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

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

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

Sponsor protocol code	10-005

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

Notes:

Sponsor organisation name	Puma Biotechnology, Inc.
Sponsor organisation address	10880 Wilshire Blvd, Suite 2150, Los Angeles, United States, 90024
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Notes:

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:

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:

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:

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:

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

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.

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

Are arms mutually exclusive?	Yes
	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.

	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.

	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.

	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.

	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	-	-

	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	-

Gender categorical Units: Subjects			
Female	47	98	
Male	1	1	

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.	

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.

	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	

No statistical analyses for this end point

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.

	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)	

No statistical analyses for this end point

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.

	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.

No statistical analyses for this end point

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.

	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	

No statistical analyses for this end point

Timeframe for reporting adverse events:	
First dose through 28 days after last dose	
Assessment type	Systematic

Dictionary name	MedDRA
Dictionary version	17.0

Reporting group title	Phase I
Reporting group description:	
Subjects with trastuzumab-refractory HER2-amplified disease. Patients were treated to determine themaximum 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.	

	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

	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			

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 %

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

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

subjects affected / exposed	1 / 8 (12.50%)	0 / 6 (0.00%)	1 / 37 (2.70%)
occurrences (all)	3	0	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

[redacted]	(0.00%) 0	0 / 6 (0.00%) 0	2 / 37 (5.41%) 2
[redacted]	12.50%) 1	0 / 6 (0.00%) 0	0 / 37 (0.00%) 0
[redacted]	12.50%) 1	0 / 6 (0.00%) 0	0 / 37 (0.00%) 0
[redacted]	12.50%) 2	2 / 6 (33.33%) 2	4 / 37 (10.81%) 4
Rash			

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

	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			

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

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

Were there any global substantial amendments to the protocol? Yes

13 April 2010	• Phase 1 eligibility criteria were changed to include no limit on the number of lines of prior therapy • Clarified that prior treatment and progression on lapatinib is not a requirement for eligibility • Definition of triple-negative disease in the eligibility criteria was changed to <5% estrogen receptor and progesterone receptor expression
11 May 2010	• Included Wyeth-Pfizer merger; Wyeth is now Wyeth Pharmaceuticals, Inc., a Pfizer Company • Changed drug supply; Wyeth will be providing neratinib in 240-mg and 80-mg capsules and 40-mg tablets.
13 July 2010	• 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	• Shari Goldfarb, MD, was added as an investigator; this amendment was not submitted to the IND.
11 January 2011	• 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	• 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	• 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	• 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.

16 January 2013	• 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	• 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.

14 October 2013	• 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)."

Notes:

Were there any global interruptions to the trial? No

None reported