Clinical trial results:
A Randomized, Open-Label, Two-Arm Study of Neratinib Plus Paclitaxel Versus Trastuzumab Plus Paclitaxel as First-Line Treatment for Erbb2-Positive Locally Recurrent or Metastatic Breast Cancer

Summary

EudraCT number	2008-007803-10
Trial protocol	HU DE IT GB ES BE LV PT LT FR GR DK MT BG
Global end of trial date	28 June 2018

Results information

Result version number	v1 (current)
This version publication date	14 July 2019
First version publication date	14 July 2019

Trial information

Trial identification

Sponsor protocol code	3144A2-3005

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00915018
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	Senior Director, Clinical Operations, Puma Biotechnology, Inc., 4242486500 4242486500, clinicaltrials@pumabiotechnology.com
Scientific contact	Senior Director, Clinical Operations, 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	28 June 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	28 June 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the independently assessed progression-free survival following treatment with neratinib in combination with paclitaxel versus trastuzumab plus paclitaxel in subjects who have not received previous treatment for erbB-2-positive locally recurrent or metastatic breast cancer.

Protection of trial subjects:

This study was conducted in accordance with the ethical principles of the International Conference for Harmonisation (ICH), guideline for Good Clinical Practice (GCP), including the Declaration of Helsinki and the applicable laws and regulations. The PI or designee promptly submitted the protocol to the applicable IRB/EC, and obtained approval to begin study-related activities. All participants provided informed consent prior to the performance of any protocol procedures and before administration of investigational product.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	21 August 2009
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	Australia: 1
Country: Number of subjects enrolled	Belgium: 4
Country: Number of subjects enrolled	Bulgaria: 1
Country: Number of subjects enrolled	Belarus: 6
Country: Number of subjects enrolled	Canada: 3
Country: Number of subjects enrolled	Switzerland: 4
Country: Number of subjects enrolled	China: 41
Country: Number of subjects enrolled	Germany: 1
Country: Number of subjects enrolled	Spain: 23
Country: Number of subjects enrolled	France: 16
Country: Number of subjects enrolled	United Kingdom: 3
Country: Number of subjects enrolled	Hong Kong: 7
Country: Number of subjects enrolled	Croatia: 4
Country: Number of subjects enrolled	Hungary: 9
Country: Number of subjects enrolled	India: 57
Country: Number of subjects enrolled	Israel: 7
Country: Number of subjects enrolled	Italy: 5

Country: Number of subjects enrolled	Japan: 81
Country: Number of subjects enrolled	Korea, Republic of: 16
Country: Number of subjects enrolled	Lithuania: 7
Country: Number of subjects enrolled	Latvia: 5
Country: Number of subjects enrolled	Malta: 3
Country: Number of subjects enrolled	Malaysia: 5
Country: Number of subjects enrolled	Poland: 10
Country: Number of subjects enrolled	Portugal: 2
Country: Number of subjects enrolled	Romania: 4
Country: Number of subjects enrolled	Singapore: 15
Country: Number of subjects enrolled	Serbia: 8
Country: Number of subjects enrolled	Taiwan: 2
Country: Number of subjects enrolled	Ukraine: 54
Country: Number of subjects enrolled	United States: 37
Country: Number of subjects enrolled	South Africa: 34
Country: Number of subjects enrolled	Bahamas: 4
Worldwide total number of subjects	479
EEA total number of subjects	97

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)	392
From 65 to 84 years	87
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Participants had to meet all inclusion criteria and not meet any exclusion criteria to participate in this study. A signed and dated informed consent was required before any screen procedures were done.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Neratinib + Paclitaxel

Arm description:

Paclitaxel in combination with neratinib (arm A: experimental arm) until objective disease progression, symptomatic deterioration, intolerable toxicity, death, or withdrawal of consent.

Arm type	Experimental
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:

Paclitaxel will be administered IV (80 mg/m2) on days 1, 8, and 15 of a 28-day cycle. Subjects will receive paclitaxel treatment for at least 6 cycles. Additional cycles can be given at the investigator's discretion.
Treatment will be stopped in case of disease progression, symptomatic deterioration, unacceptable toxicity, death, or withdrawal of consent occurs.

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

Dosage and administration details:

The number of neratinib tablets taken will depend on the prescribed dose. Neratinib (240 mg initial dose, provided as 40 mg tablets) will be taken on a daily basis, starting with day 1, by mouth with food, preferably in the morning until disease progression, symptomatic deterioration, unacceptable toxicity, death, or withdrawal of consent occurs.

Arm title	Trastuzumab + Paclitaxel

Arm description:

Paclitaxel in combination with trastuzumab (arm B: control arm) until objective disease progression, symptomatic deterioration, intolerable toxicity, death, or withdrawal of consent.

Arm type	Active comparator
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 will be administered at an initial loading dose of 4 mg/kg as an approximately 90 minutes IV infusion followed by subsequent once weekly doses of 2 mg/kg as 30-90 minute IV infusions until disease progression, symptomatic deterioration, unacceptable toxicity, death, or withdrawal of consent occurs.

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:

Paclitaxel will be administered IV (80 mg/m2) on days 1, 8, and 15 of a 28-day cycle. Subjects will receive paclitaxel treatment for at least 6 cycles. Additional cycles can be given at the investigator's discretion. Treatment will be stopped in case of disease progression, symptomatic deterioration, unacceptable toxicity, death, or withdrawal of consent occurs.

Number of subjects in period 1	Neratinib + Paclitaxel	Trastuzumab + Paclitaxel
Started	242	237
Completed	0	0
Not completed	242	237
Consent withdrawn by subject	41	37
Physician decision	-	1
Disease progression	4	-
Death	76	70
Screen failure	-	2
Discontinuation of study by sponsor	111	122
Lost to follow-up	10	5

Baseline characteristics

Reporting groups	
Reporting group title	Neratinib + Paclitaxel
Reporting group description:	
Paclitaxel in combination with neratinib (arm A: experimental arm) until objective disease progression, symptomatic deterioration, intolerable toxicity, death, or withdrawal of consent.	
Reporting group title	Trastuzumab + Paclitaxel
Reporting group description:	
Paclitaxel in combination with trastuzumab (arm B: control arm) until objective disease progression, symptomatic deterioration, intolerable toxicity, death, or withdrawal of consent.	

Reporting group values	Neratinib + Paclitaxel	Trastuzumab + Paclitaxel	Total
Number of subjects	242	237	479
Age categorical Units: Subjects			
Adults (18-64 years)	199	193	392
From 65-84 years	43	44	87
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	242	237	479
Male	0	0	0

End points

End points reporting groups

Reporting group title	Neratinib + Paclitaxel
Reporting group description:	
Paclitaxel in combination with neratinib (arm A: experimental arm) until objective disease progression, symptomatic deterioration, intolerable toxicity, death, or withdrawal of consent.	
Reporting group title	Trastuzumab + Paclitaxel
Reporting group description:	
Paclitaxel in combination with trastuzumab (arm B: control arm) until objective disease progression, symptomatic deterioration, intolerable toxicity, death, or withdrawal of consent.	

Primary: Progression-Free Survival

End point title	Progression-Free Survival
End point description:	
The primary endpoint was PFS, defined as the interval from the date of randomization until the first date on which recurrence or progression, or death due to any cause, was documented, censored at the last assessable evaluation or at the initiation of new anticancer therapy.	
End point type	Primary
End point timeframe:	
From randomization date through recurrence, progression, or death due to any cause.	

End point values	Neratinib + Paclitaxel	Trastuzumab + Paclitaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	242	237		
Units: Months				
median (confidence interval 95%)	12.9 (11.1 to 14.9)	12.9 (11.1 to 14.8)		

Statistical analyses

Statistical analysis title	PFS
Comparison groups	Neratinib + Paclitaxel v Trastuzumab + Paclitaxel
Number of subjects included in analysis	479
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8934 [1]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.015

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.813
upper limit	1.269

Notes:

[1] - Log-rank test and Cox model are stratified by randomization stratification factors: prior adjuvant trastuzumab exposure, prior lapatinib exposure, ER/PgR status (positive or negative), and region.

Secondary: Objective Response Rate

End point title	Objective Response Rate

End point description:

Objective response rate (ORR) was defined as the proportion of patients who achieved confirmed CR or PR, per RECIST (v1.0) criteria, as their best overall response. The best overall response was the best response recorded from randomization until disease progression/recurrence (taking as reference for progressive disease (PD) the smallest measurements recorded since randomization).

End point type	Secondary

End point timeframe:

From date of randomization through last tumor assessment.

End point values	Neratinib + Paclitaxel	Trastuzumab + Paclitaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	242	237		
Units: Percentage				
number (confidence interval 95%)	74.8 (68.8 to 80.1)	77.6 (71.8 to 82.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response

End point title	Duration of Response

End point description:

For patients who had a confirmed response, the duration of response (DOR) was measured from the time at which measurement criteria were first met for confirmed CR or PR, until the date of first recurrence, PD, or death was objectively documented, taking as a reference for PD the smallest measurements recorded since enrollment.

End point type	Secondary

End point timeframe:

From the time at which measurement criteria were first met for confirmed CR or PR, until the date of first recurrence, PD, or death was objectively documented, taking as a reference for PD the smallest measurements recorded since enrollment.

End point values	Neratinib + Paclitaxel	Trastuzumab + Paclitaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	181	184		
Units: Months				
median (confidence interval 95%)	13.1 (11.1 to 15.4)	12.9 (11.0 to 15.1)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
1st dose through 28 days after last dose	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups	
Reporting group title	Trastuzumab + Paclitaxel
Reporting group description:	
Paclitaxel in combination with trastuzumab (arm B: control arm) until objective disease progression, symptomatic deterioration, intolerable toxicity, death, or withdrawal of consent.	
Reporting group title	Neratinib + Paclitaxel
Reporting group description:	
Paclitaxel in combination with neratinib (arm A: experimental arm) until objective disease progression, symptomatic deterioration, intolerable toxicity, death, or withdrawal of consent.	

Serious adverse events	Trastuzumab + Paclitaxel	Neratinib + Paclitaxel	
Total subjects affected by serious adverse events			
subjects affected / exposed	57 / 234 (24.36%)	67 / 240 (27.92%)	
number of deaths (all causes)	72	79	
number of deaths resulting from adverse events	7	8	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Benign ovarian tumour			
subjects affected / exposed	0 / 234 (0.00%)	1 / 240 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cancer pain			
subjects affected / exposed	1 / 234 (0.43%)	0 / 240 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric cancer			
subjects affected / exposed	0 / 234 (0.00%)	1 / 240 (0.42%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to central nervous system			

subjects affected / exposed	5 / 234 (2.14%)	2 / 240 (0.83%)	
occurrences causally related to treatment / all	0 / 5	0 / 2	
deaths causally related to treatment / all	0 / 2	0 / 1	
Metastases to meninges			
subjects affected / exposed	1 / 234 (0.43%)	0 / 240 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Ovarian epithelial cancer			
subjects affected / exposed	1 / 234 (0.43%)	0 / 240 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureteric cancer			
subjects affected / exposed	1 / 234 (0.43%)	0 / 240 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 234 (0.43%)	0 / 240 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	1 / 234 (0.43%)	0 / 240 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	0 / 234 (0.00%)	1 / 240 (0.42%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shock			
subjects affected / exposed	0 / 234 (0.00%)	1 / 240 (0.42%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
General disorders and administration site conditions			

Adhesion			
subjects affected / exposed	0 / 234 (0.00%)	1 / 240 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disease progression			
subjects affected / exposed	0 / 234 (0.00%)	3 / 240 (1.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 3	
Fatigue			
subjects affected / exposed	1 / 234 (0.43%)	1 / 240 (0.42%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Generalised oedema			
subjects affected / exposed	0 / 234 (0.00%)	1 / 240 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multi-organ failure			
subjects affected / exposed	1 / 234 (0.43%)	0 / 240 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Oedema peripheral			
subjects affected / exposed	1 / 234 (0.43%)	1 / 240 (0.42%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	5 / 234 (2.14%)	3 / 240 (1.25%)	
occurrences causally related to treatment / all	2 / 7	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden death			
subjects affected / exposed	1 / 234 (0.43%)	0 / 240 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Swelling			

subjects affected / exposed	1 / 234 (0.43%)	0 / 240 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Contrast media allergy			
subjects affected / exposed	1 / 234 (0.43%)	0 / 240 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug hypersensitivity			
subjects affected / exposed	1 / 234 (0.43%)	1 / 240 (0.42%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Food allergy			
subjects affected / exposed	0 / 234 (0.00%)	1 / 240 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Type IV hypersensitivity reaction			
subjects affected / exposed	0 / 234 (0.00%)	1 / 240 (0.42%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Menorrhagia			
subjects affected / exposed	0 / 234 (0.00%)	1 / 240 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine polyp			
subjects affected / exposed	1 / 234 (0.43%)	0 / 240 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			

subjects affected / exposed	2 / 234 (0.85%)	1 / 240 (0.42%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	2 / 234 (0.85%)	1 / 240 (0.42%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	1 / 234 (0.43%)	0 / 240 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	2 / 234 (0.85%)	0 / 240 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Pneumothorax			
subjects affected / exposed	0 / 234 (0.00%)	1 / 240 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	0 / 234 (0.00%)	2 / 240 (0.83%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	1 / 234 (0.43%)	0 / 240 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Psychiatric disorders			
Confusional state			
subjects affected / exposed	0 / 234 (0.00%)	4 / 240 (1.67%)	
occurrences causally related to treatment / all	0 / 0	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			

subjects affected / exposed	1 / 234 (0.43%)	0 / 240 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Schizophrenia			
subjects affected / exposed	1 / 234 (0.43%)	0 / 240 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Activated partial thromboplastin time prolonged			
subjects affected / exposed	0 / 234 (0.00%)	1 / 240 (0.42%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Alanine aminotransferase increased			
subjects affected / exposed	1 / 234 (0.43%)	1 / 240 (0.42%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 234 (0.43%)	1 / 240 (0.42%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical condition abnormal			
subjects affected / exposed	0 / 234 (0.00%)	1 / 240 (0.42%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Weight decreased			
subjects affected / exposed	0 / 234 (0.00%)	1 / 240 (0.42%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Accidental overdose			

subjects affected / exposed	3 / 234 (1.28%)	2 / 240 (0.83%)	
occurrences causally related to treatment / all	3 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ankle fracture			
subjects affected / exposed	0 / 234 (0.00%)	1 / 240 (0.42%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug administration error			
subjects affected / exposed	1 / 234 (0.43%)	0 / 240 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	0 / 234 (0.00%)	1 / 240 (0.42%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intentional overdose			
subjects affected / exposed	0 / 234 (0.00%)	1 / 240 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ligament sprain			
subjects affected / exposed	1 / 234 (0.43%)	0 / 240 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower limb fracture			
subjects affected / exposed	0 / 234 (0.00%)	1 / 240 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Overdose			
subjects affected / exposed	0 / 234 (0.00%)	2 / 240 (0.83%)	
occurrences causally related to treatment / all	0 / 0	4 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax traumatic			

subjects affected / exposed	1 / 234 (0.43%)	0 / 240 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural hypotension			
subjects affected / exposed	0 / 234 (0.00%)	1 / 240 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 234 (0.43%)	0 / 240 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	0 / 234 (0.00%)	2 / 240 (0.83%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac tamponade			
subjects affected / exposed	0 / 234 (0.00%)	1 / 240 (0.42%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardio-respiratory arrest			
subjects affected / exposed	0 / 234 (0.00%)	1 / 240 (0.42%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Left ventricular dysfunction			
subjects affected / exposed	1 / 234 (0.43%)	0 / 240 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	0 / 234 (0.00%)	1 / 240 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial effusion			

subjects affected / exposed	0 / 234 (0.00%)	1 / 240 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Brain oedema			
subjects affected / exposed	0 / 234 (0.00%)	1 / 240 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebellar ischaemia			
subjects affected / exposed	1 / 234 (0.43%)	0 / 240 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coma			
subjects affected / exposed	0 / 234 (0.00%)	1 / 240 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Headache			
subjects affected / exposed	0 / 234 (0.00%)	1 / 240 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal cord compression			
subjects affected / exposed	1 / 234 (0.43%)	0 / 240 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	0 / 234 (0.00%)	1 / 240 (0.42%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 234 (0.43%)	0 / 240 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			

subjects affected / exposed	0 / 234 (0.00%)	1 / 240 (0.42%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			
subjects affected / exposed	0 / 234 (0.00%)	2 / 240 (0.83%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	0 / 234 (0.00%)	1 / 240 (0.42%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	1 / 234 (0.43%)	0 / 240 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Cataract			
subjects affected / exposed	1 / 234 (0.43%)	0 / 240 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal degeneration			
subjects affected / exposed	0 / 234 (0.00%)	1 / 240 (0.42%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uveitis			
subjects affected / exposed	0 / 234 (0.00%)	1 / 240 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 234 (0.43%)	2 / 240 (0.83%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			

subjects affected / exposed	0 / 234 (0.00%)	1 / 240 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	0 / 234 (0.00%)	2 / 240 (0.83%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	1 / 1	
Dental caries			
subjects affected / exposed	1 / 234 (0.43%)	0 / 240 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	3 / 234 (1.28%)	12 / 240 (5.00%)	
occurrences causally related to treatment / all	0 / 6	17 / 17	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 234 (0.00%)	2 / 240 (0.83%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	1 / 234 (0.43%)	0 / 240 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	0 / 234 (0.00%)	1 / 240 (0.42%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Nausea			
subjects affected / exposed	1 / 234 (0.43%)	2 / 240 (0.83%)	
occurrences causally related to treatment / all	1 / 1	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			

subjects affected / exposed	0 / 234 (0.00%)	1 / 240 (0.42%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	0 / 234 (0.00%)	1 / 240 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Volvulus			
subjects affected / exposed	0 / 234 (0.00%)	1 / 240 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	1 / 234 (0.43%)	7 / 240 (2.92%)	
occurrences causally related to treatment / all	0 / 1	5 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Biliary colic			
subjects affected / exposed	0 / 234 (0.00%)	1 / 240 (0.42%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	1 / 234 (0.43%)	0 / 240 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic failure			
subjects affected / exposed	1 / 234 (0.43%)	2 / 240 (0.83%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hepatitis			
subjects affected / exposed	1 / 234 (0.43%)	0 / 240 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperbilirubinaemia			

subjects affected / exposed	1 / 234 (0.43%)	0 / 240 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Erythema			
subjects affected / exposed	1 / 234 (0.43%)	0 / 240 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Prerenal failure			
subjects affected / exposed	0 / 234 (0.00%)	1 / 240 (0.42%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure acute			
subjects affected / exposed	0 / 234 (0.00%)	1 / 240 (0.42%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 234 (0.43%)	0 / 240 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal chest pain			
subjects affected / exposed	1 / 234 (0.43%)	1 / 240 (0.42%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	1 / 234 (0.43%)	0 / 240 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rheumatoid arthritis			
subjects affected / exposed	0 / 234 (0.00%)	1 / 240 (0.42%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 234 (0.43%)	0 / 240 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Candida infection			
subjects affected / exposed	0 / 234 (0.00%)	1 / 240 (0.42%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheter site cellulitis			
subjects affected / exposed	1 / 234 (0.43%)	0 / 240 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	6 / 234 (2.56%)	0 / 240 (0.00%)	
occurrences causally related to treatment / all	1 / 6	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dengue fever			
subjects affected / exposed	1 / 234 (0.43%)	0 / 240 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	2 / 234 (0.85%)	2 / 240 (0.83%)	
occurrences causally related to treatment / all	0 / 2	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Empyema			
subjects affected / exposed	0 / 234 (0.00%)	1 / 240 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Furuncle			
subjects affected / exposed	0 / 234 (0.00%)	1 / 240 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			

subjects affected / exposed	0 / 234 (0.00%)	3 / 240 (1.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	1 / 234 (0.43%)	0 / 240 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	0 / 234 (0.00%)	1 / 240 (0.42%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	1 / 234 (0.43%)	1 / 240 (0.42%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngitis			
subjects affected / exposed	1 / 234 (0.43%)	0 / 240 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural infection			
subjects affected / exposed	1 / 234 (0.43%)	0 / 240 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 234 (0.00%)	1 / 240 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary tuberculosis			
subjects affected / exposed	1 / 234 (0.43%)	0 / 240 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis acute			

subjects affected / exposed	1 / 234 (0.43%)	0 / 240 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash pustular			
subjects affected / exposed	0 / 234 (0.00%)	1 / 240 (0.42%)	
occurrences causally related to treatment / all	0 / 0	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	1 / 234 (0.43%)	0 / 240 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	0 / 234 (0.00%)	1 / 240 (0.42%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Sinusitis			
subjects affected / exposed	1 / 234 (0.43%)	0 / 240 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal infection			
subjects affected / exposed	0 / 234 (0.00%)	1 / 240 (0.42%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tooth abscess			
subjects affected / exposed	1 / 234 (0.43%)	0 / 240 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	1 / 234 (0.43%)	2 / 240 (0.83%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			

subjects affected / exposed	1 / 234 (0.43%)	0 / 240 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	2 / 234 (0.85%)	1 / 240 (0.42%)	
occurrences causally related to treatment / all	1 / 2	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	1 / 234 (0.43%)	7 / 240 (2.92%)	
occurrences causally related to treatment / all	1 / 1	7 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	1 / 234 (0.43%)	0 / 240 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	0 / 234 (0.00%)	3 / 240 (1.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	0 / 234 (0.00%)	2 / 240 (0.83%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Trastuzumab + Paclitaxel	Neratinib + Paclitaxel	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	230 / 234 (98.29%)	239 / 240 (99.58%)	
Vascular disorders			
Hot flush			
subjects affected / exposed	8 / 234 (3.42%)	13 / 240 (5.42%)	
occurrences (all)	35	34	

Hypertension			
subjects affected / exposed	19 / 234 (8.12%)	13 / 240 (5.42%)	
occurrences (all)	21	26	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	36 / 234 (15.38%)	53 / 240 (22.08%)	
occurrences (all)	67	145	
Fatigue			
subjects affected / exposed	64 / 234 (27.35%)	78 / 240 (32.50%)	
occurrences (all)	295	257	
Influenza like illness			
subjects affected / exposed	14 / 234 (5.98%)	10 / 240 (4.17%)	
occurrences (all)	76	25	
Oedema			
subjects affected / exposed	15 / 234 (6.41%)	11 / 240 (4.58%)	
occurrences (all)	26	17	
Oedema peripheral			
subjects affected / exposed	40 / 234 (17.09%)	34 / 240 (14.17%)	
occurrences (all)	67	63	
Pain			
subjects affected / exposed	13 / 234 (5.56%)	13 / 240 (5.42%)	
occurrences (all)	18	14	
Pyrexia			
subjects affected / exposed	44 / 234 (18.80%)	42 / 240 (17.50%)	
occurrences (all)	60	64	
Reproductive system and breast disorders			
Breast pain			
subjects affected / exposed	13 / 234 (5.56%)	5 / 240 (2.08%)	
occurrences (all)	19	6	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	47 / 234 (20.09%)	24 / 240 (10.00%)	
occurrences (all)	77	33	
Dyspnoea			

subjects affected / exposed	22 / 234 (9.40%)	28 / 240 (11.67%)	
occurrences (all)	29	56	
Epistaxis			
subjects affected / exposed	20 / 234 (8.55%)	36 / 240 (15.00%)	
occurrences (all)	60	225	
Oropharyngeal pain			
subjects affected / exposed	20 / 234 (8.55%)	20 / 240 (8.33%)	
occurrences (all)	28	28	
Rhinorrhoea			
subjects affected / exposed	17 / 234 (7.26%)	6 / 240 (2.50%)	
occurrences (all)	26	8	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	28 / 234 (11.97%)	32 / 240 (13.33%)	
occurrences (all)	50	64	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	26 / 234 (11.11%)	31 / 240 (12.92%)	
occurrences (all)	70	71	
Aspartate aminotransferase increased			
subjects affected / exposed	22 / 234 (9.40%)	26 / 240 (10.83%)	
occurrences (all)	46	36	
Blood alkaline phosphatase increased			
subjects affected / exposed	11 / 234 (4.70%)	15 / 240 (6.25%)	
occurrences (all)	13	25	
Weight decreased			
subjects affected / exposed	12 / 234 (5.13%)	38 / 240 (15.83%)	
occurrences (all)	25	90	
Weight increased			
subjects affected / exposed	14 / 234 (5.98%)	9 / 240 (3.75%)	
occurrences (all)	24	24	
Nervous system disorders			
Dizziness			
subjects affected / exposed	30 / 234 (12.82%)	52 / 240 (21.67%)	
occurrences (all)	46	85	
Dysgeusia			

subjects affected / exposed	16 / 234 (6.84%)	35 / 240 (14.58%)	
occurrences (all)	107	129	
Headache			
subjects affected / exposed	46 / 234 (19.66%)	49 / 240 (20.42%)	
occurrences (all)	98	129	
Hypoaesthesia			
subjects affected / exposed	25 / 234 (10.68%)	18 / 240 (7.50%)	
occurrences (all)	47	26	
Neuropathy peripheral			
subjects affected / exposed	60 / 234 (25.64%)	61 / 240 (25.42%)	
occurrences (all)	141	113	
Paraesthesia			
subjects affected / exposed	12 / 234 (5.13%)	21 / 240 (8.75%)	
occurrences (all)	14	60	
Peripheral sensory neuropathy			
subjects affected / exposed	53 / 234 (22.65%)	48 / 240 (20.00%)	
occurrences (all)	91	90	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	65 / 234 (27.78%)	75 / 240 (31.25%)	
occurrences (all)	214	341	
Leukopenia			
subjects affected / exposed	74 / 234 (31.62%)	72 / 240 (30.00%)	
occurrences (all)	332	382	
Lymphopenia			
subjects affected / exposed	30 / 234 (12.82%)	32 / 240 (13.33%)	
occurrences (all)	114	139	
Neutropenia			
subjects affected / exposed	79 / 234 (33.76%)	77 / 240 (32.08%)	
occurrences (all)	307	289	
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	4 / 234 (1.71%)	16 / 240 (6.67%)	
occurrences (all)	7	36	
Abdominal pain			

subjects affected / exposed	26 / 234 (11.11%)	52 / 240 (21.67%)	
occurrences (all)	48	197	
Abdominal pain upper			
subjects affected / exposed	18 / 234 (7.69%)	30 / 240 (12.50%)	
occurrences (all)	24	267	
Constipation			
subjects affected / exposed	44 / 234 (18.80%)	35 / 240 (14.58%)	
occurrences (all)	113	102	
Diarrhoea			
subjects affected / exposed	78 / 234 (33.33%)	222 / 240 (92.50%)	
occurrences (all)	247	7800	
Dyspepsia			
subjects affected / exposed	20 / 234 (8.55%)	31 / 240 (12.92%)	
occurrences (all)	51	75	
Haemorrhoids			
subjects affected / exposed	12 / 234 (5.13%)	4 / 240 (1.67%)	
occurrences (all)	16	4	
Nausea			
subjects affected / exposed	70 / 234 (29.91%)	107 / 240 (44.58%)	
occurrences (all)	191	415	
Stomatitis			
subjects affected / exposed	46 / 234 (19.66%)	59 / 240 (24.58%)	
occurrences (all)	68	154	
Vomiting			
subjects affected / exposed	37 / 234 (15.81%)	87 / 240 (36.25%)	
occurrences (all)	65	240	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	133 / 234 (56.84%)	126 / 240 (52.50%)	
occurrences (all)	173	163	
Dry skin			
subjects affected / exposed	12 / 234 (5.13%)	15 / 240 (6.25%)	
occurrences (all)	14	17	
Erythema			
subjects affected / exposed	16 / 234 (6.84%)	9 / 240 (3.75%)	
occurrences (all)	19	19	

Nail disorder			
subjects affected / exposed	31 / 234 (13.25%)	33 / 240 (13.75%)	
occurrences (all)	35	88	
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	7 / 234 (2.99%)	14 / 240 (5.83%)	
occurrences (all)	12	35	
Pruritus			
subjects affected / exposed	22 / 234 (9.40%)	19 / 240 (7.92%)	
occurrences (all)	27	24	
Rash			
subjects affected / exposed	51 / 234 (21.79%)	72 / 240 (30.00%)	
occurrences (all)	131	151	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	45 / 234 (19.23%)	34 / 240 (14.17%)	
occurrences (all)	74	69	
Back pain			
subjects affected / exposed	27 / 234 (11.54%)	37 / 240 (15.42%)	
occurrences (all)	51	168	
Bone pain			
subjects affected / exposed	12 / 234 (5.13%)	11 / 240 (4.58%)	
occurrences (all)	12	33	
Muscle spasms			
subjects affected / exposed	12 / 234 (5.13%)	17 / 240 (7.08%)	
occurrences (all)	15	34	
Musculoskeletal chest pain			
subjects affected / exposed	5 / 234 (2.14%)	13 / 240 (5.42%)	
occurrences (all)	10	15	
Musculoskeletal pain			
subjects affected / exposed	19 / 234 (8.12%)	13 / 240 (5.42%)	
occurrences (all)	22	15	
Myalgia			
subjects affected / exposed	32 / 234 (13.68%)	31 / 240 (12.92%)	
occurrences (all)	91	83	
Pain in extremity			

subjects affected / exposed	25 / 234 (10.68%)	30 / 240 (12.50%)	
occurrences (all)	41	54	
Infections and infestations			
Cystitis			
subjects affected / exposed	12 / 234 (5.13%)	14 / 240 (5.83%)	
occurrences (all)	40	25	
Influenza			
subjects affected / exposed	14 / 234 (5.98%)	11 / 240 (4.58%)	
occurrences (all)	16	18	
Nasopharyngitis			
subjects affected / exposed	34 / 234 (14.53%)	29 / 240 (12.08%)	
occurrences (all)	103	113	
Paronychia			
subjects affected / exposed	9 / 234 (3.85%)	16 / 240 (6.67%)	
occurrences (all)	9	32	
Rhinitis			
subjects affected / exposed	12 / 234 (5.13%)	2 / 240 (0.83%)	
occurrences (all)	16	4	
Upper respiratory tract infection			
subjects affected / exposed	32 / 234 (13.68%)	27 / 240 (11.25%)	
occurrences (all)	67	52	
Urinary tract infection			
subjects affected / exposed	15 / 234 (6.41%)	17 / 240 (7.08%)	
occurrences (all)	22	29	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	41 / 234 (17.52%)	76 / 240 (31.67%)	
occurrences (all)	153	236	
Dehydration			
subjects affected / exposed	3 / 234 (1.28%)	18 / 240 (7.50%)	
occurrences (all)	3	21	
Hypercreatininaemia			
subjects affected / exposed	2 / 234 (0.85%)	13 / 240 (5.42%)	
occurrences (all)	5	49	
Hyperglycaemia			

subjects affected / exposed	16 / 234 (6.84%)	9 / 240 (3.75%)	
occurrences (all)	26	16	
Hypocalcaemia			
subjects affected / exposed	4 / 234 (1.71%)	19 / 240 (7.92%)	
occurrences (all)	5	46	
Hypokalaemia			
subjects affected / exposed	9 / 234 (3.85%)	23 / 240 (9.58%)	
occurrences (all)	9	37	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 February 2010	The design was changed from a ~350- to ~400-site study. This amendment also included new baseline assessments, changes to inclusion critiera, tumor assessment requirements flow chart, prohibited concomitant treatment, concomitant medication guidelines, ECG schedule, guidelines for evaluating liver function test (LFT) changes and pneumonitis/interstitial lung disease, guidelines for blood collection, new patient monitoring and dose adjustment guidelines, Instructions for laboratory determination, reportable liver function test information. Guidelines for PK sampling for patients with LFT changes and details on determination of neratinib and its metabolite plasma concentrations were also added.
09 June 2011	The design changed from a 1,200-patient Phase 3 study to a 480-patient Phase 2 study. Analysis of p95 ERBB2 levels with an antibody-based assay was added to biomarkers evaluation. Guidelines for diarrhea management and dose adjustments for diarrhea were revised. Use of patient diaries and distribution of patient diarrhea management cards were made mandatory for all patients enrolled in the neratinib arm. Primary prophylactic use of antidiarrheal medication was mandated. The requirement to collect health outcomes questionnaires was discontinued. Adverse event and SAE reporting procedures were revised to reflect process changes at the Sponsor. Other changes and clarifications were made relative to guidelines of LVEF calculations and selection of lymph node as target vs non-target lesions at screening.
22 March 2012	The Sponsor was changed to Puma. Updates were made to biomarker sample collection. Overall survival was removed from the secondary endpoints. As a result, the study no longer included a long-term follow-up for survival period. Other updates included the frequency of tumor assessment, discontinuation of PK sample collection, and exapansion of the scenario for possible use of locally supplied trastuzumab and paclitaxel.
01 June 2016	Treatment Extension Period was added in order to provide study subjects who continue to derive benefit from investigational product (IP) the opportunity to continue to receive study drug with a reduced number of protocol required assessments. Additional changes included tumor assessments performed at the investigator’s discretion; required safety procedures for patients receiving neratinib were limited to reporting of all SAEs and non-serious adverse events leading to drug discontinuation or withdrawal from the trial; adverse event collection for patients who were not receiving neratinib was discontinued.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported