



Clinical trial results:

A Phase 1/2 Trial of Temsirolimus Plus Neratinib For Patients With Metastatic HER2-Amplified or Triple-Negative Breast Cancer

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2012-005037-37 |
| Trial protocol | GB ES DK |
| Global end of trial date | 20 July 2016 |

Results information

| | |
|--------------------------------|------------------|
| Result version number | v1 (current) |
| This version publication date | 16 December 2017 |
| First version publication date | 16 December 2017 |

Trial information

Trial identification

| | |
|-----------------------|--------|
| Sponsor protocol code | 10-005 |
|-----------------------|--------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01111825 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Puma Biotechnology, Inc. |
| Sponsor organisation address | 10880 Wilshire Blvd, Suite 2150, 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 | 29 August 2017 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 20 July 2016 |
| Global end of trial reached? | Yes |
| Global end of trial date | 20 July 2016 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The main objectives of the trial are to determine the maximum tolerated dose of temsirolimus with daily neratinib, and to determine the safety and efficacy of this combination when given to patients with advanced breast carcinoma, specifically trastuzumab-refractory HER2-amplified disease or triple-negative disease.

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 treatment for the following reasons: documented disease progression, unacceptable toxicity, withdrawal of consent, or death.

Background therapy: -

Evidence for comparator: -

| | |
|---|---------------|
| Actual start date of recruitment | 23 April 2010 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-------------------|
| Country: Number of subjects enrolled | Spain: 26 |
| Country: Number of subjects enrolled | France: 6 |
| Country: Number of subjects enrolled | United Kingdom: 9 |
| Country: Number of subjects enrolled | United States: 53 |
| Country: Number of subjects enrolled | Hong Kong: 5 |
| Worldwide total number of subjects | 99 |
| EEA total number of subjects | 41 |

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 | 0 |

| | |
|---------------------------|----|
| months) | |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 85 |
| From 65 to 84 years | 14 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

One hundred and thirty four (134) subjects with metastatic HER2 amplified or triple-negative breast cancer were screened. Ninety-nine subjects were treated.

Pre-assignment

Screening details:

One hundred and thirty four (134) subjects with metastatic HER2 amplified or triple-negative breast cancer were screened. Ninety-nine subjects were treated.

Period 1

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

Arms

| | |
|------------------------------|---------|
| Are arms mutually exclusive? | Yes |
| Arm title | Phase I |

Arm description:

Patients with trastuzumab-refractory HER2-amplified disease. Patients were treated to determine the maximum tolerated dose (MTD) of temsirolimus.

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

Dosage and administration details:

Six 40 mg tablets (240 mg) taken orally once daily with food, preferably in the morning, continuously until treatment discontinuation.

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

Dosage and administration details:

Ascending dose of temsirolimus in combination with neratinib 240 mg qd. Three cohorts of temsirolimus at 8 mg qw, 15 mg qw, or 25 mg qw intravenously (IV) on days 1, 8, 15 and 22 of a 28 day cycle.

| | |
|------------------|--------------|
| Arm title | Phase II -ve |
|------------------|--------------|

Arm description:

Subjects with triple negative breast cancer. Invasive adenocarcinoma negative for estrogen receptor (< 5%), and progesterone receptor (< 5%) expression, and lack of HER2 overexpression and/or amplification as determined by IHC (<3+) or FISH (<2.0).

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

Dosage and administration details:

Six 40 mg tablets (240 mg) taken orally once daily with food, preferably in the morning, continuously

until treatment discontinuation.

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

Dosage and administration details:

Temsirolimus administered by IV infusion at 8 mg QW on days 1, 8, 15, and 22 of a 28-day cycle. Treatment should continue until progression, unacceptable toxicity or withdrawal of consent.

| | |
|------------------|----------------|
| Arm title | Phase II HER2+ |
|------------------|----------------|

Arm description:

Subjects with HER2 overexpressed/amplified tumors, as determined by IHC (3+) or FISH (≥ 2.0).

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

Dosage and administration details:

Six 40 mg tablets (240 mg) taken orally once daily with food, preferably in the morning, continuously until treatment discontinuation.

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

Dosage and administration details:

Temsirolimus administered by IV infusion at 8 mg QW on days 1, 8, 15, and 22 of a 28-day cycle. Treatment should continue until progression, unacceptable toxicity or withdrawal of consent.

| | |
|------------------|-------------------------|
| Arm title | Phase II HER2+ Dose Esc |
|------------------|-------------------------|

Arm description:

Subjects with HER2 overexpressed/amplified tumors, as determined by IHC (3+) or FISH (≥ 2.0), dose escalation of temsirolimus.

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

Dosage and administration details:

Six 40 mg tablets (240 mg) taken orally once daily with food, preferably in the morning, continuously until treatment discontinuation

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

Dosage and administration details:

8 mg (MTD established in Phase 1), administered IV QW on days 1, 8, 15, and 22 of a 28-day cycle; escalated to 15 mg temsirolimus, administered IV QW on days 1, 8, 15, and 22 of a 28-day cycle for subjects who tolerate 8 mg.

| Number of subjects in period 1 | Phase I | Phase II -ve | Phase II HER2+ |
|---------------------------------------|---------|--------------|----------------|
| Started | 8 | 6 | 37 |
| Completed | 5 | 5 | 29 |
| Not completed | 3 | 1 | 8 |
| Consent withdrawn by subject | - | - | 1 |
| Adverse event, non-fatal | 2 | 1 | 4 |
| Discontinuation by Sponsor | - | - | - |
| Lost to follow-up | - | - | 3 |
| Disease Progression | 1 | - | - |

| Number of subjects in period 1 | Phase II HER2+ Dose Esc |
|---------------------------------------|----------------------------|
| Started | 48 |
| Completed | 27 |
| Not completed | 21 |
| Consent withdrawn by subject | - |
| Adverse event, non-fatal | - |
| Discontinuation by Sponsor | 20 |
| Lost to follow-up | 1 |
| Disease Progression | - |

Baseline characteristics

Reporting groups

| | |
|--|-------------------------|
| Reporting group title | Phase I |
| Reporting group description: Patients with trastuzumab-refractory HER2-amplified disease. Patients were treated to determine the maximum tolerated dose (MTD) of temsirolimus. | |
| Reporting group title | Phase II -ve |
| Reporting group description: Subjects with triple negative breast cancer. Invasive adenocarcinoma negative for estrogen receptor (< 5%), and progesterone receptor (< 5%) expression, and lack of HER2 overexpression and/or amplification as determined by IHC (<3+) or FISH (<2.0). | |
| Reporting group title | Phase II HER2+ |
| Reporting group description: Subjects with HER2 overexpressed/amplified tumors, as determined by IHC (3+) or FISH (>= 2.0). | |
| Reporting group title | Phase II HER2+ Dose Esc |
| Reporting group description: Subjects with HER2 overexpressed/amplified tumors, as determined by IHC (3+) or FISH (>= 2.0), dose escalation of temsirolimus. | |

| Reporting group values | Phase I | Phase II -ve | Phase II HER2+ |
|---------------------------------------|---------|--------------|----------------|
| Number of subjects | 8 | 6 | 37 |
| Age categorical Units: Subjects | | | |
| Adults (18-64 years) | 7 | 5 | 34 |
| From 65-84 years | 1 | 1 | 3 |
| 85 years and over | 0 | 0 | 0 |
| Age Continuous Units: years | | | |
| arithmetic mean | 47.5 | 53.5 | 52 |
| standard deviation | ± 10.4 | ± 13 | ± 8.3 |
| Gender categorical Units: Subjects | | | |
| Female | 8 | 6 | 37 |
| Male | 0 | 0 | 0 |

| Reporting group values | Phase II HER2+ Dose Esc | Total | |
|------------------------------------|----------------------------|-------|--|
| Number of subjects | 48 | 99 | |
| Age categorical Units: Subjects | | | |
| Adults (18-64 years) | 39 | 85 | |
| From 65-84 years | 9 | 14 | |
| 85 years and over | 0 | 0 | |
| Age Continuous Units: years | | | |
| arithmetic mean | 53.2 | - | |
| standard deviation | ± 11 | - | |

| | | | |
|--------------------|----|----|--|
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 47 | 98 | |
| Male | 1 | 1 | |

End points

End points reporting groups

| | |
|--|-------------------------|
| Reporting group title | Phase I |
| Reporting group description: Patients with trastuzumab-refractory HER2-amplified disease. Patients were treated to determine the maximum tolerated dose (MTD) of temsirolimus. | |
| Reporting group title | Phase II -ve |
| Reporting group description: Subjects with triple negative breast cancer. Invasive adenocarcinoma negative for estrogen receptor (< 5%), and progesterone receptor (< 5%) expression, and lack of HER2 overexpression and/or amplification as determined by IHC (<3+) or FISH (<2.0). | |
| Reporting group title | Phase II HER2+ |
| Reporting group description: Subjects with HER2 overexpressed/amplified tumors, as determined by IHC (3+) or FISH (>= 2.0). | |
| Reporting group title | Phase II HER2+ Dose Esc |
| Reporting group description: Subjects with HER2 overexpressed/amplified tumors, as determined by IHC (3+) or FISH (>= 2.0), dose escalation of temsirolimus. | |

Primary: Objective Response Rate

| | |
|---|---|
| End point title | Objective Response Rate ^{[1][2]} |
| End point description: ORR is defined as proportion of subjects who achieved confirmed complete response (CR) or partial response (PR) per RECIST v1.1. A complete or partial response must be confirmed no less than 4-weeks after the criteria for response are initially met. | |
| End point type | Primary |
| End point timeframe: From randomization to disease progression or last tumor assessment | |

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: Per protocol no formal statistical comparison of cohorts was performed.

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Per protocol no summary of endpoint data was planned for the Phase I group.

| End point values | Phase II -ve | Phase II HER2+ | Phase II HER2+ Dose Esc | |
|------------------------------|-----------------|-----------------|-------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 6 | 37 | 48 | |
| Units: count of participants | | | | |
| number (not applicable) | 0 | 5 | 14 | |

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival

| | |
|-----------------|--|
| End point title | Progression Free Survival ^[3] |
|-----------------|--|

End point description:

Defined as time from date of enrollment until the first disease recurrence or progression per RECIST V1.1 or death due to any cause; censored at the last assessable evaluation or at the initiation of new anti-cancer therapy. Disease assessment is based on investigator tumor assessments. If no post-baseline tumor assessment then censored at enrollment date.

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

End point timeframe:

From enrollment to disease progression or last tumor assessment

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Per protocol no summary of endpoint data was planned for the Phase I group.

| End point values | Phase II -ve | Phase II HER2+ | Phase II HER2+ Dose Esc | |
|----------------------------------|-----------------|-------------------|-------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 6 | 37 | 48 | |
| Units: months | | | | |
| median (confidence interval 95%) | 1.8 (1.8 to 2) | 4.8 (2.7 to 8.4) | 6 (3.7 to 8.3) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR)

| | |
|-----------------|---|
| End point title | Duration of Response (DOR) ^[4] |
|-----------------|---|

End point description:

Measured from the time at which measurement criteria were first met for CR or PR (whichever status was recorded first), until the date of first recurrence, PD, or death was objectively documented, taking as a reference for PD the smallest measurements recorded since enrollment, per RECIST (v1.1) criteria.

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

End point timeframe:

From first response to first progressive disease (PD) or death

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Per protocol no summary of endpoint data was planned for the Phase I group.

| End point values | Phase II -ve | Phase II HER2+ | Phase II HER2+ Dose Esc | |
|-----------------------------|------------------|-------------------|-------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 0 ^[5] | 5 | 14 | |
| Units: months | | | | |
| number (not applicable) | | | | |
| 0 to <3 months | | 1 | 2 | |
| 3 to <6 months | | 2 | 1 | |
| 6 to <9 months | | 0 | 6 | |

| | | | | |
|-----------------|--|---|---|--|
| 9 to <12 months | | 2 | 2 | |
| 12+ months | | 0 | 3 | |

Notes:

[5] - There were no subjects in this arm who achieved a response.

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Benefit Rate (CBR)

| | |
|-----------------|--|
| End point title | Clinical Benefit Rate (CBR) ^[6] |
|-----------------|--|

End point description:

Defined as the proportion of patients who achieved objective response (CR or PR) or SD for at least 24 weeks.

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

End point timeframe:

From enrollment to disease progression or death

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Per protocol no summary of endpoint data was planned for the Phase I group.

| End point values | Phase II -ve | Phase II HER2+ | Phase II HER2+ Dose Esc | |
|------------------------------|-----------------|-------------------|-------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 6 | 37 | 48 | |
| Units: count of participants | | | | |
| number (not applicable) | 0 | 8 | 19 | |

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 | Phase I |
|-----------------------|---------|

Reporting group description:

Subjects with trastuzumab-refractory HER2-amplified disease. Patients were treated to determine the maximum tolerated dose (MTD) of temsirolimus.

| | |
|-----------------------|--------------|
| Reporting group title | Phase II -ve |
|-----------------------|--------------|

Reporting group description:

Subjects with triple negative breast cancer. Invasive adenocarcinoma negative for estrogen receptor (< 5%), and progesterone receptor (< 5%) expression, and lack of HER2 overexpression and/or amplification as determined by IHC (< 3+) or FISH (< 2.0).

| | |
|-----------------------|----------------|
| Reporting group title | Phase II HER2+ |
|-----------------------|----------------|

Reporting group description:

Subjects with HER2 overexpressed/amplified tumors, as determined by IHC (3+) or FISH (>= 2.0).

| | |
|-----------------------|-------------------------|
| Reporting group title | Phase II HER2+ Dose Esc |
|-----------------------|-------------------------|

Reporting group description:

Subjects with HER2 overexpressed/amplified tumors, as determined by IHC (3+) or FISH (>= 2.0), dose escalation of temsirolimus.

| Serious adverse events | Phase I | Phase II -ve | Phase II HER2+ |
|--|----------------|----------------|------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 3 / 8 (37.50%) | 2 / 6 (33.33%) | 12 / 37 (32.43%) |
| number of deaths (all causes) | 0 | 0 | 7 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| General disorders and administration site conditions | | | |
| Chest pain | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 6 (16.67%) | 0 / 37 (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 / 8 (0.00%) | 0 / 6 (0.00%) | 2 / 37 (5.41%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|----------------|----------------|----------------|
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 6 (16.67%) | 0 / 37 (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 |
| Dyspnoea | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 2 / 6 (33.33%) | 0 / 37 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pleural effusion | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 6 (0.00%) | 0 / 37 (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 |
| Psychiatric disorders | | | |
| Mental status changes | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 6 (0.00%) | 1 / 37 (2.70%) |
| 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 | | | |
| Blood alkaline phosphatase increased | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 6 (0.00%) | 0 / 37 (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 creatine phosphokinase increased | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 6 (0.00%) | 0 / 37 (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 |
| Electrocardiogram ST segment depression | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 6 (0.00%) | 0 / 37 (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 |
| Gamma-glutamyltransferase increased | | | |

| | | | |
|---|---------------|---------------|----------------|
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 6 (0.00%) | 0 / 37 (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 |
| Haemoglobin increased | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 6 (0.00%) | 1 / 37 (2.70%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Transaminases increased | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 6 (0.00%) | 0 / 37 (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 |
| Injury, poisoning and procedural complications | | | |
| Humerus fracture | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 6 (0.00%) | 0 / 37 (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 |
| Cardiac disorders | | | |
| Acute coronary syndrome | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 6 (0.00%) | 0 / 37 (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 |
| Nervous system disorders | | | |
| Cerebral disorder | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 6 (0.00%) | 0 / 37 (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 / 8 (0.00%) | 0 / 6 (0.00%) | 0 / 37 (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 |
| Headache | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 6 (0.00%) | 0 / 37 (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 |

| | | | |
|---|----------------|---------------|----------------|
| Neuropathy peripheral | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 6 (0.00%) | 1 / 37 (2.70%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Spinal cord compression | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 6 (0.00%) | 0 / 37 (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 |
| Syncope | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 6 (0.00%) | 1 / 37 (2.70%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 6 (0.00%) | 1 / 37 (2.70%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Febrile neutropenia | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 6 (0.00%) | 1 / 37 (2.70%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Polycythaemia | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 6 (0.00%) | 1 / 37 (2.70%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ear and labyrinth disorders | | | |
| Vertigo | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 6 (0.00%) | 0 / 37 (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 |
| Eye disorders | | | |
| Eyelid oedema | | | |

| | | | |
|---|----------------|---------------|----------------|
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 6 (0.00%) | 0 / 37 (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 |
| Gastrointestinal disorders | | | |
| Constipation | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 6 (0.00%) | 1 / 37 (2.70%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diarrhoea | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 6 (0.00%) | 3 / 37 (8.11%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 3 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nausea | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 6 (0.00%) | 3 / 37 (8.11%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 2 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Stomatitis | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 6 (0.00%) | 0 / 37 (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 |
| Upper gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 6 (0.00%) | 0 / 37 (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 |
| Vomiting | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 6 (0.00%) | 2 / 37 (5.41%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skin and subcutaneous tissue disorders | | | |
| Rash | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 6 (0.00%) | 1 / 37 (2.70%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |

| | | | |
|---|----------------|---------------|----------------|
| Renal failure | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 6 (0.00%) | 0 / 37 (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 |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 6 (0.00%) | 0 / 37 (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 |
| Muscular weakness | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 6 (0.00%) | 0 / 37 (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 |
| Musculoskeletal chest pain | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 6 (0.00%) | 1 / 37 (2.70%) |
| 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 | | | |
| Cellulitis | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 6 (0.00%) | 1 / 37 (2.70%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Empyema | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 6 (0.00%) | 0 / 37 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 6 (0.00%) | 0 / 37 (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 |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 6 (0.00%) | 0 / 37 (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 |

| | | | |
|---|---------------|---------------|----------------|
| Sepsis | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 6 (0.00%) | 1 / 37 (2.70%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 6 (0.00%) | 1 / 37 (2.70%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Dehydration | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 6 (0.00%) | 1 / 37 (2.70%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Failure to thrive | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 6 (0.00%) | 1 / 37 (2.70%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypokalaemia | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 6 (0.00%) | 1 / 37 (2.70%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|--|----------------------------|--|--|
| Serious adverse events | Phase II HER2+ Dose Esc | | |
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 20 / 48 (41.67%) | | |
| number of deaths (all causes) | 27 | | |
| number of deaths resulting from adverse events | 0 | | |
| General disorders and administration site conditions | | | |
| Chest pain | | | |
| subjects affected / exposed | 0 / 48 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pyrexia | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 1 / 48 (2.08%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 0 / 48 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Dyspnoea | | | |
| subjects affected / exposed | 0 / 48 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pleural effusion | | | |
| subjects affected / exposed | 2 / 48 (4.17%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Psychiatric disorders | | | |
| Mental status changes | | | |
| subjects affected / exposed | 0 / 48 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Investigations | | | |
| Blood alkaline phosphatase increased | | | |
| subjects affected / exposed | 1 / 48 (2.08%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Blood creatine phosphokinase increased | | | |
| subjects affected / exposed | 1 / 48 (2.08%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Electrocardiogram ST segment depression | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 1 / 48 (2.08%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gamma-glutamyltransferase increased | | | |
| subjects affected / exposed | 1 / 48 (2.08%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Haemoglobin increased | | | |
| subjects affected / exposed | 0 / 48 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Transaminases increased | | | |
| subjects affected / exposed | 1 / 48 (2.08%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Injury, poisoning and procedural complications | | | |
| Humerus fracture | | | |
| subjects affected / exposed | 1 / 48 (2.08%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac disorders | | | |
| Acute coronary syndrome | | | |
| subjects affected / exposed | 1 / 48 (2.08%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nervous system disorders | | | |
| Cerebral disorder | | | |
| subjects affected / exposed | 1 / 48 (2.08%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Dizziness | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 2 / 48 (4.17%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Headache | | | |
| subjects affected / exposed | 1 / 48 (2.08%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Neuropathy peripheral | | | |
| subjects affected / exposed | 0 / 48 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Spinal cord compression | | | |
| subjects affected / exposed | 0 / 48 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Syncope | | | |
| subjects affected / exposed | 0 / 48 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 1 / 48 (2.08%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Febrile neutropenia | | | |
| subjects affected / exposed | 0 / 48 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Polycythaemia | | | |
| subjects affected / exposed | 0 / 48 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ear and labyrinth disorders | | | |

| | | | |
|---|----------------|--|--|
| Vertigo | | | |
| subjects affected / exposed | 1 / 48 (2.08%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Eye disorders | | | |
| Eyelid oedema | | | |
| subjects affected / exposed | 0 / 48 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |
| Constipation | | | |
| subjects affected / exposed | 0 / 48 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Diarrhoea | | | |
| subjects affected / exposed | 2 / 48 (4.17%) | | |
| occurrences causally related to treatment / all | 1 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nausea | | | |
| subjects affected / exposed | 0 / 48 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Stomatitis | | | |
| subjects affected / exposed | 1 / 48 (2.08%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Upper gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 1 / 48 (2.08%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vomiting | | | |
| subjects affected / exposed | 3 / 48 (6.25%) | | |
| occurrences causally related to treatment / all | 1 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|---|----------------|--|--|
| Skin and subcutaneous tissue disorders | | | |
| Rash | | | |
| subjects affected / exposed | 0 / 48 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal and urinary disorders | | | |
| Renal failure | | | |
| subjects affected / exposed | 1 / 48 (2.08%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 1 / 48 (2.08%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Muscular weakness | | | |
| subjects affected / exposed | 1 / 48 (2.08%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Musculoskeletal chest pain | | | |
| subjects affected / exposed | 1 / 48 (2.08%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| Cellulitis | | | |
| subjects affected / exposed | 1 / 48 (2.08%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Empyema | | | |
| subjects affected / exposed | 0 / 48 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Lower respiratory tract infection | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 1 / 48 (2.08%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pneumonia | | | |
| subjects affected / exposed | 1 / 48 (2.08%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Sepsis | | | |
| subjects affected / exposed | 0 / 48 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 48 (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 / 48 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Failure to thrive | | | |
| subjects affected / exposed | 0 / 48 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypokalaemia | | | |
| subjects affected / exposed | 0 / 48 (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 | Phase I | Phase II -ve | Phase II HER2+ |
|---|-----------------|-----------------|-------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 8 / 8 (100.00%) | 6 / 6 (100.00%) | 37 / 37 (100.00%) |
| Vascular disorders | | | |
| Hot flush | | | |
| subjects affected / exposed | 2 / 8 (25.00%) | 0 / 6 (0.00%) | 1 / 37 (2.70%) |
| occurrences (all) | 4 | 0 | 1 |
| Lymphoedema | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 6 (0.00%) | 1 / 37 (2.70%) |
| occurrences (all) | 1 | 0 | 1 |
| Post thrombotic syndrome | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 6 (0.00%) | 0 / 37 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 6 (0.00%) | 0 / 37 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Chest discomfort | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 6 (16.67%) | 0 / 37 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Chest pain | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 6 (0.00%) | 0 / 37 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Chills | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 6 (0.00%) | 2 / 37 (5.41%) |
| occurrences (all) | 0 | 0 | 2 |
| Fatigue | | | |
| subjects affected / exposed | 6 / 8 (75.00%) | 3 / 6 (50.00%) | 20 / 37 (54.05%) |
| occurrences (all) | 15 | 5 | 42 |
| Oedema peripheral | | | |
| subjects affected / exposed | 2 / 8 (25.00%) | 1 / 6 (16.67%) | 2 / 37 (5.41%) |
| occurrences (all) | 3 | 1 | 2 |
| Pain | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 6 (0.00%) | 0 / 37 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Pyrexia | | | |

| | | | |
|--|--|---|--|
| subjects affected / exposed occurrences (all) | 2 / 8 (25.00%) 2 | 1 / 6 (16.67%) 2 | 6 / 37 (16.22%) 6 |
| Immune system disorders Hypersensitivity subjects affected / exposed occurrences (all) | 1 / 8 (12.50%) 1 | 0 / 6 (0.00%) 0 | 0 / 37 (0.00%) 0 |
| Reproductive system and breast disorders Breast pain subjects affected / exposed occurrences (all) Vulvovaginal dryness subjects affected / exposed occurrences (all) | 1 / 8 (12.50%) 2 1 / 8 (12.50%) 1 | 0 / 6 (0.00%) 0 0 / 6 (0.00%) 0 | 0 / 37 (0.00%) 0 3 / 37 (8.11%) 3 |
| Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) Dysphonia subjects affected / exposed occurrences (all) Dyspnoea subjects affected / exposed occurrences (all) Dyspnoea exertional subjects affected / exposed occurrences (all) Epistaxis subjects affected / exposed occurrences (all) Nasal dryness subjects affected / exposed occurrences (all) Oropharyngeal pain subjects affected / exposed occurrences (all) Pleural effusion | 2 / 8 (25.00%) 5 0 / 8 (0.00%) 0 1 / 8 (12.50%) 3 0 / 8 (0.00%) 0 0 / 8 (0.00%) 0 0 / 8 (0.00%) 0 0 / 8 (0.00%) 0 0 / 8 (0.00%) 0 | 2 / 6 (33.33%) 7 0 / 6 (0.00%) 0 3 / 6 (50.00%) 8 0 / 6 (0.00%) 0 1 / 6 (16.67%) 1 1 / 6 (16.67%) 1 1 / 6 (16.67%) 1 | 4 / 37 (10.81%) 5 1 / 37 (2.70%) 1 3 / 37 (8.11%) 3 2 / 37 (5.41%) 2 3 / 37 (8.11%) 4 0 / 37 (0.00%) 0 1 / 37 (2.70%) 1 |

| | | | |
|--------------------------------------|----------------|----------------|-----------------|
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 6 (0.00%) | 0 / 37 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Rhinitis allergic | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 6 (0.00%) | 0 / 37 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Psychiatric disorders | | | |
| Insomnia | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 6 (16.67%) | 0 / 37 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 6 (0.00%) | 2 / 37 (5.41%) |
| occurrences (all) | 0 | 0 | 4 |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 6 (0.00%) | 2 / 37 (5.41%) |
| occurrences (all) | 0 | 0 | 3 |
| Blood alkaline phosphatase increased | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 6 (0.00%) | 1 / 37 (2.70%) |
| occurrences (all) | 0 | 0 | 2 |
| Blood creatinine increased | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 6 (0.00%) | 0 / 37 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Haemoglobin decreased | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 6 (0.00%) | 0 / 37 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Monocyte count increased | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 6 (16.67%) | 0 / 37 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Platelet count decreased | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 6 (0.00%) | 1 / 37 (2.70%) |
| occurrences (all) | 0 | 0 | 1 |
| Weight decreased | | | |
| subjects affected / exposed | 3 / 8 (37.50%) | 2 / 6 (33.33%) | 5 / 37 (13.51%) |
| occurrences (all) | 4 | 2 | 5 |
| Weight increased | | | |

| | | | |
|--|---------------------|---------------------|----------------------|
| subjects affected / exposed occurrences (all) | 1 / 8 (12.50%) 1 | 0 / 6 (0.00%) 0 | 0 / 37 (0.00%) 0 |
| Injury, poisoning and procedural complications | | | |
| Fall | | | |
| subjects affected / exposed occurrences (all) | 0 / 8 (0.00%) 0 | 0 / 6 (0.00%) 0 | 0 / 37 (0.00%) 0 |
| Stoma site ulcer | | | |
| subjects affected / exposed occurrences (all) | 1 / 8 (12.50%) 1 | 0 / 6 (0.00%) 0 | 0 / 37 (0.00%) 0 |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed occurrences (all) | 1 / 8 (12.50%) 1 | 0 / 6 (0.00%) 0 | 6 / 37 (16.22%) 7 |
| Dysgeusia | | | |
| subjects affected / exposed occurrences (all) | 0 / 8 (0.00%) 0 | 1 / 6 (16.67%) 1 | 4 / 37 (10.81%) 4 |
| Headache | | | |
| subjects affected / exposed occurrences (all) | 3 / 8 (37.50%) 5 | 2 / 6 (33.33%) 3 | 2 / 37 (5.41%) 2 |
| Hypoaesthesia | | | |
| subjects affected / exposed occurrences (all) | 1 / 8 (12.50%) 1 | 0 / 6 (0.00%) 0 | 0 / 37 (0.00%) 0 |
| Migraine | | | |
| subjects affected / exposed occurrences (all) | 1 / 8 (12.50%) 1 | 0 / 6 (0.00%) 0 | 0 / 37 (0.00%) 0 |
| Neuralgia | | | |
| subjects affected / exposed occurrences (all) | 1 / 8 (12.50%) 1 | 1 / 6 (16.67%) 1 | 1 / 37 (2.70%) 1 |
| Neuropathy peripheral | | | |
| subjects affected / exposed occurrences (all) | 2 / 8 (25.00%) 2 | 0 / 6 (0.00%) 0 | 7 / 37 (18.92%) 8 |
| Paraesthesia | | | |
| subjects affected / exposed occurrences (all) | 0 / 8 (0.00%) 0 | 1 / 6 (16.67%) 1 | 5 / 37 (13.51%) 9 |
| Peripheral sensory neuropathy | | | |

| | | | |
|--|---------------------|--------------------|---------------------|
| subjects affected / exposed occurrences (all) | 1 / 8 (12.50%) 3 | 0 / 6 (0.00%) 0 | 1 / 37 (2.70%) 9 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 6 (0.00%) | 2 / 37 (5.41%) |
| occurrences (all) | 0 | 0 | 2 |
| Neutropenia | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 6 (0.00%) | 1 / 37 (2.70%) |
| occurrences (all) | 0 | 0 | 2 |
| Thrombocytopenia | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 6 (0.00%) | 1 / 37 (2.70%) |
| occurrences (all) | 0 | 0 | 1 |
| Ear and labyrinth disorders | | | |
| Ear pain | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 6 (16.67%) | 0 / 37 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Eye disorders | | | |
| Dry eye | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 6 (0.00%) | 3 / 37 (8.11%) |
| occurrences (all) | 1 | 0 | 4 |
| Vision blurred | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 6 (0.00%) | 0 / 37 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 6 (0.00%) | 5 / 37 (13.51%) |
| occurrences (all) | 0 | 0 | 7 |
| Abdominal pain upper | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 6 (0.00%) | 1 / 37 (2.70%) |
| occurrences (all) | 0 | 0 | 1 |
| Cheilitis | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 6 (0.00%) | 1 / 37 (2.70%) |
| occurrences (all) | 0 | 0 | 1 |
| Constipation | | | |
| subjects affected / exposed | 2 / 8 (25.00%) | 2 / 6 (33.33%) | 7 / 37 (18.92%) |
| occurrences (all) | 3 | 2 | 7 |
| Diarrhoea | | | |

| | | | |
|--|----------------|----------------|------------------|
| subjects affected / exposed | 7 / 8 (87.50%) | 5 / 6 (83.33%) | 35 / 37 (94.59%) |
| occurrences (all) | 18 | 13 | 82 |
| Dry mouth | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 6 (0.00%) | 2 / 37 (5.41%) |
| occurrences (all) | 1 | 0 | 2 |
| Dyspepsia | | | |
| subjects affected / exposed | 3 / 8 (37.50%) | 0 / 6 (0.00%) | 1 / 37 (2.70%) |
| occurrences (all) | 3 | 0 | 1 |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 6 (16.67%) | 2 / 37 (5.41%) |
| occurrences (all) | 0 | 1 | 2 |
| Glossodynia | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 6 (0.00%) | 0 / 37 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Mouth ulceration | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 6 (0.00%) | 0 / 37 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Nausea | | | |
| subjects affected / exposed | 6 / 8 (75.00%) | 5 / 6 (83.33%) | 18 / 37 (48.65%) |
| occurrences (all) | 10 | 8 | 28 |
| Stomatitis | | | |
| subjects affected / exposed | 5 / 8 (62.50%) | 4 / 6 (66.67%) | 25 / 37 (67.57%) |
| occurrences (all) | 15 | 6 | 58 |
| Vomiting | | | |
| subjects affected / exposed | 3 / 8 (37.50%) | 3 / 6 (50.00%) | 9 / 37 (24.32%) |
| occurrences (all) | 6 | 5 | 11 |
| Skin and subcutaneous tissue disorders | | | |
| Dermatitis acneiform | | | |
| subjects affected / exposed | 2 / 8 (25.00%) | 3 / 6 (50.00%) | 4 / 37 (10.81%) |
| occurrences (all) | 2 | 5 | 5 |
| Dry skin | | | |
| subjects affected / exposed | 4 / 8 (50.00%) | 2 / 6 (33.33%) | 7 / 37 (18.92%) |
| occurrences (all) | 5 | 4 | 11 |
| Hair texture abnormal | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 6 (0.00%) | 0 / 37 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |

| | | | |
|---|----------------|----------------|------------------|
| Nail disorder | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 6 (0.00%) | 2 / 37 (5.41%) |
| occurrences (all) | 0 | 0 | 2 |
| Nail dystrophy | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 6 (0.00%) | 0 / 37 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Palmar-plantar erythrodysaesthesia syndrome | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 6 (0.00%) | 0 / 37 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Pruritus | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 2 / 6 (33.33%) | 4 / 37 (10.81%) |
| occurrences (all) | 2 | 2 | 4 |
| Rash | | | |
| subjects affected / exposed | 3 / 8 (37.50%) | 0 / 6 (0.00%) | 17 / 37 (45.95%) |
| occurrences (all) | 9 | 0 | 25 |
| Skin hyperpigmentation | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 6 (0.00%) | 0 / 37 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Skin reaction | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 6 (16.67%) | 0 / 37 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Swelling face | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 6 (0.00%) | 0 / 37 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Renal and urinary disorders | | | |
| Pollakiuria | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 6 (0.00%) | 0 / 37 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Urinary incontinence | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 6 (0.00%) | 1 / 37 (2.70%) |
| occurrences (all) | 1 | 0 | 1 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 4 / 8 (50.00%) | 3 / 6 (50.00%) | 6 / 37 (16.22%) |
| occurrences (all) | 7 | 3 | 11 |
| Back pain | | | |

| | | | |
|-----------------------------|----------------|----------------|-----------------|
| subjects affected / exposed | 1 / 8 (12.50%) | 2 / 6 (33.33%) | 6 / 37 (16.22%) |
| occurrences (all) | 1 | 3 | 7 |
| Bone pain | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 1 / 6 (16.67%) | 0 / 37 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Joint stiffness | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 6 (0.00%) | 0 / 37 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Muscle spasms | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 6 (16.67%) | 1 / 37 (2.70%) |
| occurrences (all) | 0 | 2 | 2 |
| Muscular weakness | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 6 (0.00%) | 1 / 37 (2.70%) |
| occurrences (all) | 1 | 0 | 1 |
| Musculoskeletal chest pain | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 6 (0.00%) | 3 / 37 (8.11%) |
| occurrences (all) | 3 | 0 | 4 |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 6 (0.00%) | 1 / 37 (2.70%) |
| occurrences (all) | 3 | 0 | 1 |
| Myalgia | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 6 (16.67%) | 2 / 37 (5.41%) |
| occurrences (all) | 0 | 1 | 2 |
| Neck pain | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 1 / 6 (16.67%) | 1 / 37 (2.70%) |
| occurrences (all) | 1 | 1 | 1 |
| Pain in extremity | | | |
| subjects affected / exposed | 2 / 8 (25.00%) | 1 / 6 (16.67%) | 2 / 37 (5.41%) |
| occurrences (all) | 3 | 1 | 2 |
| Infections and infestations | | | |
| Influenza | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 6 (0.00%) | 0 / 37 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Localised infection | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 6 (0.00%) | 0 / 37 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

| | | | |
|------------------------------------|----------------|----------------|-----------------|
| Nasopharyngitis | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 6 (0.00%) | 0 / 37 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Onychomycosis | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 6 (0.00%) | 0 / 37 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Paronychia | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 6 (0.00%) | 4 / 37 (10.81%) |
| occurrences (all) | 0 | 0 | 5 |
| Pharyngitis | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 6 (0.00%) | 0 / 37 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Rhinitis | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 6 (0.00%) | 0 / 37 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 6 (0.00%) | 1 / 37 (2.70%) |
| occurrences (all) | 1 | 0 | 1 |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 6 (0.00%) | 3 / 37 (8.11%) |
| occurrences (all) | 0 | 0 | 3 |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 4 / 8 (50.00%) | 1 / 6 (16.67%) | 6 / 37 (16.22%) |
| occurrences (all) | 4 | 1 | 7 |
| Dehydration | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 6 (0.00%) | 1 / 37 (2.70%) |
| occurrences (all) | 1 | 0 | 1 |
| Hyperglycaemia | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 6 (0.00%) | 2 / 37 (5.41%) |
| occurrences (all) | 0 | 0 | 5 |
| Hypertriglyceridaemia | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 6 (0.00%) | 0 / 37 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hypokalaemia | | | |

| | | | |
|-----------------------------|----------------|---------------|----------------|
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 6 (0.00%) | 3 / 37 (8.11%) |
| occurrences (all) | 1 | 0 | 6 |

| Non-serious adverse events | Phase II HER2+ Dose Esc | | |
|---|----------------------------|--|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 48 / 48 (100.00%) | | |
| Vascular disorders | | | |
| Hot flush | | | |
| subjects affected / exposed | 1 / 48 (2.08%) | | |
| occurrences (all) | 1 | | |
| Lymphoedema | | | |
| subjects affected / exposed | 2 / 48 (4.17%) | | |
| occurrences (all) | 2 | | |
| Post thrombotic syndrome | | | |
| subjects affected / exposed | 0 / 48 (0.00%) | | |
| occurrences (all) | 0 | | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 18 / 48 (37.50%) | | |
| occurrences (all) | 27 | | |
| Chest discomfort | | | |
| subjects affected / exposed | 0 / 48 (0.00%) | | |
| occurrences (all) | 0 | | |
| Chest pain | | | |
| subjects affected / exposed | 0 / 48 (0.00%) | | |
| occurrences (all) | 0 | | |
| Chills | | | |
| subjects affected / exposed | 1 / 48 (2.08%) | | |
| occurrences (all) | 1 | | |
| Fatigue | | | |
| subjects affected / exposed | 9 / 48 (18.75%) | | |
| occurrences (all) | 30 | | |
| Oedema peripheral | | | |
| subjects affected / exposed | 9 / 48 (18.75%) | | |
| occurrences (all) | 20 | | |
| Pain | | | |

| | | | |
|---|--|--|--|
| <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Pyrexia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>3 / 48 (6.25%)</p> <p>5</p> <p>4 / 48 (8.33%)</p> <p>10</p> | | |
| <p>Immune system disorders</p> <p>Hypersensitivity</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>0 / 48 (0.00%)</p> <p>0</p> | | |
| <p>Reproductive system and breast disorders</p> <p>Breast pain</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Vulvovaginal dryness</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>1 / 48 (2.08%)</p> <p>1</p> <p>0 / 48 (0.00%)</p> <p>0</p> | | |
| <p>Respiratory, thoracic and mediastinal disorders</p> <p>Cough</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Dysphonia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Dyspnoea</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Dyspnoea exertional</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Epistaxis</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Nasal dryness</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Oropharyngeal pain</p> | <p>9 / 48 (18.75%)</p> <p>13</p> <p>3 / 48 (6.25%)</p> <p>3</p> <p>9 / 48 (18.75%)</p> <p>14</p> <p>1 / 48 (2.08%)</p> <p>2</p> <p>10 / 48 (20.83%)</p> <p>73</p> <p>0 / 48 (0.00%)</p> <p>0</p> | | |

| | | | |
|--------------------------------------|-----------------|--|--|
| subjects affected / exposed | 5 / 48 (10.42%) | | |
| occurrences (all) | 6 | | |
| Pleural effusion | | | |
| subjects affected / exposed | 0 / 48 (0.00%) | | |
| occurrences (all) | 0 | | |
| Rhinitis allergic | | | |
| subjects affected / exposed | 0 / 48 (0.00%) | | |
| occurrences (all) | 0 | | |
| Psychiatric disorders | | | |
| Insomnia | | | |
| subjects affected / exposed | 4 / 48 (8.33%) | | |
| occurrences (all) | 7 | | |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 2 / 48 (4.17%) | | |
| occurrences (all) | 2 | | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 3 / 48 (6.25%) | | |
| occurrences (all) | 3 | | |
| Blood alkaline phosphatase increased | | | |
| subjects affected / exposed | 4 / 48 (8.33%) | | |
| occurrences (all) | 6 | | |
| Blood creatinine increased | | | |
| subjects affected / exposed | 3 / 48 (6.25%) | | |
| occurrences (all) | 3 | | |
| Haemoglobin decreased | | | |
| subjects affected / exposed | 3 / 48 (6.25%) | | |
| occurrences (all) | 6 | | |
| Monocyte count increased | | | |
| subjects affected / exposed | 0 / 48 (0.00%) | | |
| occurrences (all) | 0 | | |
| Platelet count decreased | | | |
| subjects affected / exposed | 4 / 48 (8.33%) | | |
| occurrences (all) | 6 | | |
| Weight decreased | | | |

| | | | |
|--|------------------|--|--|
| subjects affected / exposed | 6 / 48 (12.50%) | | |
| occurrences (all) | 6 | | |
| Weight increased | | | |
| subjects affected / exposed | 0 / 48 (0.00%) | | |
| occurrences (all) | 0 | | |
| Injury, poisoning and procedural complications | | | |
| Fall | | | |
| subjects affected / exposed | 3 / 48 (6.25%) | | |
| occurrences (all) | 3 | | |
| Stoma site ulcer | | | |
| subjects affected / exposed | 0 / 48 (0.00%) | | |
| occurrences (all) | 0 | | |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 4 / 48 (8.33%) | | |
| occurrences (all) | 7 | | |
| Dysgeusia | | | |
| subjects affected / exposed | 1 / 48 (2.08%) | | |
| occurrences (all) | 1 | | |
| Headache | | | |
| subjects affected / exposed | 11 / 48 (22.92%) | | |
| occurrences (all) | 31 | | |
| Hypoaesthesia | | | |
| subjects affected / exposed | 0 / 48 (0.00%) | | |
| occurrences (all) | 0 | | |
| Migraine | | | |
| subjects affected / exposed | 0 / 48 (0.00%) | | |
| occurrences (all) | 0 | | |
| Neuralgia | | | |
| subjects affected / exposed | 0 / 48 (0.00%) | | |
| occurrences (all) | 0 | | |
| Neuropathy peripheral | | | |
| subjects affected / exposed | 1 / 48 (2.08%) | | |
| occurrences (all) | 2 | | |
| Paraesthesia | | | |

| | | | |
|--------------------------------------|------------------|--|--|
| subjects affected / exposed | 1 / 48 (2.08%) | | |
| occurrences (all) | 1 | | |
| Peripheral sensory neuropathy | | | |
| subjects affected / exposed | 0 / 48 (0.00%) | | |
| occurrences (all) | 0 | | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 10 / 48 (20.83%) | | |
| occurrences (all) | 14 | | |
| Neutropenia | | | |
| subjects affected / exposed | 3 / 48 (6.25%) | | |
| occurrences (all) | 5 | | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 4 / 48 (8.33%) | | |
| occurrences (all) | 13 | | |
| Ear and labyrinth disorders | | | |
| Ear pain | | | |
| subjects affected / exposed | 0 / 48 (0.00%) | | |
| occurrences (all) | 0 | | |
| Eye disorders | | | |
| Dry eye | | | |
| subjects affected / exposed | 2 / 48 (4.17%) | | |
| occurrences (all) | 2 | | |
| Vision blurred | | | |
| subjects affected / exposed | 0 / 48 (0.00%) | | |
| occurrences (all) | 0 | | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 3 / 48 (6.25%) | | |
| occurrences (all) | 3 | | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 8 / 48 (16.67%) | | |
| occurrences (all) | 13 | | |
| Cheilitis | | | |
| subjects affected / exposed | 3 / 48 (6.25%) | | |
| occurrences (all) | 3 | | |
| Constipation | | | |

| | | | |
|--|------------------|--|--|
| subjects affected / exposed | 21 / 48 (43.75%) | | |
| occurrences (all) | 44 | | |
| Diarrhoea | | | |
| subjects affected / exposed | 40 / 48 (83.33%) | | |
| occurrences (all) | 673 | | |
| Dry mouth | | | |
| subjects affected / exposed | 6 / 48 (12.50%) | | |
| occurrences (all) | 6 | | |
| Dyspepsia | | | |
| subjects affected / exposed | 2 / 48 (4.17%) | | |
| occurrences (all) | 6 | | |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 2 / 48 (4.17%) | | |
| occurrences (all) | 2 | | |
| Glossodynia | | | |
| subjects affected / exposed | 0 / 48 (0.00%) | | |
| occurrences (all) | 0 | | |
| Mouth ulceration | | | |
| subjects affected / exposed | 9 / 48 (18.75%) | | |
| occurrences (all) | 16 | | |
| Nausea | | | |
| subjects affected / exposed | 20 / 48 (41.67%) | | |
| occurrences (all) | 45 | | |
| Stomatitis | | | |
| subjects affected / exposed | 29 / 48 (60.42%) | | |
| occurrences (all) | 117 | | |
| Vomiting | | | |
| subjects affected / exposed | 23 / 48 (47.92%) | | |
| occurrences (all) | 41 | | |
| Skin and subcutaneous tissue disorders | | | |
| Dermatitis acneiform | | | |
| subjects affected / exposed | 0 / 48 (0.00%) | | |
| occurrences (all) | 0 | | |
| Dry skin | | | |
| subjects affected / exposed | 4 / 48 (8.33%) | | |
| occurrences (all) | 4 | | |

| | | | |
|--|------------------------|--|--|
| Hair texture abnormal subjects affected / exposed occurrences (all) | 0 / 48 (0.00%) 0 | | |
| Nail disorder subjects affected / exposed occurrences (all) | 2 / 48 (4.17%) 2 | | |
| Nail dystrophy subjects affected / exposed occurrences (all) | 0 / 48 (0.00%) 0 | | |
| Palmar-plantar erythrodysaesthesia syndrome subjects affected / exposed occurrences (all) | 5 / 48 (10.42%) 7 | | |
| Pruritus subjects affected / exposed occurrences (all) | 7 / 48 (14.58%) 10 | | |
| Rash subjects affected / exposed occurrences (all) | 21 / 48 (43.75%) 68 | | |
| Skin hyperpigmentation subjects affected / exposed occurrences (all) | 1 / 48 (2.08%) 1 | | |
| Skin reaction subjects affected / exposed occurrences (all) | 0 / 48 (0.00%) 0 | | |
| Swelling face subjects affected / exposed occurrences (all) | 0 / 48 (0.00%) 0 | | |
| Renal and urinary disorders Pollakiuria subjects affected / exposed occurrences (all) | 0 / 48 (0.00%) 0 | | |
| Urinary incontinence subjects affected / exposed occurrences (all) | 1 / 48 (2.08%) 1 | | |
| Musculoskeletal and connective tissue disorders | | | |

| | | | |
|-----------------------------|-----------------|--|--|
| Arthralgia | | | |
| subjects affected / exposed | 5 / 48 (10.42%) | | |
| occurrences (all) | 10 | | |
| Back pain | | | |
| subjects affected / exposed | 4 / 48 (8.33%) | | |
| occurrences (all) | 4 | | |
| Bone pain | | | |
| subjects affected / exposed | 0 / 48 (0.00%) | | |
| occurrences (all) | 0 | | |
| Joint stiffness | | | |
| subjects affected / exposed | 0 / 48 (0.00%) | | |
| occurrences (all) | 0 | | |
| Muscle spasms | | | |
| subjects affected / exposed | 4 / 48 (8.33%) | | |
| occurrences (all) | 10 | | |
| Muscular weakness | | | |
| subjects affected / exposed | 0 / 48 (0.00%) | | |
| occurrences (all) | 0 | | |
| Musculoskeletal chest pain | | | |
| subjects affected / exposed | 2 / 48 (4.17%) | | |
| occurrences (all) | 3 | | |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 4 / 48 (8.33%) | | |
| occurrences (all) | 5 | | |
| Myalgia | | | |
| subjects affected / exposed | 2 / 48 (4.17%) | | |
| occurrences (all) | 3 | | |
| Neck pain | | | |
| subjects affected / exposed | 0 / 48 (0.00%) | | |
| occurrences (all) | 0 | | |
| Pain in extremity | | | |
| subjects affected / exposed | 6 / 48 (12.50%) | | |
| occurrences (all) | 8 | | |
| Infections and infestations | | | |
| Influenza | | | |

| | | | |
|------------------------------------|------------------|--|--|
| subjects affected / exposed | 3 / 48 (6.25%) | | |
| occurrences (all) | 3 | | |
| Localised infection | | | |
| subjects affected / exposed | 3 / 48 (6.25%) | | |
| occurrences (all) | 4 | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 5 / 48 (10.42%) | | |
| occurrences (all) | 9 | | |
| Onychomycosis | | | |
| subjects affected / exposed | 1 / 48 (2.08%) | | |
| occurrences (all) | 1 | | |
| Paronychia | | | |
| subjects affected / exposed | 4 / 48 (8.33%) | | |
| occurrences (all) | 5 | | |
| Pharyngitis | | | |
| subjects affected / exposed | 1 / 48 (2.08%) | | |
| occurrences (all) | 1 | | |
| Rhinitis | | | |
| subjects affected / exposed | 3 / 48 (6.25%) | | |
| occurrences (all) | 6 | | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 3 / 48 (6.25%) | | |
| occurrences (all) | 4 | | |
| Urinary tract infection | | | |
| subjects affected / exposed | 4 / 48 (8.33%) | | |
| occurrences (all) | 4 | | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 19 / 48 (39.58%) | | |
| occurrences (all) | 30 | | |
| Dehydration | | | |
| subjects affected / exposed | 1 / 48 (2.08%) | | |
| occurrences (all) | 1 | | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 1 / 48 (2.08%) | | |
| occurrences (all) | 1 | | |

| | | | |
|-----------------------------|----------------|--|--|
| Hypertriglyceridaemia | | | |
| subjects affected / exposed | 4 / 48 (8.33%) | | |
| occurrences (all) | 4 | | |
| Hypokalaemia | | | |
| subjects affected / exposed | 1 / 48 (2.08%) | | |
| occurrences (all) | 1 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
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| 13 April 2010 | <ul style="list-style-type: none">Phase 1 eligibility criteria were changed to include no limit on the number of lines of prior therapyClarified that prior treatment and progression on lapatinib is not a requirement for eligibilityDefinition of triple-negative disease in the eligibility criteria was changed to <5% estrogen receptor and progesterone receptor expression |
| 11 May 2010 | <ul style="list-style-type: none">Included Wyeth-Pfizer merger; Wyeth is now Wyeth Pharmaceuticals, Inc., a Pfizer CompanyChanged drug supply; Wyeth will be providing neratinib in 240-mg and 80-mg capsules and 40-mg tablets. |
| 13 July 2010 | <ul style="list-style-type: none">A third dose cohort to Phase 1 (15 mg of temsirolimus and 240 mg of neratinib) was added.The maximum number of patients needed to determine the MTD was increased to 18 patients. |
| 12 September 2010 | <ul style="list-style-type: none">Shari Goldfarb, MD, was added as an investigator; this amendment was not submitted to the IND. |
| 11 January 2011 | <ul style="list-style-type: none">The MTD from Phase 1 was determined to be 8 mg temsirolimus/240 mg neratinib.Pathological nodes must be ≥ 15 mm by the short axis to be considered measurable. |
| 27 September 2011 | <ul style="list-style-type: none">Signed informed consent and medication list must be obtained within 1 month prior to starting therapy instead of 2 weeks.If patients have received at least 6 months of therapy, they can be seen monthly (Day 1 of each cycle) by the MD instead of biweekly. |
| 13 March 2012 | <ul style="list-style-type: none">As of 2/10/12, the Triple-negative cohort was closed to accrual. This change in study design was not a result of safety concerns. After assessing the data of the Triple-negative patients, there was no indication that therapy with weekly temsirolimus (8 mg) and daily neratinib (240 mg) shows efficacy in terms of the ORR (CR + PR) as determined by RECIST 1.1 criteria.Added that complete or partial responses will be confirmed with a repeat CT scan after 4 weeks. Radiographic assessments (CT and Bone or PET scan) may then be completed 8 weeks ± 7 days from the confirmatory CT scan. |
| 29 May 2012 | <ul style="list-style-type: none">Study sponsorship was changed from Memorial Sloan Kettering Cancer Center (MSKCC) to Puma Biotechnology, Inc. (Puma); contact information was revised accordingly.Subjects who were unable to complete 1 week of therapy will not be included in the analysis for toxicity or response; however, they will be followed for safety. Subjects not completing 1 week of therapy may be replaced by a new subject.A new section "Follow-up Visits" was added stating that subjects will be followed for overall survival after the treatment phase is complete. |

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| 16 January 2013 | <ul style="list-style-type: none"> • Two new sites in the US, in addition to MSKCC, were activated: Weill Cornell Medical College and University of Southern California. • Inclusion Criterion for Phase 2 HER2-Amplified Cohort was revised to allow enrollment of patients with no restriction on the number of prior chemotherapy regimens received. • The enrollment period was extended from 2 years to approximately 3 years. • To mitigate or reduce the incidence of diarrhea that generally occurs in the initial treatment cycle, a revised diarrhea management plan with mandatory prophylactic use of high-dose loperamide was implemented. This allowed for patients to take a maximum dose of 12 mg of loperamide for the first 3 days, followed by 6-8 mg of loperamide per day thereafter. |
| 17 March 2013 | <ul style="list-style-type: none"> • 16 patients added in Phase 2 HER2-positive cohort. If these patients tolerated the starting dose of neratinib 240 mg/day + temsirolimus 8 mg/week in the first cycle of therapy, intra-patient dose-escalation of temsirolimus to 15 mg/week was allowed. • Patient enrollment in Phase 2 portion of study revised to minimum of 19 patients and maximum of approximately 79 patients (50 HER2+ patients). • Study expanded to centers in Spain, United Kingdom, France, and Hong Kong. • Total duration of study increased to approximately 48 months with 10 centers. • Final analysis revised: "The final analysis of the primary endpoint will occur when disease progression is reported for all patients in the Phase 2 HER2-positive cohort (first 34 patients without dose-escalation)." • End of study (EOS) stated to occur when disease progression is reported for all patients on study, or when EOS is declared early once the primary endpoint has been met. • Phase 2 secondary objectives revised to determine progression-free survival, duration of response, clinical benefit rate, and overall survival, and estimate the efficacy and safety assessment of dose escalation to 240 mg neratinib plus 15 mg temsirolimus with revised prophylactic diarrhea management regimen in pretreated HER2+ MBC patients. • Inclusion and Exclusion criteria revisions regarding informed consent for procedures. • Inclusion criterion for contraception while on study revised. • Exclusion criterion removed: Unable to consent to biopsy of metastatic disease or for whom a biopsy would be medically unsafe. • Exclusion criterion added: Previous treatment with any strong inhibitor and/or inducer of CYP3A4 enzyme or sensitive P glycoprotein. • Section "10 Patient Withdrawal and Replacement" added to clarify conditions for discontinuing IP administration and reasons for study withdrawal. • Section "12 Statistical Methods" revised to clarify all statistical analyses and methods. |

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| 14 October 2013 | <ul style="list-style-type: none"> • Number of patients in the HER2+ dose escalation cohort increased to approximately 100 and the number of centers to approximately 15 in order to expand the safety and efficacy data for the neratinib 240 mg/day plus temsirolimus 15 mg/week combination. • Minimum and maximum number of patients enrolled in Phase 2 increased from 19 to 119, and from 79 to 163, respectively. Maximum total sample size for study increased from 97 to 181 patients. • Statistical methods section and text throughout protocol revised to indicate that single-stage design was used to estimate sample size for HER2+ dose-escalation cohort. • Primary Phase 2 objective added to estimate the ORR for patients with dose escalation to 240 mg neratinib plus 15 mg, temsirolimus with a revised prophylactic diarrhea management regimen in pretreated HER2+ MBC patients. • Secondary Phase 2 objective revised to assess only safety (because the efficacy evaluation for this Phase 2 cohort was moved under primary objectives: to assess the safety of dose escalation to 240 mg neratinib plus 15 mg temsirolimus with a revised prophylactic diarrhea management regimen in pretreated HER2+ MBC patients. • Interim analysis for Phase 2 HER+ cohort added to determine if study continuation was warranted based on Simon 2-stage optimal design. • Text clarified, "final analysis of the primary endpoint will occur when disease progression is reported for all HER2-positive patients enrolled in the Phase 2 portion of study." • Text added to clarify that efficacy analyses performed on the Efficacy Evaluable population, defined as "all patients who are enrolled into the study and have completed at least one week of treatment." • Table added to clarify endpoints for laboratory assessments. • Definition of study termination clarified, "The end of study (EOS) is defined as the last visit of the last patient or the completion of any/all follow-up monitoring and data collection described in the protocol (ie, survival)." |
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Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported