



Clinical trial results:

A Phase 1 / 2 Study of HKI-272 in combination With Paclitaxel in Subjects With Solid Tumors and Breast Cancer

Summary

| | |
|--------------------------|------------------|
| EudraCT number | 2006-006412-29 |
| Trial protocol | BE |
| Global end of trial date | 07 February 2018 |

Results information

| | |
|--------------------------------|------------------|
| Result version number | v1 (current) |
| This version publication date | 24 February 2019 |
| First version publication date | 24 February 2019 |

Trial information

Trial identification

| | |
|-----------------------|---------------|
| Sponsor protocol code | 3144A1-203-WW |
|-----------------------|---------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT00445458 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Puma Biotechnology, Inc. |
| Sponsor organisation address | 10880 Wilshire Blvd, Los Angeles, United States, 90024 |
| Public contact | Clinical Operations Senior Director, Puma Biotechnology, Inc., 1 4242486500, clinicaltrials@pumabiotechnology.com |
| Scientific contact | Clinical Operations Senior Director, Puma Biotechnology, Inc., 1 4242486500, clinicaltrials@pumabiotechnology.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 | 07 February 2018 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 07 February 2018 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

Part 1: The primary objectives of part 1 are to assess the safety and tolerability, and to define the maximum tolerated dose (MTD) of HKI-272 in combination with paclitaxel in subjects with advanced solid tumors

Part 2: The primary objective of part 2 of this study is to estimate the overall response rate (ORR) for subjects with HER2 positive breast cancer treated at the MTD of HKI-272 in combination with paclitaxel.

Protection of trial subjects:

Study commencement required prior written approval of a properly constituted Institutional Review Board (IRB) or Independent Ethics Committee (IEC). Clinical trial data were monitored at regular intervals by the Sponsor or their representative throughout the study to verify compliance to study protocol, completeness, accuracy and consistency of the data and adherence to local regulations on the conduct of clinical research.

Patients were discontinued from investigational product(s) (IP) if patient required more than 2 dose reductions of neratinib, or if 120 mg of neratinib was not tolerable, or if the subject had not recovered from treatment-related toxicity after >3 weeks; disease progression, pregnancy, or patient request.

Background therapy: -

Evidence for comparator: -

| | |
|---|-------------------|
| Actual start date of recruitment | 11 September 2007 |
| 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 | India: 13 |
| Country: Number of subjects enrolled | Korea, Republic of: 6 |
| Country: Number of subjects enrolled | Poland: 8 |
| Country: Number of subjects enrolled | Ukraine: 11 |
| Country: Number of subjects enrolled | United States: 9 |
| Country: Number of subjects enrolled | Belgium: 4 |
| Country: Number of subjects enrolled | Canada: 2 |
| Country: Number of subjects enrolled | China: 42 |
| Country: Number of subjects enrolled | Hong Kong: 15 |
| Worldwide total number of subjects | 110 |
| EEA total number of subjects | 12 |

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) | 105 |
| From 65 to 84 years | 5 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Informed consent was obtained before any protocol required assessments were performed. Subjects who signed informed consent, but fail to meet inclusion/exclusion criteria or withdrew consent prior to receiving any study medication were considered screen failures.

Period 1

| | |
|------------------------------|-----------------------------------|
| Period 1 title | Treatment Period (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Non-randomised - controlled |
| Blinding used | Not blinded |

Arms

| | |
|------------------------------|----------------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Part 1 Ner160 + Paclitaxel |

Arm description:

Neratinib 160 mg orally once daily every day, in combination with paclitaxel 80 mg/m² intravenous infusion on days 1, 8 and 15 of a 28-day cycle.

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

Dosage and administration details:

2 Neratinib 80-mg capsules or 4 40-mg tablets taken 1 daily, with food, preferably in the morning, during each 28-day cycle.

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

Dosage and administration details:

Within each 28-day cycle, paclitaxel (80 mg/m²) was to be intravenously infused (over approximately 1 hour) on Days 1, 8, and 15 (Table 8).

| | |
|------------------|----------------------------|
| Arm title | Part 1 Ner240 + Paclitaxel |
|------------------|----------------------------|

Arm description:

Neratinib 240 mg orally once daily every day, in combination with paclitaxel 80 mg/m² intravenous infusion on days 1, 8 and 15 of a 28-day cycle.

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

Dosage and administration details:

Neratinib capsules or tablets (80 mg and/or 40 mg, as appropriate) were taken orally once daily, with food, preferably in the morning during each 28-day cycle.

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

Dosage and administration details:

Within each 28-day cycle, paclitaxel (80 mg/m²) was to be intravenously infused (over approximately 1 hour) on Days 1, 8, and 15.

| | |
|------------------|---------------------------------|
| Arm title | Part 2 Ner240 + Paclitaxel ArmA |
|------------------|---------------------------------|

Arm description:

Neratinib (MTD, 240 mg) qd + Paclitaxel 80 mg/m² on days 1, 8, and 15 of a 28 day cycle for subjects with not more than 1 prior cytotoxic chemotherapy treatment regimen for metastatic disease.

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

Dosage and administration details:

Neratinib capsules or tablets (80 mg and/or 40 mg, as appropriate) were taken orally once daily, with food, preferably in the morning during each 28-day cycle.

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

Dosage and administration details:

Within each 28-day cycle, paclitaxel (80 mg/m²) was to be intravenously infused (over approximately 1 hour) on Days 1, 8, and 15.

| | |
|------------------|---------------------------------|
| Arm title | Part 2 Ner240 + Paclitaxel ArmB |
|------------------|---------------------------------|

Arm description:

Neratinib (MTD, 240 mg) qd + Paclitaxel 80 mg/m² on days 1, 8, and 15 of a 28 day cycle for subjects with not more than 3 prior cytotoxic chemotherapy treatment regimen for metastatic disease.

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

Dosage and administration details:

Neratinib capsules or tablets (80 mg and/or 40 mg, as appropriate) were taken orally once daily, with food, preferably in the morning during each 28-day cycle.

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

Dosage and administration details:

Within each 28-day cycle, paclitaxel (80 mg/m²) was to be intravenously infused (over approximately 1 hour) on Days 1, 8, and 15.

| Number of subjects in period 1 | Part 1 Ner160 + Paclitaxel | Part 1 Ner240 + Paclitaxel | Part 2 Ner240 + Paclitaxel ArmA |
|---------------------------------------|---------------------------------------|---------------------------------------|--|
| Started | 3 | 5 | 71 |
| Completed | 0 | 0 | 0 |
| Not completed | 3 | 5 | 71 |
| Adverse event, serious fatal | - | 1 | 2 |
| Physician decision | - | - | 1 |
| Consent withdrawn by subject | - | - | 8 |
| Surgical Procedure | - | - | 1 |
| Adverse event, non-fatal | - | - | 4 |
| Study Discontinued by Sponsor | - | - | 1 |
| Disease Progression | 3 | 4 | 54 |

| Number of subjects in period 1 | Part 2 Ner240 + Paclitaxel ArmB |
|---------------------------------------|--|
| Started | 31 |
| Completed | 0 |
| Not completed | 31 |
| Adverse event, serious fatal | - |
| Physician decision | 1 |
| Consent withdrawn by subject | 1 |
| Surgical Procedure | - |
| Adverse event, non-fatal | - |
| Study Discontinued by Sponsor | 1 |
| Disease Progression | 28 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|------------------|
| Reporting group title | Treatment Period |
|-----------------------|------------------|

Reporting group description: -

| Reporting group values | Treatment Period | Total | |
|---|------------------|-------|--|
| Number of subjects | 110 | 110 | |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | 0 | 0 | |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | |
| Newborns (0-27 days) | 0 | 0 | |
| Infants and toddlers (28 days-23 months) | 0 | 0 | |
| Children (2-11 years) | 0 | 0 | |
| Adolescents (12-17 years) | 0 | 0 | |
| Adults (18-64 years) | 105 | 105 | |
| From 65-84 years | 5 | 5 | |
| 85 years and over | 0 | 0 | |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 50.6 | | |
| standard deviation | ± 9.8 | - | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 105 | 105 | |
| Male | 5 | 5 | |

End points

End points reporting groups

| | |
|--|---------------------------------|
| Reporting group title | Part 1 Ner160 + Paclitaxel |
| Reporting group description: Neratinib 160 mg orally once daily every day, in combination with paclitaxel 80 mg/m ² intravenous infusion on days 1, 8 and 15 of a 28-day cycle. | |
| Reporting group title | Part 1 Ner240 + Paclitaxel |
| Reporting group description: Neratinib 240 mg orally once daily every day, in combination with paclitaxel 80 mg/m ² intravenous infusion on days 1, 8 and 15 of a 28-day cycle. | |
| Reporting group title | Part 2 Ner240 + Paclitaxel ArmA |
| Reporting group description: Neratinib (MTD, 240 mg) qd + Paclitaxel 80 mg/m ² on days 1, 8, and 15 of a 28 day cycle for subjects with not more than 1 prior cytotoxic chemotherapy treatment regimen for metastatic disease. | |
| Reporting group title | Part 2 Ner240 + Paclitaxel ArmB |
| Reporting group description: Neratinib (MTD, 240 mg) qd + Paclitaxel 80 mg/m ² on days 1, 8, and 15 of a 28 day cycle for subjects with not more than 3 prior cytotoxic chemotherapy treatment regimen for metastatic disease. | |

Primary: Objective Response Rate. Part 2 of Study

| | |
|--|---|
| End point title | Objective Response Rate. Part 2 of Study ^[1] |
| End point description: Subjects with partial response (PR) or complete response (CR) with ERBB2 positive breast cancer treated at the maximum tolerated dose (MTD) of neratinib in combination with paclitaxel, per Response Evaluation Criteria In Solid Tumors Criteria (RECIST) v.1.0: CR, disappearance of all target lesions; PR, $\geq 30\%$ decrease in the sum of the longest diameter of target lesions; and no progressive disease (PD) for non-target lesions, and no new lesions. | |
| End point type | Primary |
| End point timeframe: From first dose date to progression or last tumor assessment, up to 140 weeks | |

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: There was no preplanned hypothesis testing. The objective of the study was to estimate the objective response rate within each arm.

| End point values | Part 1 Ner160 + Paclitaxel | Part 1 Ner240 + Paclitaxel | Part 2 Ner240 + Paclitaxel ArmA | Part 2 Ner240 + Paclitaxel ArmB |
|-----------------------------------|----------------------------|----------------------------|---------------------------------|---------------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 0 ^[2] | 0 ^[3] | 68 | 31 |
| Units: Percentage of Participants | | | | |
| number (confidence interval 95%) | (to) | (to) | 70.6 (58.3 to 81.0) | 77.4 (58.9 to 90.4) |

Notes:

[2] - Objective Response Rate was measured and assessed in Part 2 of the study only.

[3] - Objective Response Rate was measured and assessed in Part 2 of the study only.

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects with Dose Limiting Toxicities Part 1

| | |
|--|--|
| End point title | Number of Subjects with Dose Limiting Toxicities Part 1 ^[4] |
| End point description: Dose Limiting Toxicity in subjects with solid tumors treated with neratinib, administered daily, in combination with paclitaxel 80 mg/m ² IV on days 1, 8, and 15 of a 28 day cycle, for subjects in Part 1 of the study. | |
| End point type | Primary |
| End point timeframe: From first dose date through day 28. | |

Notes:

[4] - 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: The objective of this endpoint was to assess the maximum tolerated dose (MTD) of neratinib. There was no preplanned hypothesis testing.

| End point values | Part 1 Ner160 + Paclitaxel | Part 1 Ner240 + Paclitaxel | Part 2 Ner240 + Paclitaxel ArmA | Part 2 Ner240 + Paclitaxel ArmB |
|-----------------------------|----------------------------|----------------------------|---------------------------------|---------------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 3 | 5 | 0 ^[5] | 0 ^[6] |
| Units: Patients | 0 | 0 | | |

Notes:

[5] - DLTs were collected in Part 1 of the study only, in order to determine the Maximum Dose for Part 2.

[6] - DLTs were collected in Part 1 of the study only, in order to determine the Maximum Dose for Part 2.

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Concentration-time Curve 0-24

| | |
|--|--|
| End point title | Area Under the Concentration-time Curve 0-24 |
| End point description: Area under the concentration-time curve of neratinib; after each dosing of neratinib on Cycle 1 of Day 15, blood samples taken at regular time points. | |
| End point type | Secondary |
| End point timeframe: Area under the concentration-time curve of neratinib; after each dosing of neratinib on Cycle 1 of Day 15, blood samples taken at regular time points. | |

| End point values | Part 1 Ner160 + Paclitaxel | Part 1 Ner240 + Paclitaxel | Part 2 Ner240 + Paclitaxel ArmA | Part 2 Ner240 + Paclitaxel ArmB |
|---|----------------------------|----------------------------|---------------------------------|---------------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 3 | 4 | 63 | 27 |
| Units: h*ng/mL | | | | |
| geometric mean (geometric coefficient of variation) | 684 (± 92) | 1488 (± 29) | 1239 (± 63) | 1331 (± 61) |

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Plasma Concentration of Neratinib

| | |
|-----------------|---|
| End point title | Maximum Plasma Concentration of Neratinib |
|-----------------|---|

End point description:

Maximum plasma concentration of neratinib; after each dosing of neratinib on Cycle 1 of Day 15, blood samples taken at regular time points.

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

End point timeframe:

Samples taken at 0 hour and at 1, 2, 4, 6, 8, and 24 hours postdose on Day 15 of Cycle 1, and 1 predose sample on Day 1 in Cycle 1.

| End point values | Part 1 Ner160 + Paclitaxel | Part 1 Ner240 + Paclitaxel | Part 2 Ner240 + Paclitaxel ArmA | Part 2 Ner240 + Paclitaxel ArmB |
|---|-------------------------------|-------------------------------|---------------------------------------|---------------------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 3 | 4 | 63 | 27 |
| Units: ng/mL | | | | |
| geometric mean (geometric coefficient of variation) | 66.78 (± 25) | 91.74 (± 41) | 80.31 (± 55) | 79.13 (± 61) |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

First dose through 28 days after last dose

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 17.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|----------------------------|
| Reporting group title | Part 1 Ner160 + Paclitaxel |
|-----------------------|----------------------------|

Reporting group description:

Neratinib 160 mg orally once daily every day, in combination with paclitaxel 80 mg/m² intravenous infusion on days 1, 8 and 15 of a 28-day cycle.

| | |
|-----------------------|----------------------------|
| Reporting group title | Part 1 Ner240 + Paclitaxel |
|-----------------------|----------------------------|

Reporting group description:

Neratinib 240 mg orally once daily every day, in combination with paclitaxel 80 mg/m² intravenous infusion on days 1, 8 and 15 of a 28-day cycle.

| | |
|-----------------------|---------------------------------|
| Reporting group title | Part 2 Ner240 + Paclitaxel ArmA |
|-----------------------|---------------------------------|

Reporting group description:

Neratinib (MTD) qd + Paclitaxel 80 mg/m² on days 1, 8, and 15 of a 28 day cycle for subjects with not more than 1 prior cytotoxic chemotherapy treatment regimen for metastatic disease

| | |
|-----------------------|---------------------------------|
| Reporting group title | Part 2 Ner240 + Paclitaxel ArmB |
|-----------------------|---------------------------------|

Reporting group description:

Neratinib 240 mg qd + Paclitaxel 80 mg/m² on days 1, 8, and 15 of a 28 day cycle for subjects with not more than 3 prior cytotoxic chemotherapy treatment regimen for metastatic disease.

| Serious adverse events | Part 1 Ner160 + Paclitaxel | Part 1 Ner240 + Paclitaxel | Part 2 Ner240 + Paclitaxel ArmA |
|---|----------------------------|----------------------------|---------------------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 4 / 5 (80.00%) | 27 / 71 (38.03%) |
| number of deaths (all causes) | 0 | 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 / 3 (0.00%) | 0 / 5 (0.00%) | 4 / 71 (5.63%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 7 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metastases to central nervous system | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 5 (0.00%) | 2 / 71 (2.82%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|--|---------------|----------------|----------------|
| General disorders and administration site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 5 (0.00%) | 1 / 71 (1.41%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gait disturbance | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 5 (0.00%) | 1 / 71 (1.41%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Oedema peripheral | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 5 (0.00%) | 0 / 71 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pyrexia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 5 (20.00%) | 1 / 71 (1.41%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Chronic obstructive pulmonary disease | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 5 (20.00%) | 0 / 71 (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 |
| Dyspnoea | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 5 (20.00%) | 2 / 71 (2.82%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonitis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 5 (0.00%) | 1 / 71 (1.41%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary embolism | | | |

| | | | |
|---|---------------|----------------|----------------|
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 5 (20.00%) | 1 / 71 (1.41%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Psychiatric disorders | | | |
| Anxiety | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 5 (0.00%) | 1 / 71 (1.41%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Investigations | | | |
| Ejection fraction decreased | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 5 (0.00%) | 1 / 71 (1.41%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Electrocardiogram T wave inversion | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 5 (0.00%) | 1 / 71 (1.41%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| Femur fracture | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 5 (0.00%) | 1 / 71 (1.41%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hip fracture | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 5 (0.00%) | 1 / 71 (1.41%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tibia fracture | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 5 (0.00%) | 1 / 71 (1.41%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Sinus tachycardia | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 5 (0.00%) | 0 / 71 (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 |
| Nervous system disorders | | | |
| Brain oedema | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 5 (0.00%) | 0 / 71 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dizziness | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 5 (0.00%) | 1 / 71 (1.41%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Loss of consciousness | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 5 (20.00%) | 0 / 71 (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 |
| Transient ischaemic attack | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 5 (0.00%) | 0 / 71 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 2 / 5 (40.00%) | 0 / 71 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Febrile neutropenia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 5 (0.00%) | 1 / 71 (1.41%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Leukopenia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 5 (0.00%) | 1 / 71 (1.41%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Eye disorders | | | |

| | | | |
|---|----------------|----------------|----------------|
| Cataract | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 5 (0.00%) | 0 / 71 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Abdominal discomfort | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 5 (0.00%) | 0 / 71 (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 | 1 / 3 (33.33%) | 1 / 5 (20.00%) | 6 / 71 (8.45%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | 9 / 9 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nausea | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 5 (20.00%) | 0 / 71 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vomiting | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 5 (20.00%) | 2 / 71 (2.82%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skin and subcutaneous tissue disorders | | | |
| Ingrowing nail | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 5 (0.00%) | 1 / 71 (1.41%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Renal failure acute | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 5 (0.00%) | 1 / 71 (1.41%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Bone pain | | | |

| | | | |
|---|---------------|---------------|----------------|
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 5 (0.00%) | 1 / 71 (1.41%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pain in extremity | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 5 (0.00%) | 1 / 71 (1.41%) |
| 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 | | | |
| Bacteraemia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 5 (0.00%) | 1 / 71 (1.41%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cellulitis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 5 (0.00%) | 1 / 71 (1.41%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cystitis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 5 (0.00%) | 1 / 71 (1.41%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fungaemia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 5 (0.00%) | 1 / 71 (1.41%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Malaria | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 5 (0.00%) | 1 / 71 (1.41%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 5 (0.00%) | 2 / 71 (2.82%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 2 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sepsis | | | |

| | | | |
|---|---------------|----------------|----------------|
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 5 (20.00%) | 0 / 71 (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 |
| Metabolism and nutrition disorders | | | |
| Dehydration | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 5 (0.00%) | 2 / 71 (2.82%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 3 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypoglycaemia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 5 (0.00%) | 1 / 71 (1.41%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---------------------------------|--|--|
| Serious adverse events | Part 2 Ner240 + Paclitaxel ArmB | | |
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 4 / 31 (12.90%) | | |
| number of deaths (all causes) | 1 | | |
| number of deaths resulting from adverse events | 0 | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Breast cancer metastatic | | | |
| subjects affected / exposed | 0 / 31 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Metastases to central nervous system | | | |
| subjects affected / exposed | 1 / 31 (3.23%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| General disorders and administration site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed | 0 / 31 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gait disturbance | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 0 / 31 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Oedema peripheral | | | |
| subjects affected / exposed | 1 / 31 (3.23%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pyrexia | | | |
| subjects affected / exposed | 0 / 31 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Chronic obstructive pulmonary disease | | | |
| subjects affected / exposed | 0 / 31 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Dyspnoea | | | |
| subjects affected / exposed | 0 / 31 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pneumonitis | | | |
| subjects affected / exposed | 0 / 31 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 0 / 31 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Psychiatric disorders | | | |
| Anxiety | | | |
| subjects affected / exposed | 0 / 31 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|---|----------------|--|--|
| Investigations | | | |
| Ejection fraction decreased | | | |
| subjects affected / exposed | 0 / 31 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Electrocardiogram T wave inversion | | | |
| subjects affected / exposed | 0 / 31 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Injury, poisoning and procedural complications | | | |
| Femur fracture | | | |
| subjects affected / exposed | 0 / 31 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hip fracture | | | |
| subjects affected / exposed | 0 / 31 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Tibia fracture | | | |
| subjects affected / exposed | 0 / 31 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac disorders | | | |
| Sinus tachycardia | | | |
| subjects affected / exposed | 0 / 31 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nervous system disorders | | | |
| Brain oedema | | | |
| subjects affected / exposed | 1 / 31 (3.23%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Dizziness | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 0 / 31 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Loss of consciousness | | | |
| subjects affected / exposed | 0 / 31 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Transient ischaemic attack | | | |
| subjects affected / exposed | 1 / 31 (3.23%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 1 / 31 (3.23%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Febrile neutropenia | | | |
| subjects affected / exposed | 0 / 31 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Leukopenia | | | |
| subjects affected / exposed | 0 / 31 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Eye disorders | | | |
| Cataract | | | |
| subjects affected / exposed | 1 / 31 (3.23%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |
| Abdominal discomfort | | | |
| subjects affected / exposed | 0 / 31 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|---|----------------|--|--|
| Diarrhoea | | | |
| subjects affected / exposed | 0 / 31 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nausea | | | |
| subjects affected / exposed | 0 / 31 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vomiting | | | |
| subjects affected / exposed | 0 / 31 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Skin and subcutaneous tissue disorders | | | |
| Ingrowing nail | | | |
| subjects affected / exposed | 0 / 31 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal and urinary disorders | | | |
| Renal failure acute | | | |
| subjects affected / exposed | 0 / 31 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Bone pain | | | |
| subjects affected / exposed | 0 / 31 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pain in extremity | | | |
| subjects affected / exposed | 0 / 31 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| Bacteraemia | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 0 / 31 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cellulitis | | | |
| subjects affected / exposed | 0 / 31 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cystitis | | | |
| subjects affected / exposed | 0 / 31 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Fungaemia | | | |
| subjects affected / exposed | 0 / 31 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Malaria | | | |
| subjects affected / exposed | 0 / 31 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 31 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Sepsis | | | |
| subjects affected / exposed | 0 / 31 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Metabolism and nutrition disorders | | | |
| Dehydration | | | |
| subjects affected / exposed | 0 / 31 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypoglycaemia | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 0 / 31 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

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

| Non-serious adverse events | Part 1 Ner160 + Paclitaxel | Part 1 Ner240 + Paclitaxel | Part 2 Ner240 + Paclitaxel ArmA |
|---|-------------------------------|-------------------------------|------------------------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 3 / 3 (100.00%) | 5 / 5 (100.00%) | 70 / 71 (98.59%) |
| Vascular disorders | | | |
| Hot flush | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 5 (20.00%) | 1 / 71 (1.41%) |
| occurrences (all) | 0 | 2 | 1 |
| Hypertension | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 5 (0.00%) | 5 / 71 (7.04%) |
| occurrences (all) | 0 | 0 | 6 |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 5 (0.00%) | 13 / 71 (18.31%) |
| occurrences (all) | 0 | 0 | 21 |
| Axillary pain | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 5 (20.00%) | 0 / 71 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Fatigue | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 1 / 5 (20.00%) | 16 / 71 (22.54%) |
| occurrences (all) | 2 | 3 | 36 |
| Generalised oedema | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 5 (0.00%) | 0 / 71 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Local swelling | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 5 (0.00%) | 1 / 71 (1.41%) |
| occurrences (all) | 0 | 0 | 1 |
| Malaise | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 2 / 5 (40.00%) | 1 / 71 (1.41%) |
| occurrences (all) | 1 | 4 | 3 |

| | | | |
|--|---------------------|---------------------|------------------------|
| Mucosal inflammation subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 5 (0.00%) 0 | 6 / 71 (8.45%) 30 |
| Oedema peripheral subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 2 / 5 (40.00%) 2 | 13 / 71 (18.31%) 20 |
| Pain subjects affected / exposed occurrences (all) | 1 / 3 (33.33%) 1 | 0 / 5 (0.00%) 0 | 2 / 71 (2.82%) 2 |
| Pyrexia subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 5 (0.00%) 0 | 18 / 71 (25.35%) 35 |
| Immune system disorders Drug hypersensitivity subjects affected / exposed occurrences (all) | 1 / 3 (33.33%) 2 | 2 / 5 (40.00%) 3 | 1 / 71 (1.41%) 1 |
| Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) | 1 / 3 (33.33%) 1 | 1 / 5 (20.00%) 1 | 16 / 71 (22.54%) 29 |
| Dyspnoea subjects affected / exposed occurrences (all) | 1 / 3 (33.33%) 1 | 0 / 5 (0.00%) 0 | 9 / 71 (12.68%) 19 |
| Epistaxis subjects affected / exposed occurrences (all) | 1 / 3 (33.33%) 2 | 1 / 5 (20.00%) 1 | 5 / 71 (7.04%) 5 |
| Nasal inflammation subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 5 (0.00%) 0 | 1 / 71 (1.41%) 1 |
| Oropharyngeal pain subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 5 (0.00%) 0 | 4 / 71 (5.63%) 5 |
| Rhinorrhoea subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 5 (0.00%) 0 | 3 / 71 (4.23%) 6 |
| Psychiatric disorders | | | |

| | | | |
|--|---------------------|---------------------|------------------------|
| Insomnia subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 5 (0.00%) 0 | 1 / 71 (1.41%) 3 |
| Investigations | | | |
| Alanine aminotransferase increased subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 5 (0.00%) 0 | 10 / 71 (14.08%) 21 |
| Aspartate aminotransferase increased subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 5 (0.00%) 0 | 9 / 71 (12.68%) 18 |
| Blood alkaline phosphatase increased subjects affected / exposed occurrences (all) | 1 / 3 (33.33%) 1 | 0 / 5 (0.00%) 0 | 0 / 71 (0.00%) 0 |
| Blood urine present subjects affected / exposed occurrences (all) | 1 / 3 (33.33%) 1 | 0 / 5 (0.00%) 0 | 0 / 71 (0.00%) 0 |
| Weight decreased subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 2 / 5 (40.00%) 2 | 10 / 71 (14.08%) 22 |
| Cardiac disorders | | | |
| Arrhythmia subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 1 / 5 (20.00%) 1 | 0 / 71 (0.00%) 0 |
| Palpitations subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 5 (0.00%) 0 | 4 / 71 (5.63%) 9 |
| Nervous system disorders | | | |
| Dizziness subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 5 (0.00%) 0 | 7 / 71 (9.86%) 9 |
| Headache subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 5 (0.00%) 0 | 10 / 71 (14.08%) 15 |
| Peripheral sensory neuropathy subjects affected / exposed occurrences (all) | 2 / 3 (66.67%) 4 | 1 / 5 (20.00%) 1 | 36 / 71 (50.70%) 60 |

| | | | |
|--------------------------------------|----------------|-----------------|------------------|
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 2 / 3 (66.67%) | 2 / 5 (40.00%) | 24 / 71 (33.80%) |
| occurrences (all) | 5 | 4 | 69 |
| Leukopenia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 5 (0.00%) | 29 / 71 (40.85%) |
| occurrences (all) | 0 | 0 | 166 |
| Neutropenia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 5 (20.00%) | 37 / 71 (52.11%) |
| occurrences (all) | 0 | 2 | 143 |
| Thrombocytopenia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 5 (0.00%) | 4 / 71 (5.63%) |
| occurrences (all) | 0 | 0 | 6 |
| Ear and labyrinth disorders | | | |
| Tinnitus | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 5 (0.00%) | 0 / 71 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Gastrointestinal disorders | | | |
| Abdominal discomfort | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 5 (0.00%) | 3 / 71 (4.23%) |
| occurrences (all) | 0 | 0 | 3 |
| Abdominal distension | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 1 / 5 (20.00%) | 5 / 71 (7.04%) |
| occurrences (all) | 1 | 1 | 6 |
| Abdominal pain | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 5 (0.00%) | 8 / 71 (11.27%) |
| occurrences (all) | 0 | 0 | 11 |
| Abdominal pain upper | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 5 (0.00%) | 10 / 71 (14.08%) |
| occurrences (all) | 0 | 0 | 14 |
| Constipation | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 5 (0.00%) | 3 / 71 (4.23%) |
| occurrences (all) | 2 | 0 | 3 |
| Diarrhoea | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 5 / 5 (100.00%) | 65 / 71 (91.55%) |
| occurrences (all) | 12 | 13 | 389 |
| Dry mouth | | | |

| | | | |
|--|---------------|----------------|------------------|
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 5 (20.00%) | 4 / 71 (5.63%) |
| occurrences (all) | 0 | 1 | 4 |
| Dyspepsia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 2 / 5 (40.00%) | 8 / 71 (11.27%) |
| occurrences (all) | 0 | 2 | 12 |
| Dysphagia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 5 (20.00%) | 1 / 71 (1.41%) |
| occurrences (all) | 0 | 1 | 1 |
| Gastritis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 5 (0.00%) | 5 / 71 (7.04%) |
| occurrences (all) | 0 | 0 | 8 |
| Gingival ulceration | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 5 (0.00%) | 2 / 71 (2.82%) |
| occurrences (all) | 0 | 0 | 5 |
| Mouth ulceration | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 5 (0.00%) | 5 / 71 (7.04%) |
| occurrences (all) | 0 | 0 | 10 |
| Nausea | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 4 / 5 (80.00%) | 26 / 71 (36.62%) |
| occurrences (all) | 0 | 6 | 83 |
| Rectal haemorrhage | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 5 (20.00%) | 0 / 71 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Stomatitis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 5 (20.00%) | 13 / 71 (18.31%) |
| occurrences (all) | 0 | 1 | 18 |
| Vomiting | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 3 / 5 (60.00%) | 20 / 71 (28.17%) |
| occurrences (all) | 0 | 4 | 86 |
| Skin and subcutaneous tissue disorders | | | |
| Alopecia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 2 / 5 (40.00%) | 37 / 71 (52.11%) |
| occurrences (all) | 0 | 2 | 40 |
| Decubitus ulcer | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 5 (20.00%) | 0 / 71 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |

| | | | |
|--|---------------------|---------------------|------------------------|
| Dermatitis acneiform subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 5 (0.00%) 0 | 1 / 71 (1.41%) 1 |
| Dry skin subjects affected / exposed occurrences (all) | 1 / 3 (33.33%) 2 | 0 / 5 (0.00%) 0 | 1 / 71 (1.41%) 1 |
| Nail disorder subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 5 (0.00%) 0 | 2 / 71 (2.82%) 4 |
| Palmar-plantar erythrodysaesthesia syndrome subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 5 (0.00%) 0 | 2 / 71 (2.82%) 2 |
| Pigmentation disorder subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 5 (0.00%) 0 | 0 / 71 (0.00%) 0 |
| Pruritus subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 5 (0.00%) 0 | 7 / 71 (9.86%) 9 |
| Rash subjects affected / exposed occurrences (all) | 1 / 3 (33.33%) 1 | 2 / 5 (40.00%) 2 | 21 / 71 (29.58%) 31 |
| Renal and urinary disorders Dysuria subjects affected / exposed occurrences (all) | 1 / 3 (33.33%) 1 | 0 / 5 (0.00%) 0 | 3 / 71 (4.23%) 3 |
| Hydronephrosis subjects affected / exposed occurrences (all) | 1 / 3 (33.33%) 1 | 0 / 5 (0.00%) 0 | 0 / 71 (0.00%) 0 |
| Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 5 (0.00%) 0 | 6 / 71 (8.45%) 13 |
| Back pain subjects affected / exposed occurrences (all) | 1 / 3 (33.33%) 1 | 0 / 5 (0.00%) 0 | 3 / 71 (4.23%) 4 |
| Bone pain | | | |

| | | | |
|-----------------------------|----------------|----------------|-----------------|
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 5 (0.00%) | 5 / 71 (7.04%) |
| occurrences (all) | 0 | 0 | 8 |
| Muscle spasms | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 5 (0.00%) | 3 / 71 (4.23%) |
| occurrences (all) | 0 | 0 | 3 |
| Musculoskeletal chest pain | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 5 (20.00%) | 1 / 71 (1.41%) |
| occurrences (all) | 0 | 1 | 1 |
| Myalgia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 5 (20.00%) | 3 / 71 (4.23%) |
| occurrences (all) | 0 | 2 | 7 |
| Pain in extremity | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 5 (0.00%) | 8 / 71 (11.27%) |
| occurrences (all) | 0 | 0 | 10 |
| Infections and infestations | | | |
| Catheter site infection | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 5 (0.00%) | 0 / 71 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Gastroenteritis | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 5 (0.00%) | 0 / 71 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Gingivitis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 5 (0.00%) | 4 / 71 (5.63%) |
| occurrences (all) | 0 | 0 | 10 |
| Influenza | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 5 (20.00%) | 6 / 71 (8.45%) |
| occurrences (all) | 0 | 1 | 7 |
| Nasopharyngitis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 5 (20.00%) | 7 / 71 (9.86%) |
| occurrences (all) | 0 | 1 | 27 |
| Oral herpes | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 5 (20.00%) | 0 / 71 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Paronychia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 5 (0.00%) | 3 / 71 (4.23%) |
| occurrences (all) | 0 | 0 | 3 |

| | | | |
|---|---------------------|---------------------|------------------------|
| Upper respiratory tract infection subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 5 (0.00%) 0 | 9 / 71 (12.68%) 11 |
| Urinary tract infection subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 1 / 5 (20.00%) 2 | 10 / 71 (14.08%) 17 |
| Metabolism and nutrition disorders | | | |
| Decreased appetite subjects affected / exposed occurrences (all) | 1 / 3 (33.33%) 1 | 3 / 5 (60.00%) 4 | 16 / 71 (22.54%) 36 |
| Hypocalcaemia subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 5 (0.00%) 0 | 6 / 71 (8.45%) 8 |
| Hypokalaemia subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 1 / 5 (20.00%) 1 | 7 / 71 (9.86%) 33 |
| Hypomagnesaemia subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 1 / 5 (20.00%) 1 | 1 / 71 (1.41%) 1 |
| Hypophagia subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 1 / 5 (20.00%) 1 | 0 / 71 (0.00%) 0 |
| Hypoproteinaemia subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 5 (0.00%) 0 | 0 / 71 (0.00%) 0 |

| | | | |
|---|------------------------------------|--|--|
| Non-serious adverse events | Part 2 Ner240 + Paclitaxel ArmB | | |
| Total subjects affected by non-serious adverse events subjects affected / exposed | 31 / 31 (100.00%) | | |
| Vascular disorders | | | |
| Hot flush subjects affected / exposed occurrences (all) | 1 / 31 (3.23%) 1 | | |
| Hypertension subjects affected / exposed occurrences (all) | 2 / 31 (6.45%) 2 | | |
| General disorders and administration | | | |

| | | | |
|---|-----------------|--|--|
| site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 7 / 31 (22.58%) | | |
| occurrences (all) | 13 | | |
| Axillary pain | | | |
| subjects affected / exposed | 0 / 31 (0.00%) | | |
| occurrences (all) | 0 | | |
| Fatigue | | | |
| subjects affected / exposed | 6 / 31 (19.35%) | | |
| occurrences (all) | 11 | | |
| Generalised oedema | | | |
| subjects affected / exposed | 2 / 31 (6.45%) | | |
| occurrences (all) | 3 | | |
| Local swelling | | | |
| subjects affected / exposed | 2 / 31 (6.45%) | | |
| occurrences (all) | 4 | | |
| Malaise | | | |
| subjects affected / exposed | 0 / 31 (0.00%) | | |
| occurrences (all) | 0 | | |
| Mucosal inflammation | | | |
| subjects affected / exposed | 2 / 31 (6.45%) | | |
| occurrences (all) | 4 | | |
| Oedema peripheral | | | |
| subjects affected / exposed | 5 / 31 (16.13%) | | |
| occurrences (all) | 7 | | |
| Pain | | | |
| subjects affected / exposed | 1 / 31 (3.23%) | | |
| occurrences (all) | 1 | | |
| Pyrexia | | | |
| subjects affected / exposed | 4 / 31 (12.90%) | | |
| occurrences (all) | 5 | | |
| Immune system disorders | | | |
| Drug hypersensitivity | | | |
| subjects affected / exposed | 0 / 31 (0.00%) | | |
| occurrences (all) | 0 | | |
| Respiratory, thoracic and mediastinal disorders | | | |

| | | | |
|--------------------------------------|-----------------|--|--|
| Cough | | | |
| subjects affected / exposed | 2 / 31 (6.45%) | | |
| occurrences (all) | 2 | | |
| Dyspnoea | | | |
| subjects affected / exposed | 1 / 31 (3.23%) | | |
| occurrences (all) | 1 | | |
| Epistaxis | | | |
| subjects affected / exposed | 1 / 31 (3.23%) | | |
| occurrences (all) | 1 | | |
| Nasal inflammation | | | |
| subjects affected / exposed | 2 / 31 (6.45%) | | |
| occurrences (all) | 3 | | |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 0 / 31 (0.00%) | | |
| occurrences (all) | 0 | | |
| Rhinorrhoea | | | |
| subjects affected / exposed | 3 / 31 (9.68%) | | |
| occurrences (all) | 4 | | |
| Psychiatric disorders | | | |
| Insomnia | | | |
| subjects affected / exposed | 2 / 31 (6.45%) | | |
| occurrences (all) | 2 | | |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 6 / 31 (19.35%) | | |
| occurrences (all) | 10 | | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 4 / 31 (12.90%) | | |
| occurrences (all) | 6 | | |
| Blood alkaline phosphatase increased | | | |
| subjects affected / exposed | 0 / 31 (0.00%) | | |
| occurrences (all) | 0 | | |
| Blood urine present | | | |
| subjects affected / exposed | 0 / 31 (0.00%) | | |
| occurrences (all) | 0 | | |
| Weight decreased | | | |

| | | | |
|--|---------------------|--|--|
| subjects affected / exposed occurrences (all) | 2 / 31 (6.45%) 2 | | |
| Cardiac disorders | | | |
| Arrhythmia | | | |
| subjects affected / exposed | 0 / 31 (0.00%) | | |
| occurrences (all) | 0 | | |
| Palpitations | | | |
| subjects affected / exposed | 0 / 31 (0.00%) | | |
| occurrences (all) | 0 | | |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 4 / 31 (12.90%) | | |
| occurrences (all) | 5 | | |
| Headache | | | |
| subjects affected / exposed | 5 / 31 (16.13%) | | |
| occurrences (all) | 11 | | |
| Peripheral sensory neuropathy | | | |
| subjects affected / exposed | 17 / 31 (54.84%) | | |
| occurrences (all) | 27 | | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 12 / 31 (38.71%) | | |
| occurrences (all) | 50 | | |
| Leukopenia | | | |
| subjects affected / exposed | 15 / 31 (48.39%) | | |
| occurrences (all) | 104 | | |
| Neutropenia | | | |
| subjects affected / exposed | 17 / 31 (54.84%) | | |
| occurrences (all) | 96 | | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 1 / 31 (3.23%) | | |
| occurrences (all) | 1 | | |
| Ear and labyrinth disorders | | | |
| Tinnitus | | | |
| subjects affected / exposed | 2 / 31 (6.45%) | | |
| occurrences (all) | 2 | | |
| Gastrointestinal disorders | | | |

| | | | |
|-----------------------------|------------------|--|--|
| Abdominal discomfort | | | |
| subjects affected / exposed | 3 / 31 (9.68%) | | |
| occurrences (all) | 4 | | |
| Abdominal distension | | | |
| subjects affected / exposed | 1 / 31 (3.23%) | | |
| occurrences (all) | 2 | | |
| Abdominal pain | | | |
| subjects affected / exposed | 3 / 31 (9.68%) | | |
| occurrences (all) | 7 | | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 3 / 31 (9.68%) | | |
| occurrences (all) | 4 | | |
| Constipation | | | |
| subjects affected / exposed | 1 / 31 (3.23%) | | |
| occurrences (all) | 1 | | |
| Diarrhoea | | | |
| subjects affected / exposed | 29 / 31 (93.55%) | | |
| occurrences (all) | 190 | | |
| Dry mouth | | | |
| subjects affected / exposed | 1 / 31 (3.23%) | | |
| occurrences (all) | 2 | | |
| Dyspepsia | | | |
| subjects affected / exposed | 4 / 31 (12.90%) | | |
| occurrences (all) | 4 | | |
| Dysphagia | | | |
| subjects affected / exposed | 0 / 31 (0.00%) | | |
| occurrences (all) | 0 | | |
| Gastritis | | | |
| subjects affected / exposed | 3 / 31 (9.68%) | | |
| occurrences (all) | 3 | | |
| Gingival ulceration | | | |
| subjects affected / exposed | 2 / 31 (6.45%) | | |
| occurrences (all) | 5 | | |
| Mouth ulceration | | | |
| subjects affected / exposed | 0 / 31 (0.00%) | | |
| occurrences (all) | 0 | | |

| | | | |
|--|------------------|--|--|
| Nausea | | | |
| subjects affected / exposed | 7 / 31 (22.58%) | | |
| occurrences (all) | 9 | | |
| Rectal haemorrhage | | | |
| subjects affected / exposed | 0 / 31 (0.00%) | | |
| occurrences (all) | 0 | | |
| Stomatitis | | | |
| subjects affected / exposed | 5 / 31 (16.13%) | | |
| occurrences (all) | 10 | | |
| Vomiting | | | |
| subjects affected / exposed | 4 / 31 (12.90%) | | |
| occurrences (all) | 7 | | |
| Skin and subcutaneous tissue disorders | | | |
| Alopecia | | | |
| subjects affected / exposed | 12 / 31 (38.71%) | | |
| occurrences (all) | 15 | | |
| Decubitus ulcer | | | |
| subjects affected / exposed | 0 / 31 (0.00%) | | |
| occurrences (all) | 0 | | |
| Dermatitis acneiform | | | |
| subjects affected / exposed | 2 / 31 (6.45%) | | |
| occurrences (all) | 9 | | |
| Dry skin | | | |
| subjects affected / exposed | 0 / 31 (0.00%) | | |
| occurrences (all) | 0 | | |
| Nail disorder | | | |
| subjects affected / exposed | 2 / 31 (6.45%) | | |
| occurrences (all) | 2 | | |
| Palmar-plantar erythrodysesthesia syndrome | | | |
| subjects affected / exposed | 3 / 31 (9.68%) | | |
| occurrences (all) | 5 | | |
| Pigmentation disorder | | | |
| subjects affected / exposed | 2 / 31 (6.45%) | | |
| occurrences (all) | 2 | | |
| Pruritus | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 3 / 31 (9.68%) | | |
| occurrences (all) | 5 | | |
| Rash | | | |
| subjects affected / exposed | 8 / 31 (25.81%) | | |
| occurrences (all) | 15 | | |
| Renal and urinary disorders | | | |
| Dysuria | | | |
| subjects affected / exposed | 0 / 31 (0.00%) | | |
| occurrences (all) | 0 | | |
| Hydronephrosis | | | |
| subjects affected / exposed | 0 / 31 (0.00%) | | |
| occurrences (all) | 0 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 0 / 31 (0.00%) | | |
| occurrences (all) | 0 | | |
| Back pain | | | |
| subjects affected / exposed | 5 / 31 (16.13%) | | |
| occurrences (all) | 6 | | |
| Bone pain | | | |
| subjects affected / exposed | 1 / 31 (3.23%) | | |
| occurrences (all) | 1 | | |
| Muscle spasms | | | |
| subjects affected / exposed | 2 / 31 (6.45%) | | |
| occurrences (all) | 4 | | |
| Musculoskeletal chest pain | | | |
| subjects affected / exposed | 0 / 31 (0.00%) | | |
| occurrences (all) | 0 | | |
| Myalgia | | | |
| subjects affected / exposed | 3 / 31 (9.68%) | | |
| occurrences (all) | 5 | | |
| Pain in extremity | | | |
| subjects affected / exposed | 3 / 31 (9.68%) | | |
| occurrences (all) | 3 | | |
| Infections and infestations | | | |

| | | | |
|---|-----------------------|--|--|
| Catheter site infection subjects affected / exposed occurrences (all) | 2 / 31 (6.45%) 4 | | |
| Gastroenteritis subjects affected / exposed occurrences (all) | 0 / 31 (0.00%) 0 | | |
| Gingivitis subjects affected / exposed occurrences (all) | 1 / 31 (3.23%) 1 | | |
| Influenza subjects affected / exposed occurrences (all) | 1 / 31 (3.23%) 1 | | |
| Nasopharyngitis subjects affected / exposed occurrences (all) | 2 / 31 (6.45%) 10 | | |
| Oral herpes subjects affected / exposed occurrences (all) | 0 / 31 (0.00%) 0 | | |
| Paronychia subjects affected / exposed occurrences (all) | 2 / 31 (6.45%) 2 | | |
| Upper respiratory tract infection subjects affected / exposed occurrences (all) | 2 / 31 (6.45%) 3 | | |
| Urinary tract infection subjects affected / exposed occurrences (all) | 5 / 31 (16.13%) 5 | | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite subjects affected / exposed occurrences (all) | 8 / 31 (25.81%) 17 | | |
| Hypocalcaemia subjects affected / exposed occurrences (all) | 3 / 31 (9.68%) 3 | | |
| Hypokalaemia | | | |

| | | | |
|-----------------------------|----------------|--|--|
| subjects affected / exposed | 3 / 31 (9.68%) | | |
| occurrences (all) | 4 | | |
| Hypomagnesaemia | | | |
| subjects affected / exposed | 0 / 31 (0.00%) | | |
| occurrences (all) | 0 | | |
| Hypophagia | | | |
| subjects affected / exposed | 0 / 31 (0.00%) | | |
| occurrences (all) | 0 | | |
| Hypoproteinaemia | | | |
| subjects affected / exposed | 2 / 31 (6.45%) | | |
| occurrences (all) | 2 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|--|
| 13 June 2007 | This protocol includes removal of lung and pancreatic cancer subjects and docetaxel treatment, addition of paclitaxel treatment, increased PK testing, additional secondary outcomes, expanded definition of dose limiting toxicity, change to number of subjects enrolled, eligibility criteria and other administrative updates. |
| 12 December 2007 | This protocol includes changes to exclusion criteria, study procedures, study drug administration, growth factor guidelines, PK testing, and other administrative updates. |
| 18 March 2008 | This protocol includes updates to study design, including addition of a second arm B (non-randomized) to Part 2, exclusion criterion changed to allow enrollment of subjects with prior lapatinib exposure in Arm B of Part 2. The sample size for Arm B of Part 2 included approximately 25 subjects, with a total number of 95 subjects enrolled in study. The number of sites increased to approximately 30. Temperature for storing PK samples was updated from -70°C to -20°C. Statistical considerations and study procedures and other administrative updates were also included. |
| 08 February 2010 | This protocol includes updates to the following sections: study rationale, length of treatment period, instructions for co-administration of neratinib and digoxin, additional blood chemistry and coagulation tests and other administrative updates. |
| 05 April 2011 | This protocol includes the addition of a treatment extension period and associated study procedures and other administrative updates. |
| 22 March 2012 | This protocol includes addition of a revised treatment extension period which decreases the efficacy assessments for those subjects that continue to receive clinical benefit, along with other administrative updates. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported