



Clinical trial results:

A Phase II Randomized Clinical Trial Evaluating Neoadjuvant Therapy Regimens With Weekly Paclitaxel Plus Neratinib or Trastuzumab or Neratinib and Trastuzumab Followed by Doxorubicin and Cyclophosphamide With Postoperative Trastuzumab in Women With Locally Advanced HER2-Positive Breast Cancer

Summary

EudraCT number	2013-004391-35
Trial protocol	IT ES PT
Global end of trial date	25 November 2016

Results information

Result version number	v2 (current)
This version publication date	21 October 2018
First version publication date	03 January 2018
Version creation reason	<ul style="list-style-type: none">• Correction of full data set Screening details erroneously denoted as "xxx" will be corrected described.

Trial information

Trial identification

Sponsor protocol code	FB-7
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01008150
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	30 November 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	25 November 2016
Global end of trial reached?	Yes
Global end of trial date	25 November 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

FB-7 is a Phase II, multi-center randomized study of neratinib in combination with weekly paclitaxel with or without trastuzumab followed by doxorubicin and cyclophosphamide (AC) as neoadjuvant therapy for women with HER2-positive locally advanced breast cancer. Patients in the control arm will receive neoadjuvant trastuzumab in combination with weekly paclitaxel followed by AC. The primary aim of the study is to determine the pathologic complete response (pCR) rate in breast and axillary nodes following the neoadjuvant therapy regimens.

Protection of trial subjects:

The protocol, the investigator's brochure, and the informed consent form (ICF) for this clinical study were submitted to an independent ethics committee (IEC) or an institutional review board (IRB) for review and written approval. Any subsequent amendments to the protocol or any revisions to the ICF were submitted for IEC or IRB review and written approval. Subjects were to be discontinued from the study for any of the following reasons: disease progression, symptomatic deterioration, unacceptable toxicity, death, or withdrawal of consent. The study was monitored by an independent clinical site monitor evaluating patient and site compliance, patient safety and physician oversight.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	11 February 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Canada: 11
Country: Number of subjects enrolled	Spain: 33
Country: Number of subjects enrolled	France: 3
Country: Number of subjects enrolled	United States: 76
Country: Number of subjects enrolled	Italy: 16
Country: Number of subjects enrolled	Portugal: 2
Worldwide total number of subjects	141
EEA total number of subjects	54

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	123
From 65 to 84 years	18
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

In addition to meeting all inclusion and exclusion criteria, patients should have a life expectancy of at least ten years, excluding the diagnosis of breast cancer. For US and Canada sites only, a block from diagnostic biopsy sample and the surgical sample was submitted if gross residual disease more than one cm was removed at time of surgery.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Trastuzumab

Arm description:

Trastuzumab + Paclitaxel

Arm type	Experimental
Investigational medicinal product name	Trastuzumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Trastuzumab concurrently with paclitaxel weekly for a total of 16 doses (4 mg/kg loading dose, then 2 mg/kg weekly). Following surgery, trastuzumab (8 mg/kg loading dose, then 6 mg/kg) every 3 weeks to complete 1 year of targeted therapy (either preoperative trastuzumab therapy or neratinib therapy).

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

Dosage and administration details:

4 cycles of paclitaxel 80 mg/m² on Days 1, 8, and 15 of a 28-day cycle.

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

Dosage and administration details:

Following trastuzumab/paclitaxel therapy, every 21 days for 4 cycles, at 200 mg/m²/week.

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

Dosage and administration details:

Following trastuzumab/paclitaxel therapy, every 21 days for 4 cycles, at 20 mg/m²/week.

Arm title	Neratinib
Arm description: Neratinib + Paclitaxel	
Arm type	Active comparator
Investigational medicinal product name	Neratinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Neratinib 240 mg orally once daily beginning on Day 1 of paclitaxel and continuing through Day 28 of the final cycle of paclitaxel. Following surgery, trastuzumab (8 mg/kg loading dose, then 6 mg/kg) every 3 weeks to complete 1 year of targeted therapy (either preoperative trastuzumab therapy or neratinib therapy).

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

Dosage and administration details:

4 cycles of paclitaxel 80 mg/m² on Days 1, 8, and 15 of a 28-day cycle.

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

Dosage and administration details:

Following neratinib/paclitaxel therapy, every 21 days for 4 cycles, at 200 mg/m²/week.

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

Dosage and administration details:

Following neratinib/paclitaxel therapy, every 21 days for 4 cycles, at 20 mg/m²/week.

Arm title	Neratinib + Trastuzumab
Arm description: Neratinib + Trastuzumab + Paclitaxel	
Arm type	Experimental
Investigational medicinal product name	Trastuzumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Trastuzumab concurrently with paclitaxel, weekly for a total of 16 doses (4 mg/kg loading dose, then 2 mg/kg weekly) and Neratinib 200 mg orally once daily beginning on Day 1 of paclitaxel and continuing

through Day 28 of the final cycle of paclitaxel. Following surgery, trastuzumab (8 mg/kg loading dose, then 6 mg/kg) every 3 weeks to complete 1 year of targeted therapy (either preoperative trastuzumab therapy or neratinib therapy).

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

Dosage and administration details:

Following paclitaxel/trastuzumab/neratinib therapy, every 21 days for 4 cycles, at 20 mg/m²/week.

Investigational medicinal product name	Neratinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Neratinib 200 mg orally once daily beginning on Day 1 of paclitaxel and continuing through Day 28 of the final cycle of paclitaxel. Following surgery, trastuzumab (8 mg/kg loading dose, then 6 mg/kg) every 3 weeks to complete 1 year of targeted therapy (either preoperative trastuzumab therapy or neratinib therapy).

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

Dosage and administration details:

Following paclitaxel/trastuzumab/neratinib therapy, every 21 days for 4 cycles, at 200 mg/m²/week.

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

Dosage and administration details:

4 cycles of paclitaxel 80 mg/m² on days 1, 8, and 15 of a 28 day cycle.

Arm title	Neratinib + Trastuzumab NR
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Arm description:

Neratinib + Trastuzumab + Paclitaxel non randomized group

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:

Neratinib 200 mg orally once daily beginning on Day 1 of paclitaxel and continuing through Day 28 of the final cycle of paclitaxel. Following surgery, trastuzumab (8 mg/kg loading dose, then 6 mg/kg) every 3 weeks to complete 1 year of targeted therapy (either preoperative trastuzumab therapy or neratinib therapy).

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

Dosage and administration details:	
4 cycles of paclitaxel 80 mg/m ² on Days 1, 8, and 15 of a 28-day cycle.	
Investigational medicinal product name	Adriamycin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use
Dosage and administration details:	
Following paclitaxel/trastuzumab/neratinib therapy, every 21 days for 4 cycles, at 20 mg/m ² /week.	
Investigational medicinal product name	Cyclophosphamide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use
Dosage and administration details:	
Following paclitaxel/trastuzumab/neratinib therapy, every 21 days for 4 cycles, at 200 mg/m ² /week.	
Investigational medicinal product name	Trastuzumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use
Dosage and administration details:	
Trastuzumab concurrently with paclitaxel, weekly for a total of 16 doses (4 mg/kg loading dose, then 2 mg/kg weekly) and Neratinib 200 mg orally once daily beginning on Day 1 of paclitaxel and continuing through Day 28 of the final cycle of paclitaxel. Following surgery, trastuzumab (8 mg/kg loading dose, then 6 mg/kg) every 3 weeks to complete 1 year of targeted therapy (either preoperative trastuzumab therapy or neratinib therapy).	

Number of subjects in period 1	Trastuzumab	Neratinib	Neratinib + Trastuzumab
Started	43	43	43
Completed	37	37	35
Not completed	6	6	8
Consent withdrawn by subject	2	4	6
Physician decision	1	-	1
Subject Noncompliant	1	-	-
Adverse event, non-fatal	-	-	1
Lost to follow-up	2	1	-
Lack of efficacy	-	1	-

Number of subjects in period 1	Neratinib + Trastuzumab NR
Started	12
Completed	11
Not completed	1
Consent withdrawn by subject	-
Physician decision	1

Subject Noncompliant	-
Adverse event, non-fatal	-
Lost to follow-up	-
Lack of efficacy	-

Baseline characteristics

Reporting groups

Reporting group title	Trastuzumab
Reporting group description: Trastuzumab + Paclitaxel	
Reporting group title	Neratinib
Reporting group description: Neratinib + Paclitaxel	
Reporting group title	Neratinib + Trastuzumab
Reporting group description: Neratinib + Trastuzumab + Paclitaxel	
Reporting group title	Neratinib + Trastuzumab NR
Reporting group description: Neratinib + Trastuzumab + Paclitaxel non randomized group	

Reporting group values	Trastuzumab	Neratinib	Neratinib + Trastuzumab
Number of subjects	43	43	43
Age categorical Units: Subjects			
Adults (18-64 years)	41	36	35
From 65-84 years	2	7	8
Age Continuous Units: years			
arithmetic mean	50.5	54.2	50.8
standard deviation	± 9.8	± 10.1	± 12.5
Gender categorical Units: Subjects			
Female	43	43	43
Male	0	0	0

Reporting group values	Neratinib + Trastuzumab NR	Total	
Number of subjects	12	141	
Age categorical Units: Subjects			
Adults (18-64 years)	11	123	
From 65-84 years	1	18	
Age Continuous Units: years			
arithmetic mean	48.6	-	
standard deviation	± 11.9		
Gender categorical Units: Subjects			
Female	12	141	
Male	0	0	

End points

End points reporting groups

Reporting group title	Trastuzumab
Reporting group description: Trastuzumab + Paclitaxel	
Reporting group title	Neratinib
Reporting group description: Neratinib + Paclitaxel	
Reporting group title	Neratinib + Trastuzumab
Reporting group description: Neratinib + Trastuzumab + Paclitaxel	
Reporting group title	Neratinib + Trastuzumab NR
Reporting group description: Neratinib + Trastuzumab + Paclitaxel non randomized group	

Primary: Pathologic Complete Response in breast and nodes

End point title	Pathologic Complete Response in breast and nodes
End point description: Pathologic Complete Response in breast and axillary lymph nodes. As measured by no histologic evidence of invasive tumor cells in the surgical breast specimen, axillary nodes after neoadjuvant chemotherapy [Time Frame: At time of surgery]	
End point type	Primary
End point timeframe: From randomization to disease progression or death	

End point values	Trastuzumab	Neratinib	Neratinib + Trastuzumab	Neratinib + Trastuzumab NR
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	42	42	42	12
Units: Percentage of patients				
number (confidence interval 95%)	38.1 (23.57 to 54.36)	33.33 (19.57 to 49.55)	50 (34.19 to 65.81)	41.67 (15.17 to 72.33)

Statistical analyses

Statistical analysis title	Stratified CMH Test
Comparison groups	Trastuzumab v Neratinib

Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	other ^[1]
P-value	= 0.6266
Method	Cochran-Mantel-Haenszel

Notes:

[1] - Descriptive.

Statistical analysis title	Stratified CMH Test
Comparison groups	Trastuzumab v Neratinib + Trastuzumab
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	other ^[2]
P-value	= 0.2198
Method	Cochran-Mantel-Haenszel

Notes:

[2] - Descriptive

Statistical analysis title	Stratified CMH Test
Comparison groups	Neratinib v Neratinib + Trastuzumab
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	other ^[3]
P-value	= 0.2416
Method	Cochran-Mantel-Haenszel

Notes:

[3] - Descriptive

Secondary: Pathologic Complete Response in breast

End point title	Pathologic Complete Response in breast
End point description: Pathologic complete response in breast. As measured by no histologic evidence of invasive tumor cells in the surgical breast specimen.	
End point type	Secondary
End point timeframe: Time Frame: At time of surgery	

End point values	Trastuzumab	Neratinib	Neratinib + Trastuzumab	Neratinib + Trastuzumab NR
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	42	42	42	12
Units: Percent of Patients				
number (confidence interval 95%)	50 (34.19 to 65.81)	38.1 (23.57 to 54.36)	52.38 (36.42 to 68)	50 (21.09 to 78.91)

Statistical analyses

No statistical analyses for this end point

Secondary: Recurrence-free Interval

End point title	Recurrence-free Interval
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End point description:

24-month Kaplan-Meier estimate of time to first disease recurrence.

End point type	Secondary
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End point timeframe:

From time of randomization to 24 months

End point values	Trastuzumab	Neratinib	Neratinib + Trastuzumab	Neratinib + Trastuzumab NR
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	42	42	42	12
Units: 24-month RFI				
number (confidence interval 95%)	100 (100 to 100)	91.7 (76.5 to 97.3)	93.6 (76.6 to 98.4)	100 (100 to 100)

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival

End point title	Overall Survival
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End point description:

24 month Kaplan-Meier estimate of overall survival.

End point type	Secondary
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End point timeframe:

From randomization to time of death, censored at 24 months.

End point values	Trastuzumab	Neratinib	Neratinib + Trastuzumab	Neratinib + Trastuzumab NR
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	42	42	42	12
Units: Rate				
number (confidence interval 95%)	100 (100 to 100)	100 (100 to 100)	100 (100 to 100)	100 (100 to 100)

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Complete Response

End point title	Clinical Complete Response
End point description: As measured by physical exam; resolution of all target and non-target lesions identified at baseline and no new lesions or other signs of disease progression, for subjects with palpable disease at baseline.	
End point type	Secondary
End point timeframe: At completion of paclitaxel therapy	

End point values	Trastuzumab	Neratinib	Neratinib + Trastuzumab	Neratinib + Trastuzumab NR
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	38	35	38	10
Units: Percentage of participants				
number (confidence interval 95%)	55.26 (38.3 to 71.38)	60 (42.11 to 76.13)	57.89 (40.82 to 73.69)	20 (2.52 to 55.61)

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Complete Response

End point title	Clinical Complete Response
End point description: As measured by physical exam; resolution of all target and non-target lesions identified at baseline and no new lesions or other signs of disease progression.	
End point type	Secondary
End point timeframe: At the completion of AC	

End point values	Trastuzumab	Neratinib	Neratinib + Trastuzumab	Neratinib + Trastuzumab NR
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	38	35	38	10
Units: Percentage of participants				
number (confidence interval 95%)	65.79 (48.65 to 80.37)	71.43 (53.7 to 85.36)	73.68 (56.9 to 86.6)	60 (26.24 to 87.84)

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
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	17.0
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Reporting groups

Reporting group title	Trastuzumab
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Reporting group description:

Trastuzumab

Reporting group title	Neratinib + Trastuzumab
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Reporting group description:

Neratinib + Trastuzumab

Reporting group title	Neratinib + Trastuzumab NR
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Reporting group description:

Neratinib + Trastuzumab NR

Reporting group title	Neratinib
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Reporting group description:

Neratinib

Serious adverse events	Trastuzumab	Neratinib + Trastuzumab	Neratinib + Trastuzumab NR
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 42 (16.67%)	10 / 42 (23.81%)	2 / 12 (16.67%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Radiation skin injury			
subjects affected / exposed	1 / 42 (2.38%)	0 / 42 (0.00%)	0 / 12 (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
Vascular disorders			
Embolism			
subjects affected / exposed	2 / 42 (4.76%)	1 / 42 (2.38%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematoma			

subjects affected / exposed	0 / 42 (0.00%)	1 / 42 (2.38%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Arrhythmia supraventricular			
subjects affected / exposed	0 / 42 (0.00%)	0 / 42 (0.00%)	0 / 12 (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 valve disease			
subjects affected / exposed	1 / 42 (2.38%)	0 / 42 (0.00%)	0 / 12 (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
Left ventricular dysfunction			
subjects affected / exposed	1 / 42 (2.38%)	0 / 42 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Syncope			
subjects affected / exposed	0 / 42 (0.00%)	0 / 42 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	1 / 42 (2.38%)	1 / 42 (2.38%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 42 (0.00%)	1 / 42 (2.38%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza like illness			

subjects affected / exposed	1 / 42 (2.38%)	0 / 42 (0.00%)	0 / 12 (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
Oedema peripheral			
subjects affected / exposed	1 / 42 (2.38%)	0 / 42 (0.00%)	0 / 12 (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
Pyrexia			
subjects affected / exposed	0 / 42 (0.00%)	1 / 42 (2.38%)	0 / 12 (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
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 42 (2.38%)	0 / 42 (0.00%)	0 / 12 (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
Colitis			
subjects affected / exposed	0 / 42 (0.00%)	1 / 42 (2.38%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	0 / 42 (0.00%)	2 / 42 (4.76%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	0 / 42 (0.00%)	1 / 42 (2.38%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 42 (0.00%)	1 / 42 (2.38%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			

Cholecystitis			
subjects affected / exposed	0 / 42 (0.00%)	0 / 42 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 42 (2.38%)	0 / 42 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 42 (0.00%)	0 / 42 (0.00%)	0 / 12 (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
Depression			
subjects affected / exposed	0 / 42 (0.00%)	0 / 42 (0.00%)	0 / 12 (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
Infections and infestations			
Bacteraemia			
subjects affected / exposed	0 / 42 (0.00%)	0 / 42 (0.00%)	0 / 12 (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
Cellulitis			
subjects affected / exposed	1 / 42 (2.38%)	0 / 42 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cystitis			
subjects affected / exposed	0 / 42 (0.00%)	0 / 42 (0.00%)	0 / 12 (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
Device related infection			

subjects affected / exposed	0 / 42 (0.00%)	0 / 42 (0.00%)	0 / 12 (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
Erysipelas			
subjects affected / exposed	0 / 42 (0.00%)	1 / 42 (2.38%)	0 / 12 (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
Infection			
subjects affected / exposed	1 / 42 (2.38%)	1 / 42 (2.38%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenic infection			
subjects affected / exposed	1 / 42 (2.38%)	0 / 42 (0.00%)	0 / 12 (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
Osteomyelitis			
subjects affected / exposed	1 / 42 (2.38%)	0 / 42 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	0 / 42 (0.00%)	1 / 42 (2.38%)	0 / 12 (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
Hyponatraemia			
subjects affected / exposed	0 / 42 (0.00%)	1 / 42 (2.38%)	0 / 12 (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

Serious adverse events	Neratinib		
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 42 (16.67%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

Injury, poisoning and procedural complications			
Radiation skin injury			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Embolism			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Haematoma			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Arrhythmia supraventricular			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac valve disease			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Left ventricular dysfunction			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Syncope			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Febrile neutropenia			

subjects affected / exposed	0 / 42 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Influenza like illness			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Oedema peripheral			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pyrexia			
subjects affected / exposed	2 / 42 (4.76%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Colitis			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Nausea			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Depression			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Bacteraemia			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Cellulitis			

subjects affected / exposed	0 / 42 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cystitis			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Device related infection			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Erysipelas			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infection			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Neutropenic infection			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Osteomyelitis			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hyponatraemia			

subjects affected / exposed	0 / 42 (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	Trastuzumab	Neratinib + Trastuzumab	Neratinib + Trastuzumab NR
Total subjects affected by non-serious adverse events			
subjects affected / exposed	41 / 42 (97.62%)	42 / 42 (100.00%)	12 / 12 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour pain			
subjects affected / exposed	0 / 42 (0.00%)	0 / 42 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Vascular disorders			
Embolism			
subjects affected / exposed	0 / 42 (0.00%)	1 / 42 (2.38%)	1 / 12 (8.33%)
occurrences (all)	0	1	1
Hypertension			
subjects affected / exposed	7 / 42 (16.67%)	2 / 42 (4.76%)	0 / 12 (0.00%)
occurrences (all)	9	2	0
Hypotension			
subjects affected / exposed	0 / 42 (0.00%)	0 / 42 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	9 / 42 (21.43%)	10 / 42 (23.81%)	0 / 12 (0.00%)
occurrences (all)	15	18	0
Catheter site pain			
subjects affected / exposed	1 / 42 (2.38%)	1 / 42 (2.38%)	2 / 12 (16.67%)
occurrences (all)	1	1	2
Chest pain			
subjects affected / exposed	0 / 42 (0.00%)	3 / 42 (7.14%)	1 / 12 (8.33%)
occurrences (all)	0	3	1
Chills			

subjects affected / exposed	0 / 42 (0.00%)	1 / 42 (2.38%)	1 / 12 (8.33%)
occurrences (all)	0	1	2
Early satiety			
subjects affected / exposed	0 / 42 (0.00%)	0 / 42 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Fatigue			
subjects affected / exposed	18 / 42 (42.86%)	18 / 42 (42.86%)	8 / 12 (66.67%)
occurrences (all)	18	23	18
Mucosal inflammation			
subjects affected / exposed	7 / 42 (16.67%)	8 / 42 (19.05%)	1 / 12 (8.33%)
occurrences (all)	9	12	1
Oedema peripheral			
subjects affected / exposed	2 / 42 (4.76%)	3 / 42 (7.14%)	2 / 12 (16.67%)
occurrences (all)	2	6	2
Pain			
subjects affected / exposed	4 / 42 (9.52%)	5 / 42 (11.90%)	2 / 12 (16.67%)
occurrences (all)	5	6	2
Pyrexia			
subjects affected / exposed	1 / 42 (2.38%)	6 / 42 (14.29%)	3 / 12 (25.00%)
occurrences (all)	2	7	4
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	2 / 42 (4.76%)	6 / 42 (14.29%)	1 / 12 (8.33%)
occurrences (all)	4	7	3
Reproductive system and breast disorders			
Breast pain			
subjects affected / exposed	3 / 42 (7.14%)	2 / 42 (4.76%)	0 / 12 (0.00%)
occurrences (all)	3	2	0
Pelvic pain			
subjects affected / exposed	0 / 42 (0.00%)	0 / 42 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			
Atelectasis			
subjects affected / exposed	0 / 42 (0.00%)	0 / 42 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Cough			

subjects affected / exposed occurrences (all)	8 / 42 (19.05%) 9	6 / 42 (14.29%) 6	0 / 12 (0.00%) 0
Dyspnoea subjects affected / exposed occurrences (all)	6 / 42 (14.29%) 8	2 / 42 (4.76%) 2	0 / 12 (0.00%) 0
Epistaxis subjects affected / exposed occurrences (all)	8 / 42 (19.05%) 8	7 / 42 (16.67%) 8	1 / 12 (8.33%) 1
Oropharyngeal pain subjects affected / exposed occurrences (all)	1 / 42 (2.38%) 1	3 / 42 (7.14%) 3	0 / 12 (0.00%) 0
Rhinorrhoea subjects affected / exposed occurrences (all)	3 / 42 (7.14%) 3	1 / 42 (2.38%) 1	0 / 12 (0.00%) 0
Psychiatric disorders Anxiety subjects affected / exposed occurrences (all)	4 / 42 (9.52%) 4	4 / 42 (9.52%) 4	0 / 12 (0.00%) 0
Insomnia subjects affected / exposed occurrences (all)	8 / 42 (19.05%) 9	3 / 42 (7.14%) 3	3 / 12 (25.00%) 3
Mood altered subjects affected / exposed occurrences (all)	3 / 42 (7.14%) 3	1 / 42 (2.38%) 1	0 / 12 (0.00%) 0
Investigations Alanine aminotransferase subjects affected / exposed occurrences (all)	2 / 42 (4.76%) 2	3 / 42 (7.14%) 7	1 / 12 (8.33%) 1
Alanine aminotransferase increased subjects affected / exposed occurrences (all)	7 / 42 (16.67%) 13	17 / 42 (40.48%) 26	7 / 12 (58.33%) 12
Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	6 / 42 (14.29%) 14	14 / 42 (33.33%) 16	8 / 12 (66.67%) 12
Blood alkaline phosphatase			

subjects affected / exposed	1 / 42 (2.38%)	0 / 42 (0.00%)	2 / 12 (16.67%)
occurrences (all)	1	0	2
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 42 (0.00%)	3 / 42 (7.14%)	0 / 12 (0.00%)
occurrences (all)	0	4	0
Blood bilirubin increased			
subjects affected / exposed	0 / 42 (0.00%)	0 / 42 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Blood creatinine increased			
subjects affected / exposed	0 / 42 (0.00%)	4 / 42 (9.52%)	0 / 12 (0.00%)
occurrences (all)	0	5	0
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 42 (0.00%)	4 / 42 (9.52%)	0 / 12 (0.00%)
occurrences (all)	0	8	0
Haemoglobin			
subjects affected / exposed	2 / 42 (4.76%)	2 / 42 (4.76%)	2 / 12 (16.67%)
occurrences (all)	3	3	5
Neutrophil count			
subjects affected / exposed	5 / 42 (11.90%)	1 / 42 (2.38%)	0 / 12 (0.00%)
occurrences (all)	5	2	0
Weight decreased			
subjects affected / exposed	2 / 42 (4.76%)	4 / 42 (9.52%)	3 / 12 (25.00%)
occurrences (all)	2	4	3
White blood cell count			
subjects affected / exposed	5 / 42 (11.90%)	1 / 42 (2.38%)	1 / 12 (8.33%)
occurrences (all)	5	2	3
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	0 / 42 (0.00%)	1 / 42 (2.38%)	1 / 12 (8.33%)
occurrences (all)	0	1	2
Cardiac disorders			
Tachycardia			
subjects affected / exposed	1 / 42 (2.38%)	0 / 42 (0.00%)	1 / 12 (8.33%)
occurrences (all)	1	0	2
Nervous system disorders			

Dizziness			
subjects affected / exposed	4 / 42 (9.52%)	6 / 42 (14.29%)	4 / 12 (33.33%)
occurrences (all)	4	7	5
Dysgeusia			
subjects affected / exposed	3 / 42 (7.14%)	7 / 42 (16.67%)	3 / 12 (25.00%)
occurrences (all)	3	8	3
Dyskinesia			
subjects affected / exposed	1 / 42 (2.38%)	0 / 42 (0.00%)	1 / 12 (8.33%)
occurrences (all)	1	0	1
Headache			
subjects affected / exposed	10 / 42 (23.81%)	7 / 42 (16.67%)	4 / 12 (33.33%)
occurrences (all)	10	7	5
Hypoaesthesia			
subjects affected / exposed	0 / 42 (0.00%)	4 / 42 (9.52%)	1 / 12 (8.33%)
occurrences (all)	0	4	1
Neuropathy peripheral			
subjects affected / exposed	6 / 42 (14.29%)	3 / 42 (7.14%)	0 / 12 (0.00%)
occurrences (all)	6	3	0
Neurotoxicity			
subjects affected / exposed	2 / 42 (4.76%)	3 / 42 (7.14%)	0 / 12 (0.00%)
occurrences (all)	2	3	0
Paraesthesia			
subjects affected / exposed	4 / 42 (9.52%)	5 / 42 (11.90%)	1 / 12 (8.33%)
occurrences (all)	5	7	1
Peripheral sensory neuropathy			
subjects affected / exposed	8 / 42 (19.05%)	4 / 42 (9.52%)	3 / 12 (25.00%)
occurrences (all)	9	7	3
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	9 / 42 (21.43%)	8 / 42 (19.05%)	2 / 12 (16.67%)
occurrences (all)	19	12	3
Leukopenia			
subjects affected / exposed	5 / 42 (11.90%)	2 / 42 (4.76%)	0 / 12 (0.00%)
occurrences (all)	6	3	0
Neutropenia			

subjects affected / exposed occurrences (all)	13 / 42 (30.95%) 21	8 / 42 (19.05%) 12	3 / 12 (25.00%) 6
Ear and labyrinth disorders Tinnitus subjects affected / exposed occurrences (all)	2 / 42 (4.76%) 2	1 / 42 (2.38%) 1	1 / 12 (8.33%) 1
Eye disorders Conjunctivitis subjects affected / exposed occurrences (all) Photopsia subjects affected / exposed occurrences (all) Vision blurred subjects affected / exposed occurrences (all)	0 / 42 (0.00%) 0 0 / 42 (0.00%) 0 3 / 42 (7.14%) 3	3 / 42 (7.14%) 3 0 / 42 (0.00%) 0 1 / 42 (2.38%) 1	0 / 12 (0.00%) 0 1 / 12 (8.33%) 1 1 / 12 (8.33%) 1
Gastrointestinal disorders Abdominal distension subjects affected / exposed occurrences (all) Abdominal pain subjects affected / exposed occurrences (all) Abdominal pain upper subjects affected / exposed occurrences (all) Constipation subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Dry mouth subjects affected / exposed occurrences (all) Dyspepsia	0 / 42 (0.00%) 0 3 / 42 (7.14%) 3 3 / 42 (7.14%) 3 6 / 42 (14.29%) 7 16 / 42 (38.10%) 18 0 / 42 (0.00%) 0	2 / 42 (4.76%) 3 4 / 42 (9.52%) 6 3 / 42 (7.14%) 3 11 / 42 (26.19%) 14 41 / 42 (97.62%) 157 3 / 42 (7.14%) 3	2 / 12 (16.67%) 3 3 / 12 (25.00%) 5 2 / 12 (16.67%) 2 7 / 12 (58.33%) 8 12 / 12 (100.00%) 53 1 / 12 (8.33%) 1

subjects affected / exposed	9 / 42 (21.43%)	6 / 42 (14.29%)	2 / 12 (16.67%)
occurrences (all)	11	6	3
Dysphagia			
subjects affected / exposed	0 / 42 (0.00%)	2 / 42 (4.76%)	1 / 12 (8.33%)
occurrences (all)	0	2	1
Flatulence			
subjects affected / exposed	1 / 42 (2.38%)	1 / 42 (2.38%)	1 / 12 (8.33%)
occurrences (all)	1	1	1
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 42 (2.38%)	1 / 42 (2.38%)	1 / 12 (8.33%)
occurrences (all)	1	1	1
Haemorrhoids			
subjects affected / exposed	1 / 42 (2.38%)	4 / 42 (9.52%)	0 / 12 (0.00%)
occurrences (all)	1	4	0
Nausea			
subjects affected / exposed	12 / 42 (28.57%)	20 / 42 (47.62%)	8 / 12 (66.67%)
occurrences (all)	13	30	10
Oesophagitis			
subjects affected / exposed	0 / 42 (0.00%)	0 / 42 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Oral pain			
subjects affected / exposed	2 / 42 (4.76%)	1 / 42 (2.38%)	1 / 12 (8.33%)
occurrences (all)	3	3	2
Rectal haemorrhage			
subjects affected / exposed	0 / 42 (0.00%)	0 / 42 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Stomatitis			
subjects affected / exposed	2 / 42 (4.76%)	7 / 42 (16.67%)	1 / 12 (8.33%)
occurrences (all)	3	7	1
Vomiting			
subjects affected / exposed	7 / 42 (16.67%)	13 / 42 (30.95%)	6 / 12 (50.00%)
occurrences (all)	7	19	8
Hepatobiliary disorders			
Hyperbilirubinaemia			
subjects affected / exposed	1 / 42 (2.38%)	0 / 42 (0.00%)	2 / 12 (16.67%)
occurrences (all)	1	0	4

Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	4 / 42 (9.52%)	1 / 42 (2.38%)	0 / 12 (0.00%)
occurrences (all)	11	1	0
Alopecia			
subjects affected / exposed	20 / 42 (47.62%)	15 / 42 (35.71%)	6 / 12 (50.00%)
occurrences (all)	28	16	9
Dermatitis acneiform			
subjects affected / exposed	0 / 42 (0.00%)	2 / 42 (4.76%)	1 / 12 (8.33%)
occurrences (all)	0	2	2
Dry skin			
subjects affected / exposed	0 / 42 (0.00%)	2 / 42 (4.76%)	3 / 12 (25.00%)
occurrences (all)	0	2	4
Erythema			
subjects affected / exposed	0 / 42 (0.00%)	2 / 42 (4.76%)	1 / 12 (8.33%)
occurrences (all)	0	2	1
Nail disorder			
subjects affected / exposed	3 / 42 (7.14%)	3 / 42 (7.14%)	0 / 12 (0.00%)
occurrences (all)	3	3	0
Pruritus			
subjects affected / exposed	5 / 42 (11.90%)	2 / 42 (4.76%)	1 / 12 (8.33%)
occurrences (all)	6	2	2
Rash			
subjects affected / exposed	9 / 42 (21.43%)	6 / 42 (14.29%)	5 / 12 (41.67%)
occurrences (all)	9	13	5
Rash generalised			
subjects affected / exposed	0 / 42 (0.00%)	0 / 42 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Skin disorder			
subjects affected / exposed	0 / 42 (0.00%)	0 / 42 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	2
Skin hyperpigmentation			
subjects affected / exposed	0 / 42 (0.00%)	1 / 42 (2.38%)	1 / 12 (8.33%)
occurrences (all)	0	1	1
Renal and urinary disorders			

Dysuria			
subjects affected / exposed	2 / 42 (4.76%)	1 / 42 (2.38%)	0 / 12 (0.00%)
occurrences (all)	2	1	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	6 / 42 (14.29%)	3 / 42 (7.14%)	0 / 12 (0.00%)
occurrences (all)	7	3	0
Back pain			
subjects affected / exposed	0 / 42 (0.00%)	4 / 42 (9.52%)	0 / 12 (0.00%)
occurrences (all)	0	4	0
Bone pain			
subjects affected / exposed	3 / 42 (7.14%)	0 / 42 (0.00%)	1 / 12 (8.33%)
occurrences (all)	3	0	1
Flank pain			
subjects affected / exposed	0 / 42 (0.00%)	0 / 42 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Muscle tightness			
subjects affected / exposed	0 / 42 (0.00%)	0 / 42 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Muscular weakness			
subjects affected / exposed	1 / 42 (2.38%)	1 / 42 (2.38%)	0 / 12 (0.00%)
occurrences (all)	1	1	0
Musculoskeletal chest pain			
subjects affected / exposed	1 / 42 (2.38%)	0 / 42 (0.00%)	1 / 12 (8.33%)
occurrences (all)	3	0	1
Musculoskeletal pain			
subjects affected / exposed	5 / 42 (11.90%)	3 / 42 (7.14%)	0 / 12 (0.00%)
occurrences (all)	5	3	0
Myalgia			
subjects affected / exposed	4 / 42 (9.52%)	2 / 42 (4.76%)	1 / 12 (8.33%)
occurrences (all)	4	4	1
Pain in jaw			
subjects affected / exposed	0 / 42 (0.00%)	0 / 42 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Infections and infestations			

Folliculitis			
subjects affected / exposed	3 / 42 (7.14%)	0 / 42 (0.00%)	0 / 12 (0.00%)
occurrences (all)	11	0	0
Infection			
subjects affected / exposed	5 / 42 (11.90%)	2 / 42 (4.76%)	0 / 12 (0.00%)
occurrences (all)	5	5	0
Influenza			
subjects affected / exposed	2 / 42 (4.76%)	3 / 42 (7.14%)	0 / 12 (0.00%)
occurrences (all)	2	3	0
Localised infection			
subjects affected / exposed	0 / 42 (0.00%)	1 / 42 (2.38%)	1 / 12 (8.33%)
occurrences (all)	0	1	1
Nasopharyngitis			
subjects affected / exposed	3 / 42 (7.14%)	2 / 42 (4.76%)	1 / 12 (8.33%)
occurrences (all)	3	3	1
Rhinitis			
subjects affected / exposed	0 / 42 (0.00%)	0 / 42 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Urinary tract infection			
subjects affected / exposed	4 / 42 (9.52%)	0 / 42 (0.00%)	0 / 12 (0.00%)
occurrences (all)	4	0	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	2 / 42 (4.76%)	11 / 42 (26.19%)	2 / 12 (16.67%)
occurrences (all)	2	12	4
Dehydration			
subjects affected / exposed	2 / 42 (4.76%)	1 / 42 (2.38%)	1 / 12 (8.33%)
occurrences (all)	2	1	1
Hyperglycaemia			
subjects affected / exposed	4 / 42 (9.52%)	3 / 42 (7.14%)	0 / 12 (0.00%)
occurrences (all)	4	5	0
Hypocalcaemia			
subjects affected / exposed	1 / 42 (2.38%)	4 / 42 (9.52%)	0 / 12 (0.00%)
occurrences (all)	1	4	0
Hypokalaemia			

subjects affected / exposed	1 / 42 (2.38%)	6 / 42 (14.29%)	6 / 12 (50.00%)
occurrences (all)	1	6	11
Hypomagnesaemia			
subjects affected / exposed	0 / 42 (0.00%)	3 / 42 (7.14%)	0 / 12 (0.00%)
occurrences (all)	0	5	0
Hyponatraemia			
subjects affected / exposed	1 / 42 (2.38%)	4 / 42 (9.52%)	1 / 12 (8.33%)
occurrences (all)	1	4	1

Non-serious adverse events	Neratinib		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	42 / 42 (100.00%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour pain			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences (all)	0		
Vascular disorders			
Embolism			
subjects affected / exposed	4 / 42 (9.52%)		
occurrences (all)	4		
Hypertension			
subjects affected / exposed	8 / 42 (19.05%)		
occurrences (all)	9		
Hypotension			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	7 / 42 (16.67%)		
occurrences (all)	24		
Catheter site pain			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Chest pain			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences (all)	0		

Chills			
subjects affected / exposed	2 / 42 (4.76%)		
occurrences (all)	2		
Early satiety			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences (all)	0		
Fatigue			
subjects affected / exposed	22 / 42 (52.38%)		
occurrences (all)	31		
Mucosal inflammation			
subjects affected / exposed	3 / 42 (7.14%)		
occurrences (all)	4		
Oedema peripheral			
subjects affected / exposed	5 / 42 (11.90%)		
occurrences (all)	9		
Pain			
subjects affected / exposed	9 / 42 (21.43%)		
occurrences (all)	13		
Pyrexia			
subjects affected / exposed	6 / 42 (14.29%)		
occurrences (all)	6		
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	5 / 42 (11.90%)		
occurrences (all)	6		
Reproductive system and breast disorders			
Breast pain			
subjects affected / exposed	4 / 42 (9.52%)		
occurrences (all)	4		
Pelvic pain			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences (all)	0		
Respiratory, thoracic and mediastinal disorders			
Atelectasis			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences (all)	0		

Cough subjects affected / exposed occurrences (all)	4 / 42 (9.52%) 5		
Dyspnoea subjects affected / exposed occurrences (all)	4 / 42 (9.52%) 4		
Epistaxis subjects affected / exposed occurrences (all)	8 / 42 (19.05%) 8		
Oropharyngeal pain subjects affected / exposed occurrences (all)	1 / 42 (2.38%) 1		
Rhinorrhoea subjects affected / exposed occurrences (all)	2 / 42 (4.76%) 2		
Psychiatric disorders Anxiety subjects affected / exposed occurrences (all)	5 / 42 (11.90%) 5		
Insomnia subjects affected / exposed occurrences (all)	6 / 42 (14.29%) 6		
Mood altered subjects affected / exposed occurrences (all)	4 / 42 (9.52%) 5		
Investigations Alanine aminotransferase subjects affected / exposed occurrences (all)	2 / 42 (4.76%) 2		
Alanine aminotransferase increased subjects affected / exposed occurrences (all)	16 / 42 (38.10%) 23		
Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	13 / 42 (30.95%) 16		
Blood alkaline phosphatase			

subjects affected / exposed	2 / 42 (4.76%)		
occurrences (all)	2		
Blood alkaline phosphatase increased			
subjects affected / exposed	2 / 42 (4.76%)		
occurrences (all)	2		
Blood bilirubin increased			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences (all)	0		
Blood creatinine increased			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Haemoglobin			
subjects affected / exposed	5 / 42 (11.90%)		
occurrences (all)	9		
Neutrophil count			
subjects affected / exposed	6 / 42 (14.29%)		
occurrences (all)	6		
Weight decreased			
subjects affected / exposed	6 / 42 (14.29%)		
occurrences (all)	6		
White blood cell count			
subjects affected / exposed	4 / 42 (9.52%)		
occurrences (all)	5		
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences (all)	0		
Cardiac disorders			
Tachycardia			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences (all)	0		
Nervous system disorders			

Dizziness			
subjects affected / exposed	5 / 42 (11.90%)		
occurrences (all)	5		
Dysgeusia			
subjects affected / exposed	8 / 42 (19.05%)		
occurrences (all)	8		
Dyskinesia			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences (all)	0		
Headache			
subjects affected / exposed	7 / 42 (16.67%)		
occurrences (all)	7		
Hypoaesthesia			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Neuropathy peripheral			
subjects affected / exposed	5 / 42 (11.90%)		
occurrences (all)	8		
Neurotoxicity			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Paraesthesia			
subjects affected / exposed	4 / 42 (9.52%)		
occurrences (all)	4		
Peripheral sensory neuropathy			
subjects affected / exposed	8 / 42 (19.05%)		
occurrences (all)	9		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	5 / 42 (11.90%)		
occurrences (all)	6		
Leukopenia			
subjects affected / exposed	6 / 42 (14.29%)		
occurrences (all)	12		
Neutropenia			

subjects affected / exposed occurrences (all)	9 / 42 (21.43%) 10		
Ear and labyrinth disorders Tinnitus subjects affected / exposed occurrences (all)	0 / 42 (0.00%) 0		
Eye disorders Conjunctivitis subjects affected / exposed occurrences (all) Photopsia subjects affected / exposed occurrences (all) Vision blurred subjects affected / exposed occurrences (all)	3 / 42 (7.14%) 3 0 / 42 (0.00%) 0 6 / 42 (14.29%) 7		
Gastrointestinal disorders Abdominal distension subjects affected / exposed occurrences (all) Abdominal pain subjects affected / exposed occurrences (all) Abdominal pain upper subjects affected / exposed occurrences (all) Constipation subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Dry mouth subjects affected / exposed occurrences (all) Dyspepsia	3 / 42 (7.14%) 3 3 / 42 (7.14%) 3 0 / 42 (0.00%) 0 12 / 42 (28.57%) 14 42 / 42 (100.00%) 136 3 / 42 (7.14%) 4		

subjects affected / exposed	13 / 42 (30.95%)		
occurrences (all)	15		
Dysphagia			
subjects affected / exposed	2 / 42 (4.76%)		
occurrences (all)	3		
Flatulence			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Haemorrhoids			
subjects affected / exposed	2 / 42 (4.76%)		
occurrences (all)	2		
Nausea			
subjects affected / exposed	25 / 42 (59.52%)		
occurrences (all)	39		
Oesophagitis			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences (all)	0		
Oral pain			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Rectal haemorrhage			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences (all)	0		
Stomatitis			
subjects affected / exposed	6 / 42 (14.29%)		
occurrences (all)	10		
Vomiting			
subjects affected / exposed	16 / 42 (38.10%)		
occurrences (all)	23		
Hepatobiliary disorders			
Hyperbilirubinaemia			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	2		

Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	4 / 42 (9.52%)		
occurrences (all)	8		
Alopecia			
subjects affected / exposed	22 / 42 (52.38%)		
occurrences (all)	30		
Dermatitis acneiform			
subjects affected / exposed	3 / 42 (7.14%)		
occurrences (all)	4		
Dry skin			
subjects affected / exposed	4 / 42 (9.52%)		
occurrences (all)	4		
Erythema			
subjects affected / exposed	2 / 42 (4.76%)		
occurrences (all)	2		
Nail disorder			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Pruritus			
subjects affected / exposed	4 / 42 (9.52%)		
occurrences (all)	5		
Rash			
subjects affected / exposed	9 / 42 (21.43%)		
occurrences (all)	14		
Rash generalised			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences (all)	0		
Skin disorder			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Skin hyperpigmentation			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences (all)	0		
Renal and urinary disorders			

Dysuria			
subjects affected / exposed	4 / 42 (9.52%)		
occurrences (all)	4		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 42 (4.76%)		
occurrences (all)	2		
Back pain			
subjects affected / exposed	3 / 42 (7.14%)		
occurrences (all)	4		
Bone pain			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences (all)	0		
Flank pain			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences (all)	0		
Muscle tightness			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences (all)	0		
Muscular weakness			
subjects affected / exposed	3 / 42 (7.14%)		
occurrences (all)	4		
Musculoskeletal chest pain			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Musculoskeletal pain			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences (all)	0		
Myalgia			
subjects affected / exposed	3 / 42 (7.14%)		
occurrences (all)	4		
Pain in jaw			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences (all)	0		
Infections and infestations			

Folliculitis			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Infection			
subjects affected / exposed	2 / 42 (4.76%)		
occurrences (all)	2		
Influenza			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences (all)	0		
Localised infection			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences (all)	0		
Nasopharyngitis			
subjects affected / exposed	2 / 42 (4.76%)		
occurrences (all)	2		
Rhinitis			
subjects affected / exposed	0 / 42 (0.00%)		
occurrences (all)	0		
Urinary tract infection			
subjects affected / exposed	3 / 42 (7.14%)		
occurrences (all)	3		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	11 / 42 (26.19%)		
occurrences (all)	14		
Dehydration			
subjects affected / exposed	3 / 42 (7.14%)		
occurrences (all)	4		
Hyperglycaemia			
subjects affected / exposed	8 / 42 (19.05%)		
occurrences (all)	8		
Hypocalcaemia			
subjects affected / exposed	5 / 42 (11.90%)		
occurrences (all)	5		
Hypokalaemia			

subjects affected / exposed	7 / 42 (16.67%)		
occurrences (all)	12		
Hypomagnesaemia			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences (all)	1		
Hyponatraemia			
subjects affected / exposed	6 / 42 (14.29%)		
occurrences (all)	6		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 June 2011	Amendment #1: Eligibility criteria regarding disease staging, documentation required from sites upon death of study subjects, and Appendix E were updated.
20 August 2012	Amendment #2: Pharmaceutical sponsorship changed from Wyeth Pharmaceuticals Inc., a Pfizer Company, to Puma Biotechnology, Inc. Third arm added, including neratinib, trastuzumab, and paclitaxel.
14 November 2012	Amendment #3: Informed consent updated.
04 January 2013	Amendment #4: Informed consent updated.
24 June 2013	Amendment #5: Protocol Chair updated.
12 July 2013	Amendment #6: Breast biopsy changed from required to optional in study procedures.
15 November 2013	Amendment #7 (EU Only): Study was expanded to European Union (EU), and Puma Biotechnology, Inc. added as Sponsor for EU region.
20 November 2013	Amendment #8 (US and Canada only): Arm 1 (paclitaxel plus trastuzumab) and Arm 2 (paclitaxel plus neratinib) closed to accrual in the United States (US). US patients previously randomized to Arm 1 or Arm 2 should continue to receive study treatment and follow-up as per protocol. Subsequent US patients were entered on Arm 3-NR (non-randomized) until completion of US accrual.
11 February 2014	Amendment #7.1 (France Only): Several inclusion/exclusion criteria were revised in order to be consistent with SmPc of trastuzumab and paclitaxel for patients undergoing treatment with these agents.
22 May 2014	Amendment 9: Accrual closed in the U.S.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/24077916>

