Clinical trial results:
Phase 2 Study of Neratinib (HKI-272) in Subjects with Advanced Breast Cancer

Summary

EudraCT number	2005-003098-26
Trial protocol	BE FR
Global end of trial date	22 January 2018

Results information

Result version number	v2 (current)
This version publication date	06 May 2019
First version publication date	01 January 2017
Version creation reason	• New data added to full data set Update to reflect final study close out.

Trial information

Trial identification

Sponsor protocol code	3144A1-201-WW

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00300781
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., 1 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	22 January 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	22 January 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Determine the sixteen (16) week progression-free survival (PFS) rate for Neratinib (HKI-272) in women with advanced breast cancer.

Protection of trial subjects:

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.

Neratinib administration was stopped in subjects if neratinib was not well tolerated, if subjects had documented disease progression, if subjects had clinical evidence of congestive heart failure (CHF) requiring medical intervention, if subjects had a decrease in LVEF of ≥25 points from baseline if the LVEF remained in
the range of ≥50 points, or a decrease in LVEF of ≥10 points from baseline to a final LVEF value <50 points, if pregnancy was confirmed, if a need was determined for initiation of bisphosphonates or palliative radiation therapy, including whole-brain irradiation for documented CNS disease, if subjects were on any of the prohibited concomitant therapies of the protocol, if dose administration was delayed for more than 3 weeks, if subjects needed more than 2 dose reductions because of toxicity.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	04 August 2006
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: 24
Country: Number of subjects enrolled	China: 28
Country: Number of subjects enrolled	India: 28
Country: Number of subjects enrolled	Mexico: 5
Country: Number of subjects enrolled	Russian Federation: 10
Country: Number of subjects enrolled	United States: 41

Worldwide total number of subjects	136
EEA total number of subjects	24

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	13
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Subjects who satisfied the all inclusion criteria were eligible to participate in this study if none of the exclusion criteria were met.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	NER240, w prior HER2 tx

Arm description:

Neratinib 240 mg qd, for HER2+ patients who have received prior Trastuzumab or HER2 treatment. Arm enrolled women with HER2-positive breast cancer and erbB2 gene amplification confirmed in tumor tissue; and disease progression during or after trastuzumab-containing adjuvant therapy, or following at least 6 weeks of standard doses of trastuzumab in a metastatic or locally advanced setting

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 was supplied to the investigative sites as 80-mg capsules and was administered in daily oral doses of 240 mg with food, preferably in the morning.

Arm title	NER240, w/o prior HER2 tx

Arm description:

Neratinib 240 mg qd, HER2+ and no prior Trastuzumab or HER2 treatment. Women with HER2-positive breast cancer and erbB2 gene amplification confirmed in tumor tissue and no prior trastuzumab or other erbB2-targeted treatment. Enrollment in this was not applicable to subjects from France who enrolled in the study because the country’s ethics committee did not approve of the enrollment of trastuzumab-naïve subjects in the study.

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 was supplied to the investigative sites as 80-mg capsules and was administered in daily oral doses of 240 mg with food, preferably in the morning.

Number of subjects in period 1	NER240, w prior HER2 tx	NER240, w/o prior HER2 tx
Started	66	70
Completed	0	0
Not completed	66	70
Physician decision	2	-
Consent withdrawn by subject	2	2
Adverse event, non-fatal	4	5
Death	4	3
Symptomatic Deterioration	1	-
Lost to follow-up	-	2
Disease Progression	53	57
Protocol deviation	-	1

Baseline characteristics

Reporting groups	
Reporting group title	NER240, w prior HER2 tx
Reporting group description:	
Neratinib 240 mg qd, for HER2+ patients who have received prior Trastuzumab or HER2 treatment. Arm enrolled women with HER2-positive breast cancer and erbB2 gene amplification confirmed in tumor tissue; and disease progression during or after trastuzumab-containing adjuvant therapy, or following at least 6 weeks of standard doses of trastuzumab in a metastatic or locally advanced setting	
Reporting group title	NER240, w/o prior HER2 tx
Reporting group description:	
Neratinib 240 mg qd, HER2+ and no prior Trastuzumab or HER2 treatment. Women with HER2-positive breast cancer and erbB2 gene amplification confirmed in tumor tissue and no prior trastuzumab or other erbB2-targeted treatment. Enrollment in this was not applicable to subjects from France who enrolled in the study because the country's ethics committee did not approve of the enrollment of trastuzumab-naïve subjects in the study.	

Reporting group values	NER240, w prior HER2 tx	NER240, w/o prior HER2 tx	Total
Number of subjects	66	70	136
Age categorical Units: Subjects			
Adults (18-64 years)	59	64	123
From 65-84 years	7	6	13
Gender categorical Units: Subjects			
Female	66	70	136

End points

End points reporting groups

Reporting group title	NER240, w prior HER2 tx

Reporting group description:

Neratinib 240 mg qd, for HER2+ patients who have received prior Trastuzumab or HER2 treatment. Arm enrolled women with HER2-positive breast cancer and erbB2 gene amplification confirmed in tumor tissue; and disease progression during or after trastuzumab-containing adjuvant therapy, or following at least 6 weeks of standard doses of trastuzumab in a metastatic or locally advanced setting

Reporting group title	NER240, w/o prior HER2 tx

Reporting group description:

Neratinib 240 mg qd, HER2+ and no prior Trastuzumab or HER2 treatment. Women with HER2-positive breast cancer and erbB2 gene amplification confirmed in tumor tissue and no prior trastuzumab or other erbB2-targeted treatment. Enrollment in this was not applicable to subjects from France who enrolled in the study because the country's ethics committee did not approve of the enrollment of trastuzumab-naïve subjects in the study.

Primary: 16-week Progression Free Survival Rate - Independent Assessment

End point title	16-week Progression Free Survival Rate - Independent Assessment[1]

End point description:

The proportion of subjects who were alive and progression free 16 weeks after the first dose of neratinib. The 16-week PFS rate was estimated using the Kaplan Meier method. Subjects for whom disease progression or death was not observed were censored at the date of their last tumor assessment. The determination of progression was made by an independent radiologist. The primary efficacy endpoint was analyzed separately for the 2 treatment arms. For this study, the null hypothesis was an uninteresting 16-week PFS rate of 30% or less for each treatment arm. The alternative hypothesis, the sufficiently promising rate, was set at 50%. The proportion and corresponding 90% and 95% CI of subjects who were progression free and surviving at 16 weeks were estimated.

End point type	Primary

End point timeframe:

From first dose of Neratinib through 16 weeks

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The primary efficacy endpoint of PFS at 16 weeks was analyzed separately for each baseline trastuzumab status arm with no comparison between the arms. The proportion and corresponding 95% CI were estimated using the Kaplan-Meier method.

End point values	NER240, w prior HER2 tx	NER240, w/o prior HER2 tx		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	66	70		
Units: Percentage				
number (confidence interval 95%)	58.9 (45.8 to 71.9)	77.1 (66.5 to 87.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Best Overall Response, Independent Assessment

End point title	Best Overall Response, Independent Assessment

End point description:

The best tumor response is the best response, according to RECIST, recorded from the first dose of study drug until disease progression and/or recurrence (taking as reference for PD the smallest measurements previously). To be assigned a best tumor response of CR or PR, the initial assessment must be confirmed by repeat evaluations that should be performed no less than 4 weeks later. The response is assessed by a independent radiologist, for evaluable population. The evaluable population was defined as all subjects who met the eligibility criteria, received at least 1 week of neratinib, and had at least 1 follow-up tumor assessment after receiving the first dose of neratinib.

End point type	Secondary

End point timeframe:

From First Dose of Neratinib through disease progression or recurrence.

End point values	NER240, w prior HER2 tx	NER240, w/o prior HER2 tx		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	63[2]	65[3]		
Units: Percentage of Patients				
number (not applicable)				
Complete Response	0	1.5		
Partial Response	25.4	52.3		
Stable Disease	41.3	33.8		
Progressive Disease	27	7.7		
Unknown	3.2	3.1		
Missing	3.2	1.5		

Notes:

[2] - Evaluable Population only

[3] - Evaluable Population Only

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Response Rate - Independent Assessment

End point title	Overall Response Rate - Independent Assessment

End point description:

The overall response rate is the percentage of subjects with a complete response or partial response (CR, PR), To be assigned a best tumor response of CR or PR, the initial assessment must be confirmed by repeat evaluations that should be performed no less than 4 weeks later. The response is assessed by a independent radiologist, for evaluable population. The evaluable population was defined as all subjects who met the eligibility criteria, received at least 1 week of neratinib, and had at least 1 follow-up tumor assessment after receiving the first dose of neratinib.

End point type	Secondary

End point timeframe:

From first dose through disease progression or recurrence

End point values	NER240, w prior HER2 tx	NER240, w/o prior HER2 tx		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	63[4]	66[5]		
Units: Percentage of Subjects				
number (confidence interval 95%)	25.4 (15.3 to 37.9)	53.8 (41.0 to 66.3)		

Notes:

[4] - Evaluable Population

[5] - Evaluable Population

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response - Independent Assessment

End point title	Duration of Response - Independent Assessment

End point description:

The time at which criteria are met for CR or PR (whichever status is recorded first) until the first date on which recurrence, PD or death is documented, censored at the date of last tumor assessment; response criteria are based on RECIST criteria as determined by independent radiologist.

End point type	Secondary

End point timeframe:

From the beginning of response until first recurrence, death, progression.

End point values	NER240, w prior HER2 tx	NER240, w/o prior HER2 tx		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	35		
Units: Weeks				
median (confidence interval 95%)	40.3 (32.3 to 80.1)	60 (40.0 to 104.7)		

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	NER240, w/o prior HER2 tx
Reporting group description:	
Neratinib 240 mg, HER2+ and no prior Trastuzumab or HER2 treatment	
Reporting group title	NER240, w prior HER2 tx
Reporting group description:	
Neratinib 240 mg, HER2+ and prior Trastuzumab or HER2 treatment	

Serious adverse events	NER240, w/o prior HER2 tx	NER240, w prior HER2 tx	
Total subjects affected by serious adverse events			
subjects affected / exposed	17 / 70 (24.29%)	19 / 66 (28.79%)	
number of deaths (all causes)	3	4	
number of deaths resulting from adverse events	2	2	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lymphangiosis carcinomatosa			
subjects affected / exposed	0 / 70 (0.00%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Malignant ascites			
subjects affected / exposed	1 / 70 (1.43%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant pleural effusion			
subjects affected / exposed	1 / 70 (1.43%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to central nervous system			

subjects affected / exposed	1 / 70 (1.43%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Vascular disorders			
Lymphoedema			
subjects affected / exposed	0 / 70 (0.00%)	1 / 66 (1.52%)	
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 / 70 (1.43%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	0 / 70 (0.00%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malaise			
subjects affected / exposed	1 / 70 (1.43%)	0 / 66 (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	1 / 70 (1.43%)	0 / 66 (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	1 / 70 (1.43%)	2 / 66 (3.03%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hypoxia			

subjects affected / exposed	0 / 70 (0.00%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 70 (1.43%)	2 / 66 (3.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	1 / 70 (1.43%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Psychiatric disorders			
Confusional state			
subjects affected / exposed	0 / 70 (0.00%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 70 (1.43%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	2 / 2	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 70 (1.43%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood creatinine increased			
subjects affected / exposed	1 / 70 (1.43%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 70 (0.00%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	1 / 70 (1.43%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrioventricular block			
subjects affected / exposed	1 / 70 (1.43%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			
subjects affected / exposed	1 / 70 (1.43%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Dyskinesia			
subjects affected / exposed	0 / 70 (0.00%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	0 / 70 (0.00%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuropathy peripheral			
subjects affected / exposed	0 / 70 (0.00%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
VIIth nerve paralysis			
subjects affected / exposed	0 / 70 (0.00%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			

subjects affected / exposed	1 / 70 (1.43%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	4 / 70 (5.71%)	4 / 66 (6.06%)	
occurrences causally related to treatment / all	6 / 6	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	0 / 70 (0.00%)	2 / 66 (3.03%)	
occurrences causally related to treatment / all	0 / 0	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	6 / 70 (8.57%)	3 / 66 (4.55%)	
occurrences causally related to treatment / all	5 / 8	5 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	0 / 70 (0.00%)	2 / 66 (3.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Muscular weakness			
subjects affected / exposed	0 / 70 (0.00%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal pain			
subjects affected / exposed	0 / 70 (0.00%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Disseminated tuberculosis			

subjects affected / exposed	1 / 70 (1.43%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Folliculitis			
subjects affected / exposed	1 / 70 (1.43%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis E			
subjects affected / exposed	1 / 70 (1.43%)	0 / 66 (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	1 / 70 (1.43%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinusitis			
subjects affected / exposed	0 / 70 (0.00%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 70 (1.43%)	2 / 66 (3.03%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	4 / 70 (5.71%)	2 / 66 (3.03%)	
occurrences causally related to treatment / all	4 / 4	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	0 / 70 (0.00%)	1 / 66 (1.52%)	
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	NER240, w/o prior HER2 tx	NER240, w prior HER2 tx	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	70 / 70 (100.00%)	66 / 66 (100.00%)	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	5 / 70 (7.14%)	1 / 66 (1.52%)	
occurrences (all)	8	1	
Aspartate aminotransferase increased			
subjects affected / exposed	5 / 70 (7.14%)	1 / 66 (1.52%)	
occurrences (all)	8	1	
Weight decreased			
subjects affected / exposed	4 / 70 (5.71%)	3 / 66 (4.55%)	
occurrences (all)	4	4	
Nervous system disorders			
Dizziness			
subjects affected / exposed	6 / 70 (8.57%)	5 / 66 (7.58%)	
occurrences (all)	9	9	
Dysgeusia			
subjects affected / exposed	0 / 70 (0.00%)	6 / 66 (9.09%)	
occurrences (all)	0	6	
Headache			
subjects affected / exposed	14 / 70 (20.00%)	12 / 66 (18.18%)	
occurrences (all)	25	16	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	8 / 70 (11.43%)	4 / 66 (6.06%)	
occurrences (all)	11	6	
Leukopenia			
subjects affected / exposed	2 / 70 (2.86%)	4 / 66 (6.06%)	
occurrences (all)	3	5	
General disorders and administration site conditions			
Asthenia			

subjects affected / exposed	10 / 70 (14.29%)	3 / 66 (4.55%)	
occurrences (all)	17	3	
Fatigue			
subjects affected / exposed	7 / 70 (10.00%)	26 / 66 (39.39%)	
occurrences (all)	15	38	
Oedema peripheral			
subjects affected / exposed	5 / 70 (7.14%)	4 / 66 (6.06%)	
occurrences (all)	5	4	
Pyrexia			
subjects affected / exposed	12 / 70 (17.14%)	5 / 66 (7.58%)	
occurrences (all)	17	6	
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	5 / 70 (7.14%)	1 / 66 (1.52%)	
occurrences (all)	5	1	
Abdominal pain			
subjects affected / exposed	6 / 70 (8.57%)	19 / 66 (28.79%)	
occurrences (all)	8	22	
Abdominal pain upper			
subjects affected / exposed	1 / 70 (1.43%)	4 / 66 (6.06%)	
occurrences (all)	1	5	
Constipation			
subjects affected / exposed	2 / 70 (2.86%)	5 / 66 (7.58%)	
occurrences (all)	2	6	
Diarrhoea			
subjects affected / exposed	64 / 70 (91.43%)	63 / 66 (95.45%)	
occurrences (all)	184	210	
Dry mouth			
subjects affected / exposed	4 / 70 (5.71%)	4 / 66 (6.06%)	
occurrences (all)	8	5	
Dyspepsia			
subjects affected / exposed	7 / 70 (10.00%)	4 / 66 (6.06%)	
occurrences (all)	12	7	
Haemorrhoids			
subjects affected / exposed	4 / 70 (5.71%)	1 / 66 (1.52%)	
occurrences (all)	6	1	

Nausea			
subjects affected / exposed	23 / 70 (32.86%)	27 / 66 (40.91%)	
occurrences (all)	36	43	
Stomatitis			
subjects affected / exposed	4 / 70 (5.71%)	4 / 66 (6.06%)	
occurrences (all)	4	6	
Vomiting			
subjects affected / exposed	23 / 70 (32.86%)	16 / 66 (24.24%)	
occurrences (all)	34	27	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	6 / 70 (8.57%)	8 / 66 (12.12%)	
occurrences (all)	10	8	
Dyspnoea			
subjects affected / exposed	4 / 70 (5.71%)	8 / 66 (12.12%)	
occurrences (all)	4	11	
Epistaxis			
subjects affected / exposed	5 / 70 (7.14%)	1 / 66 (1.52%)	
occurrences (all)	11	1	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	4 / 70 (5.71%)	3 / 66 (4.55%)	
occurrences (all)	4	6	
Dermatitis acneiform			
subjects affected / exposed	9 / 70 (12.86%)	2 / 66 (3.03%)	
occurrences (all)	9	2	
Dry skin			
subjects affected / exposed	3 / 70 (4.29%)	4 / 66 (6.06%)	
occurrences (all)	4	4	
Nail disorder			
subjects affected / exposed	0 / 70 (0.00%)	5 / 66 (7.58%)	
occurrences (all)	0	6	
Pruritus			
subjects affected / exposed	4 / 70 (5.71%)	8 / 66 (12.12%)	
occurrences (all)	5	10	
Rash			

subjects affected / exposed	9 / 70 (12.86%)	14 / 66 (21.21%)	
occurrences (all)	19	20	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	4 / 70 (5.71%)	3 / 66 (4.55%)	
occurrences (all)	5	5	
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	6 / 70 (8.57%)	1 / 66 (1.52%)	
occurrences (all)	7	2	
Pollakiuria			
subjects affected / exposed	1 / 70 (1.43%)	4 / 66 (6.06%)	
occurrences (all)	1	6	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	7 / 70 (10.00%)	7 / 66 (10.61%)	
occurrences (all)	10	10	
Back pain			
subjects affected / exposed	8 / 70 (11.43%)	5 / 66 (7.58%)	
occurrences (all)	8	6	
Muscle spasms			
subjects affected / exposed	2 / 70 (2.86%)	4 / 66 (6.06%)	
occurrences (all)	2	5	
Musculoskeletal chest pain			
subjects affected / exposed	3 / 70 (4.29%)	4 / 66 (6.06%)	
occurrences (all)	4	4	
Musculoskeletal pain			
subjects affected / exposed	3 / 70 (4.29%)	5 / 66 (7.58%)	
occurrences (all)	4	7	
Pain in extremity			
subjects affected / exposed	7 / 70 (10.00%)	5 / 66 (7.58%)	
occurrences (all)	9	7	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	5 / 70 (7.14%)	2 / 66 (3.03%)	
occurrences (all)	5	2	

Paronychia			
subjects affected / exposed	6 / 70 (8.57%)	0 / 66 (0.00%)	
occurrences (all)	7	0	
Upper respiratory tract infection			
subjects affected / exposed	2 / 70 (2.86%)	4 / 66 (6.06%)	
occurrences (all)	2	4	
Urinary tract infection			
subjects affected / exposed	1 / 70 (1.43%)	7 / 66 (10.61%)	
occurrences (all)	1	8	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	12 / 70 (17.14%)	15 / 66 (22.73%)	
occurrences (all)	16	27	
Dehydration			
subjects affected / exposed	3 / 70 (4.29%)	4 / 66 (6.06%)	
occurrences (all)	4	5	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 April 2006	This amendment included updates to staffing information, starting dose of neratinib (changed from 320 mg to 240 mg), Phase 1 safety information, and Sponsor team contact information.
30 November 2006	This amendment included updates to Sponsor's contacts, addition of study synopsis, removal of pharmacogenomics optional sampling, removal of month 1 week 4 tumor assessment, change to eligibility with regard to use of adjuvant trastuzumab, allowance of enrollment of up to 20 subjects with prior lapatinib treatment, modified recommended dose adjustment for Adverse Events of Diarrhea Grade 2 or 3 last >2 days on medical therapy or associated with fever or dehydration and related to neratinib, clarification of RECIST criteria and target lesions considered too small to measure, and inclusion of definition of medication errors.
19 January 2010	This amendment included additional blood chemistry and coagulation testing for patients with signs or symptoms of hepatic injury, guidelines to provide dose adjustment, guidelines in the event of hepatic toxicity, corrected the definition of time to tumor progression, removed of all language added for Brazil-specific amendments, and administrative changes to study team personnel and contact information.
25 February 2010	This amendment included addition of treatment extension period, which allowed patients who still derived benefit from study participation to remain on the study and enabled the Sponsor (Pfizer) to continue to provide investigational product (IP) to the patients 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 to be documented and the data sent to the Sponsor. To limit the patient's burden in terms of protocol-required efficacy assessments, tumor assessment was to be performed as clinically indicated at the Investigator's discretion according to standard of care; however, no efficacy data were collected.
22 March 2012	This amendment documented the change in sponsorship from Pfizer to Puma and further reduced the data collection requirements.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported