating withdrawal (A dose reduction to 30mg and 20mg was possible if 40mg was not tolerated) and 80 mg/square meter (m²) Paclitaxel concentrate for intravenous infusion once weekly starting after treatment failure on afatinib monotherapy

| Serious adverse events | Afatinib monotherapy | Afatinib and Vinorelbine combination therapy | Afatinib and Paclitaxel combination therapy |
|---|----------------------|--|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 18 / 74 (24.32%) | 5 / 13 (38.46%) | 10 / 26 (38.46%) |
| number of deaths (all causes) | 6 | 1 | 5 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Breast cancer metastatic | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | 0 / 13 (0.00%) | 1 / 26 (3.85%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Malignant neoplasm progression | | | |

| | | | |
|---|----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 74 (0.00%) | 1 / 13 (7.69%) | 1 / 26 (3.85%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| Metastases to central nervous system | | | |
| subjects affected / exposed | 2 / 74 (2.70%) | 0 / 13 (0.00%) | 1 / 26 (3.85%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| Neoplasm progression | | | |
| subjects affected / exposed | 4 / 74 (5.41%) | 0 / 13 (0.00%) | 2 / 26 (7.69%) |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 3 | 0 / 0 | 0 / 1 |
| Vascular disorders | | | |
| Hypotension | | | |
| subjects affected / exposed | 1 / 74 (1.35%) | 0 / 13 (0.00%) | 0 / 26 (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 |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 3 / 74 (4.05%) | 1 / 13 (7.69%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Chest pain | | | |
| subjects affected / exposed | 1 / 74 (1.35%) | 0 / 13 (0.00%) | 1 / 26 (3.85%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pain | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | 1 / 13 (7.69%) | 0 / 26 (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 |
| Pyrexia | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | 2 / 13 (15.38%) | 1 / 26 (3.85%) |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 3 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|----------------|-----------------|----------------|
| Respiratory, thoracic and mediastinal disorders | | | |
| Dysphonia | | | |
| subjects affected / exposed | 1 / 74 (1.35%) | 0 / 13 (0.00%) | 0 / 26 (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 |
| Dyspnoea | | | |
| subjects affected / exposed | 3 / 74 (4.05%) | 2 / 13 (15.38%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Interstitial lung disease | | | |
| subjects affected / exposed | 1 / 74 (1.35%) | 0 / 13 (0.00%) | 0 / 26 (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 |
| Pleural effusion | | | |
| subjects affected / exposed | 1 / 74 (1.35%) | 0 / 13 (0.00%) | 0 / 26 (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 arrest | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | 1 / 13 (7.69%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Respiratory distress | | | |
| subjects affected / exposed | 1 / 74 (1.35%) | 0 / 13 (0.00%) | 0 / 26 (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 failure | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | 0 / 13 (0.00%) | 1 / 26 (3.85%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Product issues | | | |
| Device leakage | | | |
| subjects affected / exposed | 1 / 74 (1.35%) | 0 / 13 (0.00%) | 0 / 26 (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 occlusion | | | |
| subjects affected / exposed | 1 / 74 (1.35%) | 0 / 13 (0.00%) | 0 / 26 (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 | 0 / 74 (0.00%) | 0 / 13 (0.00%) | 1 / 26 (3.85%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Cardio-respiratory arrest | | | |
| subjects affected / exposed | 1 / 74 (1.35%) | 0 / 13 (0.00%) | 0 / 26 (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 |
| Nervous system disorders | | | |
| Brain oedema | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | 0 / 13 (0.00%) | 1 / 26 (3.85%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dizziness | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | 0 / 13 (0.00%) | 1 / 26 (3.85%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Neuralgia | | | |
| subjects affected / exposed | 1 / 74 (1.35%) | 0 / 13 (0.00%) | 0 / 26 (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 |
| Seizure | | | |
| subjects affected / exposed | 1 / 74 (1.35%) | 0 / 13 (0.00%) | 0 / 26 (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 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |

| | | | |
|---|----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 74 (0.00%) | 1 / 13 (7.69%) | 0 / 26 (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 |
| Febrile neutropenia | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | 1 / 13 (7.69%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 2 / 74 (2.70%) | 2 / 13 (15.38%) | 1 / 26 (3.85%) |
| occurrences causally related to treatment / all | 0 / 4 | 1 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diarrhoea | | | |
| subjects affected / exposed | 3 / 74 (4.05%) | 0 / 13 (0.00%) | 1 / 26 (3.85%) |
| occurrences causally related to treatment / all | 2 / 4 | 0 / 0 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nausea | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | 0 / 13 (0.00%) | 2 / 26 (7.69%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vomiting | | | |
| subjects affected / exposed | 2 / 74 (2.70%) | 1 / 13 (7.69%) | 1 / 26 (3.85%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| Hepatic function abnormal | | | |
| subjects affected / exposed | 1 / 74 (1.35%) | 0 / 13 (0.00%) | 0 / 26 (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 |
| Renal and urinary disorders | | | |
| Azotaemia | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | 0 / 13 (0.00%) | 1 / 26 (3.85%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|----------------|----------------|----------------|
| Renal failure | | | |
| subjects affected / exposed | 1 / 74 (1.35%) | 0 / 13 (0.00%) | 1 / 26 (3.85%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary tract obstruction | | | |
| subjects affected / exposed | 1 / 74 (1.35%) | 0 / 13 (0.00%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | 1 / 13 (7.69%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pathological fracture | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | 0 / 13 (0.00%) | 1 / 26 (3.85%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Diarrhoea infectious | | | |
| subjects affected / exposed | 1 / 74 (1.35%) | 0 / 13 (0.00%) | 0 / 26 (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 / 74 (1.35%) | 0 / 13 (0.00%) | 0 / 26 (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 |
| Liver abscess | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | 1 / 13 (7.69%) | 0 / 26 (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 |
| Pneumonia | | | |
| subjects affected / exposed | 1 / 74 (1.35%) | 0 / 13 (0.00%) | 0 / 26 (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 |

| | | | |
|---|----------------|----------------|----------------|
| Upper respiratory tract infection subjects affected / exposed | 1 / 74 (1.35%) | 0 / 13 (0.00%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary tract infection subjects affected / exposed | 0 / 74 (0.00%) | 0 / 13 (0.00%) | 1 / 26 (3.85%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urosepsis subjects affected / exposed | 1 / 74 (1.35%) | 0 / 13 (0.00%) | 0 / 26 (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 |
| Metabolism and nutrition disorders Decreased appetite subjects affected / exposed | 2 / 74 (2.70%) | 0 / 13 (0.00%) | 0 / 26 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

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

| Non-serious adverse events | Afatinib monotherapy | Afatinib and Vinorelbine combination therapy | Afatinib and Paclitaxel combination therapy |
|---|-------------------------|--|---|
| Total subjects affected by non-serious adverse events subjects affected / exposed | 67 / 74 (90.54%) | 13 / 13 (100.00%) | 23 / 26 (88.46%) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) Neoplasm progression subjects affected / exposed | 6 / 74 (8.11%) | 0 / 13 (0.00%) | 1 / 26 (3.85%) |
| occurrences (all) | 6 | 0 | 1 |
| Vascular disorders Phlebitis subjects affected / exposed | 0 / 74 (0.00%) | 2 / 13 (15.38%) | 0 / 26 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| General disorders and administration site conditions Asthenia | | | |

| | | | |
|--|------------------------|----------------------|----------------------|
| subjects affected / exposed occurrences (all) | 5 / 74 (6.76%) 5 | 2 / 13 (15.38%) 8 | 7 / 26 (26.92%) 8 |
| Fatigue subjects affected / exposed occurrences (all) | 7 / 74 (9.46%) 7 | 0 / 13 (0.00%) 0 | 5 / 26 (19.23%) 5 |
| Mucosal inflammation subjects affected / exposed occurrences (all) | 15 / 74 (20.27%) 22 | 0 / 13 (0.00%) 0 | 1 / 26 (3.85%) 2 |
| Oedema subjects affected / exposed occurrences (all) | 0 / 74 (0.00%) 0 | 1 / 13 (7.69%) 1 | 0 / 26 (0.00%) 0 |
| Oedema peripheral subjects affected / exposed occurrences (all) | 1 / 74 (1.35%) 1 | 0 / 13 (0.00%) 0 | 2 / 26 (7.69%) 2 |
| Pain subjects affected / exposed occurrences (all) | 0 / 74 (0.00%) 0 | 1 / 13 (7.69%) 1 | 1 / 26 (3.85%) 1 |
| Pyrexia subjects affected / exposed occurrences (all) | 4 / 74 (5.41%) 5 | 1 / 13 (7.69%) 2 | 2 / 26 (7.69%) 2 |
| Ulcer subjects affected / exposed occurrences (all) | 0 / 74 (0.00%) 0 | 1 / 13 (7.69%) 1 | 0 / 26 (0.00%) 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough subjects affected / exposed occurrences (all) | 8 / 74 (10.81%) 8 | 0 / 13 (0.00%) 0 | 3 / 26 (11.54%) 4 |
| Dyspnoea subjects affected / exposed occurrences (all) | 8 / 74 (10.81%) 8 | 0 / 13 (0.00%) 0 | 2 / 26 (7.69%) 2 |
| Epistaxis subjects affected / exposed occurrences (all) | 6 / 74 (8.11%) 6 | 0 / 13 (0.00%) 0 | 2 / 26 (7.69%) 2 |
| Oropharyngeal pain | | | |

| | | | |
|--|---------------------|---------------------|----------------------|
| subjects affected / exposed occurrences (all) | 3 / 74 (4.05%) 3 | 0 / 13 (0.00%) 0 | 2 / 26 (7.69%) 2 |
| Rhinorrhoea subjects affected / exposed occurrences (all) | 4 / 74 (5.41%) 5 | 0 / 13 (0.00%) 0 | 0 / 26 (0.00%) 0 |
| Psychiatric disorders Insomnia subjects affected / exposed occurrences (all) | 1 / 74 (1.35%) 1 | 0 / 13 (0.00%) 0 | 3 / 26 (11.54%) 3 |
| Investigations Alanine aminotransferase subjects affected / exposed occurrences (all) | 0 / 74 (0.00%) 0 | 1 / 13 (7.69%) 1 | 0 / 26 (0.00%) 0 |
| Alanine aminotransferase increased subjects affected / exposed occurrences (all) | 5 / 74 (6.76%) 5 | 0 / 13 (0.00%) 0 | 4 / 26 (15.38%) 6 |
| Aspartate aminotransferase subjects affected / exposed occurrences (all) | 0 / 74 (0.00%) 0 | 1 / 13 (7.69%) 1 | 0 / 26 (0.00%) 0 |
| Aspartate aminotransferase increased subjects affected / exposed occurrences (all) | 3 / 74 (4.05%) 3 | 1 / 13 (7.69%) 1 | 3 / 26 (11.54%) 3 |
| Blood alkaline phosphatase increased subjects affected / exposed occurrences (all) | 4 / 74 (5.41%) 4 | 0 / 13 (0.00%) 0 | 0 / 26 (0.00%) 0 |
| Blood glucose decreased subjects affected / exposed occurrences (all) | 0 / 74 (0.00%) 0 | 1 / 13 (7.69%) 1 | 0 / 26 (0.00%) 0 |
| Blood lactate dehydrogenase increased subjects affected / exposed occurrences (all) | 2 / 74 (2.70%) 2 | 0 / 13 (0.00%) 0 | 2 / 26 (7.69%) 2 |
| Blood uric acid increased subjects affected / exposed occurrences (all) | 2 / 74 (2.70%) 3 | 0 / 13 (0.00%) 0 | 2 / 26 (7.69%) 2 |
| Neutrophil count decreased | | | |

| | | | |
|--|------------------------|----------------------|------------------------|
| subjects affected / exposed occurrences (all) | 0 / 74 (0.00%) 0 | 2 / 13 (15.38%) 3 | 1 / 26 (3.85%) 1 |
| Weight decreased subjects affected / exposed occurrences (all) | 10 / 74 (13.51%) 11 | 1 / 13 (7.69%) 1 | 4 / 26 (15.38%) 5 |
| Injury, poisoning and procedural complications | | | |
| Wound | | | |
| subjects affected / exposed occurrences (all) | 0 / 74 (0.00%) 0 | 1 / 13 (7.69%) 1 | 0 / 26 (0.00%) 0 |
| Wound secretion | | | |
| subjects affected / exposed occurrences (all) | 0 / 74 (0.00%) 0 | 1 / 13 (7.69%) 1 | 0 / 26 (0.00%) 0 |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed occurrences (all) | 3 / 74 (4.05%) 3 | 1 / 13 (7.69%) 1 | 1 / 26 (3.85%) 1 |
| Headache | | | |
| subjects affected / exposed occurrences (all) | 7 / 74 (9.46%) 8 | 1 / 13 (7.69%) 1 | 2 / 26 (7.69%) 5 |
| Hypoaesthesia | | | |
| subjects affected / exposed occurrences (all) | 3 / 74 (4.05%) 3 | 1 / 13 (7.69%) 1 | 3 / 26 (11.54%) 3 |
| Neuropathy peripheral | | | |
| subjects affected / exposed occurrences (all) | 0 / 74 (0.00%) 0 | 0 / 13 (0.00%) 0 | 3 / 26 (11.54%) 3 |
| Peripheral sensory neuropathy | | | |
| subjects affected / exposed occurrences (all) | 0 / 74 (0.00%) 0 | 0 / 13 (0.00%) 0 | 4 / 26 (15.38%) 5 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed occurrences (all) | 7 / 74 (9.46%) 7 | 4 / 13 (30.77%) 4 | 13 / 26 (50.00%) 17 |
| Leukopenia | | | |
| subjects affected / exposed occurrences (all) | 1 / 74 (1.35%) 2 | 4 / 13 (30.77%) 7 | 5 / 26 (19.23%) 7 |
| Neutropenia | | | |

| | | | |
|--|-------------------------|-----------------------|-----------------------|
| subjects affected / exposed occurrences (all) | 1 / 74 (1.35%) 1 | 9 / 13 (69.23%) 24 | 9 / 26 (34.62%) 36 |
| Thrombocytopenia subjects affected / exposed occurrences (all) | 2 / 74 (2.70%) 3 | 1 / 13 (7.69%) 3 | 1 / 26 (3.85%) 1 |
| Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences (all) | 0 / 74 (0.00%) 0 | 0 / 13 (0.00%) 0 | 2 / 26 (7.69%) 2 |
| Eye disorders Dry eye subjects affected / exposed occurrences (all) | 3 / 74 (4.05%) 3 | 1 / 13 (7.69%) 1 | 1 / 26 (3.85%) 1 |
| Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all) | 5 / 74 (6.76%) 5 | 0 / 13 (0.00%) 0 | 1 / 26 (3.85%) 1 |
| Abdominal pain upper subjects affected / exposed occurrences (all) | 1 / 74 (1.35%) 1 | 0 / 13 (0.00%) 0 | 3 / 26 (11.54%) 3 |
| Anal inflammation subjects affected / exposed occurrences (all) | 0 / 74 (0.00%) 0 | 1 / 13 (7.69%) 1 | 0 / 26 (0.00%) 0 |
| Constipation subjects affected / exposed occurrences (all) | 0 / 74 (0.00%) 0 | 0 / 13 (0.00%) 0 | 3 / 26 (11.54%) 3 |
| Diarrhoea subjects affected / exposed occurrences (all) | 50 / 74 (67.57%) 101 | 3 / 13 (23.08%) 4 | 9 / 26 (34.62%) 18 |
| Haemorrhoids subjects affected / exposed occurrences (all) | 3 / 74 (4.05%) 3 | 1 / 13 (7.69%) 1 | 2 / 26 (7.69%) 2 |
| Mouth ulceration subjects affected / exposed occurrences (all) | 8 / 74 (10.81%) 8 | 2 / 13 (15.38%) 2 | 2 / 26 (7.69%) 2 |
| Nausea | | | |

| | | | |
|---|------------------------|----------------------|------------------------|
| subjects affected / exposed occurrences (all) | 9 / 74 (12.16%) 9 | 1 / 13 (7.69%) 1 | 4 / 26 (15.38%) 13 |
| Stomatitis subjects affected / exposed occurrences (all) | 3 / 74 (4.05%) 4 | 1 / 13 (7.69%) 1 | 0 / 26 (0.00%) 0 |
| Vomiting subjects affected / exposed occurrences (all) | 6 / 74 (8.11%) 6 | 2 / 13 (15.38%) 2 | 4 / 26 (15.38%) 5 |
| Skin and subcutaneous tissue disorders | | | |
| Acne subjects affected / exposed occurrences (all) | 5 / 74 (6.76%) 6 | 0 / 13 (0.00%) 0 | 0 / 26 (0.00%) 0 |
| Alopecia subjects affected / exposed occurrences (all) | 2 / 74 (2.70%) 2 | 1 / 13 (7.69%) 1 | 10 / 26 (38.46%) 10 |
| Dermatitis subjects affected / exposed occurrences (all) | 5 / 74 (6.76%) 5 | 2 / 13 (15.38%) 2 | 1 / 26 (3.85%) 1 |
| Eczema subjects affected / exposed occurrences (all) | 4 / 74 (5.41%) 5 | 1 / 13 (7.69%) 2 | 1 / 26 (3.85%) 1 |
| Eczema asteatotic subjects affected / exposed occurrences (all) | 1 / 74 (1.35%) 1 | 1 / 13 (7.69%) 1 | 0 / 26 (0.00%) 0 |
| Nail bed inflammation subjects affected / exposed occurrences (all) | 0 / 74 (0.00%) 0 | 1 / 13 (7.69%) 1 | 0 / 26 (0.00%) 0 |
| Palmar-plantar erythrodysesthesia syndrome subjects affected / exposed occurrences (all) | 13 / 74 (17.57%) 15 | 1 / 13 (7.69%) 1 | 3 / 26 (11.54%) 3 |
| Pruritus subjects affected / exposed occurrences (all) | 5 / 74 (6.76%) 6 | 0 / 13 (0.00%) 0 | 2 / 26 (7.69%) 2 |
| Rash | | | |

| | | | |
|---|------------------------|----------------------|----------------------|
| subjects affected / exposed occurrences (all) | 37 / 74 (50.00%) 42 | 3 / 13 (23.08%) 4 | 4 / 26 (15.38%) 8 |
| Rash pruritic subjects affected / exposed occurrences (all) | 0 / 74 (0.00%) 0 | 1 / 13 (7.69%) 2 | 2 / 26 (7.69%) 2 |
| Skin hyperpigmentation subjects affected / exposed occurrences (all) | 2 / 74 (2.70%) 2 | 0 / 13 (0.00%) 0 | 2 / 26 (7.69%) 2 |
| Renal and urinary disorders Dysuria subjects affected / exposed occurrences (all) | 0 / 74 (0.00%) 0 | 1 / 13 (7.69%) 1 | 0 / 26 (0.00%) 0 |
| Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) | 2 / 74 (2.70%) 2 | 0 / 13 (0.00%) 0 | 2 / 26 (7.69%) 3 |
| Back pain subjects affected / exposed occurrences (all) | 2 / 74 (2.70%) 3 | 2 / 13 (15.38%) 2 | 0 / 26 (0.00%) 0 |
| Musculoskeletal pain subjects affected / exposed occurrences (all) | 5 / 74 (6.76%) 5 | 0 / 13 (0.00%) 0 | 1 / 26 (3.85%) 1 |
| Pain in extremity subjects affected / exposed occurrences (all) | 0 / 74 (0.00%) 0 | 1 / 13 (7.69%) 1 | 1 / 26 (3.85%) 1 |
| Infections and infestations Bronchitis subjects affected / exposed occurrences (all) | 0 / 74 (0.00%) 0 | 1 / 13 (7.69%) 1 | 0 / 26 (0.00%) 0 |
| Escherichia urinary tract infection subjects affected / exposed occurrences (all) | 0 / 74 (0.00%) 0 | 1 / 13 (7.69%) 1 | 0 / 26 (0.00%) 0 |
| Folliculitis subjects affected / exposed occurrences (all) | 4 / 74 (5.41%) 5 | 0 / 13 (0.00%) 0 | 0 / 26 (0.00%) 0 |
| Gastroenteritis | | | |

| | | | |
|---|-----------------------|----------------------|----------------------|
| subjects affected / exposed occurrences (all) | 0 / 74 (0.00%) 0 | 1 / 13 (7.69%) 1 | 0 / 26 (0.00%) 0 |
| Nasopharyngitis subjects affected / exposed occurrences (all) | 1 / 74 (1.35%) 1 | 0 / 13 (0.00%) 0 | 2 / 26 (7.69%) 3 |
| Paronychia subjects affected / exposed occurrences (all) | 9 / 74 (12.16%) 12 | 2 / 13 (15.38%) 2 | 1 / 26 (3.85%) 6 |
| Periodontitis subjects affected / exposed occurrences (all) | 0 / 74 (0.00%) 0 | 1 / 13 (7.69%) 1 | 0 / 26 (0.00%) 0 |
| Pulpitis dental subjects affected / exposed occurrences (all) | 0 / 74 (0.00%) 0 | 1 / 13 (7.69%) 1 | 0 / 26 (0.00%) 0 |
| Respiratory tract infection subjects affected / exposed occurrences (all) | 0 / 74 (0.00%) 0 | 0 / 13 (0.00%) 0 | 2 / 26 (7.69%) 4 |
| Upper respiratory tract infection subjects affected / exposed occurrences (all) | 4 / 74 (5.41%) 4 | 0 / 13 (0.00%) 0 | 1 / 26 (3.85%) 3 |
| Urinary tract infection subjects affected / exposed occurrences (all) | 3 / 74 (4.05%) 3 | 0 / 13 (0.00%) 0 | 3 / 26 (11.54%) 4 |
| Viral infection subjects affected / exposed occurrences (all) | 0 / 74 (0.00%) 0 | 0 / 13 (0.00%) 0 | 2 / 26 (7.69%) 3 |
| Metabolism and nutrition disorders | | | |
| Decreased appetite subjects affected / exposed occurrences (all) | 5 / 74 (6.76%) 5 | 0 / 13 (0.00%) 0 | 4 / 26 (15.38%) 4 |
| Hypocalcaemia subjects affected / exposed occurrences (all) | 2 / 74 (2.70%) 2 | 0 / 13 (0.00%) 0 | 2 / 26 (7.69%) 3 |
| Hypokalaemia subjects affected / exposed occurrences (all) | 3 / 74 (4.05%) 6 | 0 / 13 (0.00%) 0 | 2 / 26 (7.69%) 4 |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|--|
| 22 December 2010 | The schedule for tumour assessments was clarified. Use of contraception post study for each of the trial medications was defined, at the request of the Competent Authorities and to align the text with the summaries of product characteristics (SmPCs) for paclitaxel and vinorelbine. Vinorelbine infusion time was clarified. An explanation was added regarding handling of hospitalisations for administrative reasons. |
| 27 April 2011 | It was clarified that haematology (complete blood count) results were required prior to chemotherapy. Guidance on the use of radiotherapy during the trial was added. Palliative radiotherapy became allowed. An exclusion criterion was amended to allow palliative radiotherapy. Guidance on the timing of study medication intake was corrected. The requirement for a platelet count value before treatment with paclitaxel was added. The adverse event reporting periods were corrected. It was clarified that the reference SmPC was not the local version. |
| 29 July 2011 | 'LUX-Breast 2' was added to the title to indicate that this trial is part of the LUX-breast program |
| 06 December 2011 | Text was added regarding drug-induced liver injury (DILI) in line with new corporate standards. An exclusion criterion was added to clarify that the intention was to include patients who required first-line treatment for metastatic breast cancer. Guidance on missed doses was added. Text was added regarding AE that are considered 'always serious' in line with new corporate standards. |
| 06 November 2012 | Timing of ECHO and MUGA scans during combination therapy was added and clarified. Guidance on the concomitant use of P-gp inhibitors and inducers- was updated, and a list medications in this class was added. Information about the incidence of keratitis in licensed epidermal growth factor receptor (EGFR) inhibitors was added. The requirement for a platelet count to be available prior to the start of each vinorelbine infusion was added, a statement on vinorelbine dose adjustment for severe hepatic impairment was added, and instructions for diluting vinorelbine were amended following the release of an updated SmPC for vinorelbine. The name of the manufacturer of paclitaxel was removed following a shortage of paclitaxel from Hospira United Kingdom. Reporting of worsening of underlying disease or other pre-existing conditions, change in vital signs, Electrocardiogram, physical examination and laboratory test results were modified for alignment with project standard definitions. |
| 27 June 2013 | The inclusion of patients after progression on Afatinib monotherapy (part A) into the afatinib + vinorelbine combination in Part B was stopped. Patients in part A could only go into the Afatinib + Paclitaxel arm. Enrolment of new patients into the trial was also stopped. The description of bottles of afatinib was removed in case future supplies were switched to the marketed product |

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.

Enrollment of patients into the afatinib and vinorelbine combination option was stopped prematurely following a benefit-risk analysis in other trial. Any patients who were already benefiting from this combination were allowed to continue.

Notes: