Clinical trial results:
A Phase 2 Randomized Open Label Study of Neratinib versus Lapatinib plus Capecitabine for the Treatment of ErbB-2 Positive Locally Advanced or Metastatic Breast Cancer

Summary

EudraCT number	2008-005425-11
Trial protocol	HU SI BE DE ES CZ IT GR FR AT GB BG NL
Global end of trial date	20 June 2018

Results information

Result version number	v2 (current)
This version publication date	06 July 2019
First version publication date	25 December 2016
Version creation reason	• New data added to full data set Update to reflect final study close out.
Summary attachment (see zip file)	3144A2-3003 PDS (3144A2-3003 (B1891003) Public Disclosure Synopsis .doc.pdf)

Trial information

Trial identification

Sponsor protocol code	3144A2-3003-WW

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00777101
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	Sr. Director, Clinical Operations, Puma Biotechnology, Inc., 1 4242486500, clinicaltrials@pumabiotechnology.com
Scientific contact	Sr. 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	20 June 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	20 June 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Compare the investigator assessed progression-free survival (PFS) following treatment with single agent neratinib versus lapatinib plus capecitabine in subjects with erbB2 positive locally advanced or metastatic breast cancer.

Protection of trial subjects:

This study was designed and monitored in accordance with Sponsor procedures, which comply with the ethical principles of the International Council for Harmonisation (ICH) Good Clinical Practice (GCP), including the Declaration of Helsinki and the applicable laws and regulations. The protocol, the investigator's brochure (IB), and the informed consent form (ICF) for this clinical study were submitted to an institutional review board (IRB) or an independent ethics committee (IEC) for review and written approval. Any subsequent amendments to the protocol or any revisions to the ICF were submitted for IRB or IEC review and written approval. This study was conducted in accordance with the International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice (GCP) and the ethical principles that have their origins in the Declaration of Helsinki. All investigators have provided written commitments to comply with GCP standards and the protocol. Clinical trial data were monitored at regular intervals by the Sponsor or their representative throughout the study to verify compliance to study protocol, completeness, accuracy and consistency of the data and adherence to local regulations on the conduct of clinical research. Participants were discontinued from active treatment if any of the following occurred: documented disease progression, adverse event (AE), symptomatic deterioration, subject request, investigator request, protocol violation, discontinuation of the study by the sponsor, lost to follow up, or death.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	04 February 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	Belgium: 2
Country: Number of subjects enrolled	Bulgaria: 5
Country: Number of subjects enrolled	Switzerland: 5
Country: Number of subjects enrolled	Czech Republic: 2
Country: Number of subjects enrolled	Germany: 3
Country: Number of subjects enrolled	Spain: 11
Country: Number of subjects enrolled	Australia: 5
Country: Number of subjects enrolled	France: 4
Country: Number of subjects enrolled	United Kingdom: 2
Country: Number of subjects enrolled	Greece: 1

Country: Number of subjects enrolled	Hong Kong: 5
Country: Number of subjects enrolled	Croatia: 3
Country: Number of subjects enrolled	Hungary: 16
Country: Number of subjects enrolled	Italy: 2
Country: Number of subjects enrolled	Jordan: 2
Country: Number of subjects enrolled	Japan: 40
Country: Number of subjects enrolled	Korea, Republic of: 25
Country: Number of subjects enrolled	Mexico: 2
Country: Number of subjects enrolled	Poland: 8
Country: Number of subjects enrolled	Romania: 5
Country: Number of subjects enrolled	Russian Federation: 20
Country: Number of subjects enrolled	Singapore: 1
Country: Number of subjects enrolled	Serbia: 3
Country: Number of subjects enrolled	Slovenia: 3
Country: Number of subjects enrolled	Thailand: 2
Country: Number of subjects enrolled	Taiwan: 5
Country: Number of subjects enrolled	United States: 46
Country: Number of subjects enrolled	South Africa: 5
Worldwide total number of subjects	233
EEA total number of subjects	67

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)	198
From 65 to 84 years	35
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Subjects were to have met all inclusion and exclusion criteria as described in the protocol before any study procedures were undertaken.

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	Neratinb

Arm description:

Neratinib 240 mg qd.

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: six 40 mg tablets (total dose 240 mg) orally, once daily with food, preferably in the morning, continuously

Arm title	Lapatinib + Capecitabine

Arm description:

Lapatinib 1250 mg qd + Capecitabine 2000 mg/m2 qd.

Arm type	Active comparator
Investigational medicinal product name	Lapatinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Five 250 mg tablets (total dose 1250 mg) orally, once daily, 1 hour before or after breakfast, continuously

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

Dosage and administration details:

Capecitabine: 150 mg or 500 mg tablets, for total of 2000 mg/m2 in 2 evenly divided doses orally with water within 30 minutes after a meal. Dose was taken daily for Days 1 to 14 of a 21 day cycle

Number of subjects in period 1	Neratinb	Lapatinib + Capecitabine
Started	117	116
Completed	0	0
Not completed	117	116
Consent withdrawn by subject	17	8
Death	61	57
Study terminated by sponsor	37	48
Lost to follow-up	2	3

Baseline characteristics

Reporting groups	
Reporting group title	Treatment Period

Reporting group description: -

Reporting group values	Treatment Period	Total	
Number of subjects	233	233	
Age categorical Units: Subjects			
Adults (18-64 years)	198	198	
From 65-84 years	35	35	
Age continuous Units: years			
arithmetic mean	53.8		
standard deviation	± 10.3	-	
Gender categorical Units: Subjects			
Female	233	233	

End points

End points reporting groups	
Reporting group title	Neratinb
Reporting group description:	
Neratinib 240 mg qd.	
Reporting group title	Lapatinib + Capecitabine
Reporting group description:	
Lapatinib 1250 mg qd + Capecitabine 2000 mg/m2 qd.	

Primary: Progression Free Survival	
End point title	Progression Free Survival
End point description:	
The primary endpoint was PFS, which was defined as the time interval from the date of randomization until the earliest date of progression (per RECIST) or death due to any cause. For subjects without death or progression, censorship was at the last valid tumor assessment. The efficacy analysis was based on the ITT population defined as all subjects randomly assigned in the study. Non-inferiority of neratinib vs lapatinib + capecitabine was to be concluded if the upper limit of the 95% confidence interval (CI) for the hazard ratio was 1.15 or less.	
End point type	Primary
End point timeframe:	
From date of randomization to the last tumor assessment, PD, or death.	

End point values	Neratinb	Lapatinib + Capecitabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	117	116		
Units: Months				
median (confidence interval 95%)	4.53 (3.12 to 5.65)	6.83 (5.85 to 8.21)		

Statistical analyses

Statistical analysis title	Non inferiority test of Progression Free Survival
Comparison groups	Neratinb v Lapatinib + Capecitabine
Number of subjects included in analysis	233
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Hazard ratio (HR)
Point estimate	1.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.89
upper limit	1.6

Secondary: Overall Response Rate

End point title	Overall Response Rate

End point description:

The ORR was defined as the proportion of subjects demonstrating a confirmed objective response (complete response or partial response, per RECIST) during the study.

End point type	Secondary

End point timeframe:

From date of randomization through the last tumor assessment.

End point values	Neratinb	Lapatinib + Capecitabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	117	116		
Units: Percentage of Patients				
number (confidence interval 95%)	29.1 (21.0 to 38.2)	40.5 (31.5 to 50.2)		

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	Neratinib
Reporting group description: Neratinib 240 mg qd	
Reporting group title	Lapatinib + Capecitabine
Reporting group description: Lapatinib 1250 mg qd + Capecitabine 2000 mg/m2 qd	

Serious adverse events	Neratinib	Lapatinib + Capecitabine	
Total subjects affected by serious adverse events			
subjects affected / exposed	31 / 116 (26.72%)	24 / 115 (20.87%)	
number of deaths (all causes)	62	58	
number of deaths resulting from adverse events	8	4	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cervix carcinoma stage 0			
subjects affected / exposed	1 / 116 (0.86%)	0 / 115 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to meninges			
subjects affected / exposed	1 / 116 (0.86%)	0 / 115 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Circulatory collapse			
subjects affected / exposed	1 / 116 (0.86%)	0 / 115 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Deep vein thrombosis			

subjects affected / exposed	1 / 116 (0.86%)	0 / 115 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	0 / 116 (0.00%)	1 / 115 (0.87%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphoedema			
subjects affected / exposed	0 / 116 (0.00%)	1 / 115 (0.87%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subclavian artery stenosis			
subjects affected / exposed	0 / 116 (0.00%)	1 / 115 (0.87%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 116 (0.86%)	0 / 115 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chills			
subjects affected / exposed	1 / 116 (0.86%)	0 / 115 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disease progression			
subjects affected / exposed	1 / 116 (0.86%)	0 / 115 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Fatigue			
subjects affected / exposed	1 / 116 (0.86%)	2 / 115 (1.74%)	
occurrences causally related to treatment / all	2 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			

subjects affected / exposed	1 / 116 (0.86%)	0 / 115 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	2 / 116 (1.72%)	3 / 115 (2.61%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden death			
subjects affected / exposed	0 / 116 (0.00%)	1 / 115 (0.87%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory, thoracic and mediastinal disorders			
Alveolitis			
subjects affected / exposed	0 / 116 (0.00%)	1 / 115 (0.87%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	2 / 116 (1.72%)	0 / 115 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 116 (0.86%)	6 / 115 (5.22%)	
occurrences causally related to treatment / all	0 / 2	0 / 9	
deaths causally related to treatment / all	0 / 1	0 / 1	
Pulmonary embolism			
subjects affected / exposed	1 / 116 (0.86%)	0 / 115 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	4 / 116 (3.45%)	0 / 115 (0.00%)	
occurrences causally related to treatment / all	0 / 5	0 / 0	
deaths causally related to treatment / all	0 / 3	0 / 0	
Injury, poisoning and procedural complications			

Ankle fracture			
subjects affected / exposed	0 / 116 (0.00%)	1 / 115 (0.87%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radius fracture			
subjects affected / exposed	0 / 116 (0.00%)	1 / 115 (0.87%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 116 (0.86%)	0 / 115 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	0 / 116 (0.00%)	1 / 115 (0.87%)	
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 / 116 (0.00%)	1 / 115 (0.87%)	
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	2 / 116 (1.72%)	0 / 115 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Dizziness			
subjects affected / exposed	0 / 116 (0.00%)	2 / 115 (1.74%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalopathy			
subjects affected / exposed	0 / 116 (0.00%)	1 / 115 (0.87%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Headache			
subjects affected / exposed	1 / 116 (0.86%)	1 / 115 (0.87%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	0 / 116 (0.00%)	1 / 115 (0.87%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Presyncope			
subjects affected / exposed	1 / 116 (0.86%)	0 / 115 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	1 / 116 (0.86%)	1 / 115 (0.87%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	1 / 116 (0.86%)	0 / 115 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	3 / 116 (2.59%)	0 / 115 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	1 / 116 (0.86%)	0 / 115 (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 / 116 (2.59%)	4 / 115 (3.48%)	
occurrences causally related to treatment / all	4 / 4	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	

Gingival bleeding			
subjects affected / exposed	1 / 116 (0.86%)	0 / 115 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal haemorrhage			
subjects affected / exposed	1 / 116 (0.86%)	0 / 115 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	2 / 116 (1.72%)	3 / 115 (2.61%)	
occurrences causally related to treatment / all	2 / 2	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			
subjects affected / exposed	0 / 116 (0.00%)	1 / 115 (0.87%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	2 / 116 (1.72%)	3 / 115 (2.61%)	
occurrences causally related to treatment / all	3 / 4	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatic failure			
subjects affected / exposed	0 / 116 (0.00%)	1 / 115 (0.87%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hepatic function abnormal			
subjects affected / exposed	1 / 116 (0.86%)	0 / 115 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Nail disorder			
subjects affected / exposed	0 / 116 (0.00%)	1 / 115 (0.87%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Skin irritation			
subjects affected / exposed	0 / 116 (0.00%)	1 / 115 (0.87%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal failure acute			
subjects affected / exposed	0 / 116 (0.00%)	1 / 115 (0.87%)	
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	2 / 116 (1.72%)	1 / 115 (0.87%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Flank pain			
subjects affected / exposed	1 / 116 (0.86%)	0 / 115 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bronchopneumonia			
subjects affected / exposed	1 / 116 (0.86%)	1 / 115 (0.87%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	0 / 116 (0.00%)	1 / 115 (0.87%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	1 / 116 (0.86%)	0 / 115 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			

subjects affected / exposed	1 / 116 (0.86%)	0 / 115 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mastitis			
subjects affected / exposed	0 / 116 (0.00%)	1 / 115 (0.87%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 116 (0.00%)	2 / 115 (1.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 116 (0.86%)	0 / 115 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin infection			
subjects affected / exposed	0 / 116 (0.00%)	1 / 115 (0.87%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	0 / 116 (0.00%)	1 / 115 (0.87%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	0 / 116 (0.00%)	1 / 115 (0.87%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound sepsis			
subjects affected / exposed	0 / 116 (0.00%)	1 / 115 (0.87%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Metabolism and nutrition disorders			
Decreased appetite			

subjects affected / exposed	1 / 116 (0.86%)	0 / 115 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	3 / 116 (2.59%)	1 / 115 (0.87%)	
occurrences causally related to treatment / all	5 / 6	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	0 / 116 (0.00%)	1 / 115 (0.87%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	0 / 116 (0.00%)	1 / 115 (0.87%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypovolaemia			
subjects affected / exposed	0 / 116 (0.00%)	1 / 115 (0.87%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Neratinib	Lapatinib + Capecitabine	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	113 / 116 (97.41%)	114 / 115 (99.13%)	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	11 / 116 (9.48%)	15 / 115 (13.04%)	
occurrences (all)	21	35	
Aspartate aminotransferase increased			
subjects affected / exposed	10 / 116 (8.62%)	19 / 115 (16.52%)	
occurrences (all)	17	37	
Blood alkaline phosphatase increased			

subjects affected / exposed	8 / 116 (6.90%)	4 / 115 (3.48%)	
occurrences (all)	10	13	
Blood bilirubin increased			
subjects affected / exposed	0 / 116 (0.00%)	6 / 115 (5.22%)	
occurrences (all)	0	23	
Weight decreased			
subjects affected / exposed	15 / 116 (12.93%)	13 / 115 (11.30%)	
occurrences (all)	19	13	
Nervous system disorders			
Dizziness			
subjects affected / exposed	6 / 116 (5.17%)	13 / 115 (11.30%)	
occurrences (all)	8	16	
Dysgeusia			
subjects affected / exposed	4 / 116 (3.45%)	8 / 115 (6.96%)	
occurrences (all)	5	18	
Headache			
subjects affected / exposed	24 / 116 (20.69%)	12 / 115 (10.43%)	
occurrences (all)	47	19	
Peripheral sensory neuropathy			
subjects affected / exposed	5 / 116 (4.31%)	10 / 115 (8.70%)	
occurrences (all)	8	14	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	9 / 116 (7.76%)	5 / 115 (4.35%)	
occurrences (all)	11	7	
Leukopenia			
subjects affected / exposed	5 / 116 (4.31%)	12 / 115 (10.43%)	
occurrences (all)	13	34	
Neutropenia			
subjects affected / exposed	5 / 116 (4.31%)	17 / 115 (14.78%)	
occurrences (all)	14	57	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	22 / 116 (18.97%)	13 / 115 (11.30%)	
occurrences (all)	29	23	
Fatigue			

subjects affected / exposed	30 / 116 (25.86%)	30 / 115 (26.09%)	
occurrences (all)	64	46	
Influenza like illness			
subjects affected / exposed	4 / 116 (3.45%)	6 / 115 (5.22%)	
occurrences (all)	6	7	
Mucosal inflammation			
subjects affected / exposed	6 / 116 (5.17%)	19 / 115 (16.52%)	
occurrences (all)	12	32	
Pain			
subjects affected / exposed	7 / 116 (6.03%)	8 / 115 (6.96%)	
occurrences (all)	10	8	
Pyrexia			
subjects affected / exposed	6 / 116 (5.17%)	10 / 115 (8.70%)	
occurrences (all)	9	14	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	11 / 116 (9.48%)	14 / 115 (12.17%)	
occurrences (all)	78	23	
Abdominal pain upper			
subjects affected / exposed	8 / 116 (6.90%)	12 / 115 (10.43%)	
occurrences (all)	12	14	
Constipation			
subjects affected / exposed	8 / 116 (6.90%)	12 / 115 (10.43%)	
occurrences (all)	9	14	
Diarrhoea			
subjects affected / exposed	100 / 116 (86.21%)	82 / 115 (71.30%)	
occurrences (all)	792	341	
Dyspepsia			
subjects affected / exposed	13 / 116 (11.21%)	11 / 115 (9.57%)	
occurrences (all)	14	13	
Nausea			
subjects affected / exposed	50 / 116 (43.10%)	48 / 115 (41.74%)	
occurrences (all)	69	85	
Stomatitis			
subjects affected / exposed	9 / 116 (7.76%)	28 / 115 (24.35%)	
occurrences (all)	101	63	

Vomiting			
subjects affected / exposed	38 / 116 (32.76%)	25 / 115 (21.74%)	
occurrences (all)	83	51	
Hepatobiliary disorders			
Hyperbilirubinaemia			
subjects affected / exposed	3 / 116 (2.59%)	27 / 115 (23.48%)	
occurrences (all)	4	109	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	17 / 116 (14.66%)	6 / 115 (5.22%)	
occurrences (all)	23	7	
Dyspnoea			
subjects affected / exposed	9 / 116 (7.76%)	7 / 115 (6.09%)	
occurrences (all)	9	10	
Oropharyngeal pain			
subjects affected / exposed	7 / 116 (6.03%)	10 / 115 (8.70%)	
occurrences (all)	11	10	
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	3 / 116 (2.59%)	6 / 115 (5.22%)	
occurrences (all)	4	9	
Alopecia			
subjects affected / exposed	0 / 116 (0.00%)	6 / 115 (5.22%)	
occurrences (all)	0	8	
Dry skin			
subjects affected / exposed	8 / 116 (6.90%)	10 / 115 (8.70%)	
occurrences (all)	9	11	
Nail disorder			
subjects affected / exposed	3 / 116 (2.59%)	13 / 115 (11.30%)	
occurrences (all)	3	32	
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	9 / 116 (7.76%)	77 / 115 (66.96%)	
occurrences (all)	40	237	
Pruritus			
subjects affected / exposed	4 / 116 (3.45%)	17 / 115 (14.78%)	
occurrences (all)	10	22	

Rash			
subjects affected / exposed	26 / 116 (22.41%)	41 / 115 (35.65%)	
occurrences (all)	50	68	
Rash macular			
subjects affected / exposed	0 / 116 (0.00%)	6 / 115 (5.22%)	
occurrences (all)	0	6	
Skin hyperpigmentation			
subjects affected / exposed	0 / 116 (0.00%)	12 / 115 (10.43%)	
occurrences (all)	0	12	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	9 / 116 (7.76%)	8 / 115 (6.96%)	
occurrences (all)	11	11	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	7 / 116 (6.03%)	4 / 115 (3.48%)	
occurrences (all)	7	7	
Back pain			
subjects affected / exposed	13 / 116 (11.21%)	5 / 115 (4.35%)	
occurrences (all)	17	6	
Myalgia			
subjects affected / exposed	6 / 116 (5.17%)	0 / 115 (0.00%)	
occurrences (all)	7	0	
Neck pain			
subjects affected / exposed	6 / 116 (5.17%)	0 / 115 (0.00%)	
occurrences (all)	6	0	
Infections and infestations			
Cystitis			
subjects affected / exposed	7 / 116 (6.03%)	5 / 115 (4.35%)	
occurrences (all)	7	6	
Nasopharyngitis			
subjects affected / exposed	3 / 116 (2.59%)	10 / 115 (8.70%)	
occurrences (all)	10	13	
Paronychia			
subjects affected / exposed	6 / 116 (5.17%)	24 / 115 (20.87%)	
occurrences (all)	8	48	

Upper respiratory tract infection			
subjects affected / exposed	7 / 116 (6.03%)	5 / 115 (4.35%)	
occurrences (all)	10	9	
Urinary tract infection			
subjects affected / exposed	6 / 116 (5.17%)	10 / 115 (8.70%)	
occurrences (all)	6	15	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	33 / 116 (28.45%)	23 / 115 (20.00%)	
occurrences (all)	55	44	
Hypokalaemia			
subjects affected / exposed	3 / 116 (2.59%)	7 / 115 (6.09%)	
occurrences (all)	3	13	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 February 2009	This protocol included updates to eligibility criteria, permitted and prohibited concomitant medication, modification of test schedules, and addition of exploratory end point, procedures, dose adjustment guidelines and attachments.
23 March 2010	This protocol updated the study from a phase 3 study of 1000 subjects to demonstrate the superiority of neratinib over lapatinib plus capecitabine to a phase 2 study of 230 subjects designed to demonstrate non-inferiority. The primary endpoint, Progression Free Suvival, is measured by investigator assessment rather than independent assessment.
09 August 2011	This protocol included addition of Pfizer protocol reference number (B1891003) throughout the protocol, change in duration of study and subject participation, removal of the long term follow up portion of the study, change / reduction of frequency of procedures for subjects who remain on study beyond cycle 16, clarification that RECIST version 1.0 is used, clarification to the dose adjustment guidelines related to LVEF changes, revision of adverse event/Serious adverse event reporting as per Pfizer SOP, and administrative updates due to the acquisition of Wyeth by Pfizer, including a new global SAE reporting fax number.
22 March 2012	This protocol updated the Sponsor to Puma, and includes a Treatment Extension Period, which allowed participants who still derived benefit from study participation to remain on the study and enabled the Sponsor to continue to provide investigational product (IP) to the participants after the primary objectives had been reached. During the Treatment Extension Period, the required procedures were limited to IP administration and monitoring for safety and tolerability; adverse events (AEs) and serious adverse events (SAEs) were documented. To limit the participant's burden in terms of protocol-required efficacy assessments, tumor assessments were performed as clinically indicated at the investigator's discretion according to standard of care; however no efficacy data were collected.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

10 participants in the neratinib and 7 participants in lapatinib arm continued follow up at the time of the database lock. These participants were categorized as "study terminated by sponsor" in the disposition table.

Notes: