Clinical trial results:
A Randomized Double-blind Placebo-Controlled Trial of Neratinib (HKI-272) After Trastuzumab in Women With Early-Stage HER-2/neu Overexpressed/Amplified Breast Cancer.

Summary

EudraCT number	2008-007345-31
Trial protocol	HU DE IT SK CZ ES BE GB LT NL FR DK SE GR MT BG PT
Global end of trial date	04 October 2019

Results information

Result version number	v1 (current)
This version publication date	18 October 2020
First version publication date	18 October 2020

Trial information

Trial identification

Sponsor protocol code	3144A2-3004-WW

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00878709
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Puma Biotechnology, Inc.
Sponsor organisation address	10880 Wilshire Blvd, Suite 2150, Los Angeles, United States, 90024
Public contact	Clinical Operations Senior Director, Puma Biotechnology, Inc, 1 4242486500, clinicaltrials@pumabiotechnology.com
Scientific contact	Clinical Operations Senior Director, Puma Biotechnology, Inc., 1 4242486500, clinicaltrials@pumabiotechnology.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	04 October 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	04 October 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was to compare invasive disease free survival of women with early-stage HER2-overexpressed/amplified breast cancer who received neratinib or placebo in an extended adjuvant setting after one year of adjuvant trastuzumab.

Protection of trial subjects:

Study commencement required prior written approval of a properly constituted Institutional Review Board (IRB) or Independent Ethics Committee (IEC). Clinical trial data were monitored at regular intervals by the Sponsor or their representative throughout the study to verify compliance to study protocol, completeness, accuracy and consistency of the data and adherence to local regulations on the conduct of clinical research. Patients were discontinued from study drug treatment (but remained in the study, if appropriate) under the following circumstances: patient completed twelve months of protocol-specified treatment, clinically documented disease recurrence as determined by the investigator, adverse event, patient request, investigator request, protocol violation, lost to follow-up, discontinuation of the study by the sponsor or death.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	09 July 2009
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Macedonia, the former Yugoslav Republic of: 19
Country: Number of subjects enrolled	United Kingdom: 80
Country: Number of subjects enrolled	United States: 899
Country: Number of subjects enrolled	Czech Republic: 35
Country: Number of subjects enrolled	Netherlands: 27
Country: Number of subjects enrolled	Bahamas: 4
Country: Number of subjects enrolled	Taiwan: 12
Country: Number of subjects enrolled	Korea, Republic of: 37
Country: Number of subjects enrolled	Australia: 106
Country: Number of subjects enrolled	Belgium: 26
Country: Number of subjects enrolled	Bulgaria: 34
Country: Number of subjects enrolled	Canada: 93
Country: Number of subjects enrolled	China: 49
Country: Number of subjects enrolled	Colombia: 21
Country: Number of subjects enrolled	Croatia: 47

Country: Number of subjects enrolled	Denmark: 112
Country: Number of subjects enrolled	France: 112
Country: Number of subjects enrolled	Germany: 131
Country: Number of subjects enrolled	Greece: 39
Country: Number of subjects enrolled	Hong Kong: 30
Country: Number of subjects enrolled	Hungary: 61
Country: Number of subjects enrolled	Israel: 23
Country: Number of subjects enrolled	Italy: 78
Country: Number of subjects enrolled	Japan: 205
Country: Number of subjects enrolled	Lithuania: 25
Country: Number of subjects enrolled	Malaysia: 4
Country: Number of subjects enrolled	Malta: 12
Country: Number of subjects enrolled	Mexico: 1
Country: Number of subjects enrolled	New Zealand: 31
Country: Number of subjects enrolled	Peru: 3
Country: Number of subjects enrolled	Poland: 68
Country: Number of subjects enrolled	Romania: 13
Country: Number of subjects enrolled	Serbia: 35
Country: Number of subjects enrolled	Singapore: 4
Country: Number of subjects enrolled	Slovakia: 21
Country: Number of subjects enrolled	Spain: 245
Country: Number of subjects enrolled	Sweden: 7
Country: Number of subjects enrolled	Switzerland: 13
Country: Number of subjects enrolled	Turkey: 78
Worldwide total number of subjects	2840
EEA total number of subjects	1173

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)	2492
From 65 to 84 years	348
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The institutional review board /independent ethics committee must review and approve the protocol and informed consent form (ICF) before any subjects provide consent.

Pre-assignment

Screening details:

Each subject must participate in the informed consent process and sign and date an ICF for this protocol before any protocol-required procedures are performed.

Period 1

Period 1 title	Treatment (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Neratinib

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:

Six (6) Neratinib 40 mg tablets, given continuously for 1 year (ie, 52 weeks), as long as tolerated, there is no evidence of recurrent breast cancer or a new breast cancer, the subject is lost to follow-up, or withdraws consent.

Arm title	Placebo

Arm description:

Placebo qd

Arm type	Placebo
Investigational medicinal product name	placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Six (6) Placebo tablets, given continuously for 1 year (ie, 52 weeks), as long as tolerated, there is no evidence of recurrent breast cancer or a new breast cancer, the subject is lost to follow-up, or withdraws consent.

Number of subjects in period 1	Neratinib	Placebo
Started	1420	1420
Completed	1095	1183
Not completed	325	237
Consent withdrawn by subject	197	120
Other reasons	93	84
Lost to follow-up	35	33

Baseline characteristics

Reporting groups	
Reporting group title	Neratinib
Reporting group description: Neratinib 240 mg qd	
Reporting group title	Placebo
Reporting group description: Placebo qd	

Reporting group values	Neratinib	Placebo	Total
Number of subjects	1420	1420	2840
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	52.3	52.3	
standard deviation	± 10.08	± 10.28	-
Gender categorical Units: Subjects			
Female	1420	1420	2840
Race/Ethnicity Units: Subjects			
Asian	188	197	385
Black or African American	27	47	74
White	1165	1135	2300
Other	40	41	81

Subject analysis sets	
Subject analysis set title	Intent to treat (ITT) population
Subject analysis set type	Intention-to-treat
Subject analysis set description: The Intent-to-treat (ITT) is defined as all subjects who were randomized.	

Reporting group values	Intent to treat (ITT) population		
Number of subjects	2840		
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	52.29		
standard deviation	± 10.18		

Gender categorical Units: Subjects			
Female	2840		
Race/Ethnicity Units: Subjects			
Asian	385		
Black or African American	74		
White	2300		
Other	81		

End points

End points reporting groups

Reporting group title	Neratinib
Reporting group description: Neratinib 240 mg qd	
Reporting group title	Placebo
Reporting group description: Placebo qd	
Subject analysis set title	Intent to treat (ITT) population
Subject analysis set type	Intention-to-treat
Subject analysis set description: The Intent-to-treat (ITT) is defined as all subjects who were randomized.	

Primary: Invasive Disease-free Survival (iDFS) in Neratinib Arm Compared to Placebo Arm at Year 2

End point title	Invasive Disease-free Survival (iDFS) in Neratinib Arm Compared to Placebo Arm at Year 2
End point description: Invasive disease-free survival time is defined as the time from date of randomization until the first disease recurrence of the following events: invasive ipsilateral breast tumor recurrence, invasive contralateral breast cancer, local/regional invasive recurrence, distant recurrence and death from any cause.	
End point type	Primary
End point timeframe: From randomization until time of event up to 2 years	

End point values	Neratinib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1420	1420		
Units: percentage of patients				
number (not applicable)	4.7	7.5		

Statistical analyses

Statistical analysis title	Invasive Disease-free Survival (iDFS)
Statistical analysis description: The 2-sided P-value was based on stratified log-rank test (stratification factors: prior Trastuzumab (concurrent or sequential), nodal status (<=3 or >=4) and ER/PgR status (positive or negative). The hazard ratio and corresponding 95% CI from the stratified cox proportional hazard model were also presented.	
Comparison groups	Neratinib v Placebo

Number of subjects included in analysis	2840
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.008
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.66
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.49
upper limit	0.9

Primary: Kaplan-Meier Estimates of Invasive Disease-free Survival (iDFS) at Year 2 by Treatment Arms

End point title	Kaplan-Meier Estimates of Invasive Disease-free Survival (iDFS) at Year 2 by Treatment Arms

End point description:

Invasive disease-free survival time is defined as the time from date of randomization until the first disease recurrence of the following events: invasive ipsilateral breast tumor recurrence, invasive contralateral breast cancer, local/regional invasive recurrence, distant recurrence and death from any cause.

End point type	Primary

End point timeframe:

From randomization until time of event up to 2 years

End point values	Neratinib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1420	1420		
Units: 2-year disease free survival rate				
number (confidence interval 95%)	94.2 (92.6 to 95.4)	91.9 (90.2 to 93.2)		

Statistical analyses

Statistical analysis title	Invasive Disease-free Survival (iDFS)
Comparison groups	Neratinib v Placebo
Number of subjects included in analysis	2840
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.008
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.66

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.49
upper limit	0.9

Secondary: Disease-free Survival Including Ductal Carcinoma in Situ (DFS-DCIS) in Neratinib Arm Compared to Placebo Arm at Year 2

End point title	Disease-free Survival Including Ductal Carcinoma in Situ (DFS-DCIS) in Neratinib Arm Compared to Placebo Arm at Year 2

End point description:

Disease-free survival including DCIS time is defined as the time from date of randomization until the first occurrence of DCIS or an iDFS event (an iDFS event including invasive ipsilateral breast tumor recurrence, invasive contralateral breast cancer, local/regional invasive recurrence, or distant recurrence and death from any cause.

End point type	Secondary

End point timeframe:

From randomization until time of event up to 2 years.

End point values	Neratinib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1420	1420		
Units: percentage				
number (not applicable)	4.7	8.0		

Statistical analyses

Statistical analysis title	DFS-DCIS

Statistical analysis description:

The hazard ratio is estimated by stratified Cox model. The Cox model is stratified by prior trastuzumab (concurrent or sequential), nodal status (<= 3 or >= 4) and ER/PgR status (positive or negative).

Comparison groups	Neratinib v Placebo
Number of subjects included in analysis	2840
Analysis specification	Pre-specified
Analysis type	other[1]
Parameter estimate	Hazard ratio (HR)
Point estimate	0.61
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.45
upper limit	0.83

Notes:

[1] - Estimation

Secondary: Distant Disease-free Survival (DDFS) in Neratinib Arm Compared to Placebo Arm at Year 2

End point title	Distant Disease-free Survival (DDFS) in Neratinib Arm Compared to Placebo Arm at Year 2

End point description:

Distant disease-free survival time is defined as the time from date of randomization until the first occurrence of distant recurrence or death from any cause.

End point type	Secondary

End point timeframe:

From randomization until time of event up to 2 years

End point values	Neratinib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1420	1420		
Units: percentage				
number (not applicable)	3.8	5.4		

Statistical analyses

Statistical analysis title	DDFS

Statistical analysis description:

The hazard ratio is estimated by stratified Cox model. The Cox model is stratified by prior trastuzumab (concurrent or sequential), nodal status (<= 3 or >= 4) and ER/PgR status (positive or negative).

Comparison groups	Neratinib v Placebo
Number of subjects included in analysis	2840
Analysis specification	Pre-specified
Analysis type	other[2]
Parameter estimate	Hazard ratio (HR)
Point estimate	0.74
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.52
upper limit	1.05

Notes:

[2] - Estimation

Secondary: Time to Distant Recurrence (TTDR) in Neratinib Arm Compared to Placebo Arm at Year 2

End point title	Time to Distant Recurrence (TTDR) in Neratinib Arm Compared to Placebo Arm at Year 2

End point description:

Time to distant recurrence is defined as the time from date of randomization until the first occurrence of distant recurrence or death from breast cancer.

End point type	Secondary

End point timeframe:

From randomization until time of event up to 2 years.

End point values	Neratinib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1420	1420		
Units: percentage				
number (not applicable)	3.7	5.3		

Statistical analyses

Statistical analysis title	TTDR

Statistical analysis description:

The hazard ratio is estimated by stratified Cox model. The Cox model is stratified by prior trastuzumab (concurrent or sequential), nodal status (<= 3 or >= 4) and ER/PgR status (positive or negative).

Comparison groups	Neratinib v Placebo
Number of subjects included in analysis	2840
Analysis specification	Pre-specified
Analysis type	other[3]
Parameter estimate	Hazard ratio (HR)
Point estimate	0.73
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.51
upper limit	1.04

Notes:

[3] - Estimation

Secondary: Cumulative Incidence of Central Nervous System Recurrence (CNS) at Year 2

End point title	Cumulative Incidence of Central Nervous System Recurrence (CNS) at Year 2

End point description:

Cumulative incidence of CNS recurrence as a site of first distant recurrence is defined as time from randomization to CNS recurrence as first distant recurrence. Competing events include distant recurrence at other sites as first distant recurrence and death from any cause prior to distant recurrence.

End point type	Secondary

End point timeframe:

From randomization until time of event up to 2 years.

End point values	Neratinib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1420	1420		
Units: percentage				
number (confidence interval 95%)	0.92 (0.49 to 1.59)	1.16 (0.68 to 1.87)		

Statistical analyses

No statistical analyses for this end point

Secondary: Kaplan-Meier Estimates of Overall Survival (OS) by Treatment Arms

End point title	Kaplan-Meier Estimates of Overall Survival (OS) by Treatment Arms

End point description:

OS was defined as the time from randomization to death due to any cause, censored at the last date known alive.

End point type	Secondary

End point timeframe:

Randomization until death due to any cause (up to 119 Months)

End point values	Neratinib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1420	1420		
Units: Survival rate at 8 year				
number (confidence interval 95%)	90.09 (88.27 to 91.64)	90.20 (88.43 to 91.70)		

Statistical analyses

Statistical analysis title	OS

Statistical analysis description:

The 2-sided P-value was based on stratified log-rank test (stratification factors: prior Trastuzumab (concurrent or sequential), nodal status (<=3 or >=4) and ER/PgR status (positive or negative). The hazard ratio and corresponding 95% CI from the stratified Cox proportional hazard model were also presented.

Comparison groups	Neratinib v Placebo

Number of subjects included in analysis	2840
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6914
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.952
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.747
upper limit	1.212

Other pre-specified: Invasive Disease-free Survival (iDFS) in Neratinib Arm Compared to Placebo Arm at Year 5

End point title	Invasive Disease-free Survival (iDFS) in Neratinib Arm Compared to Placebo Arm at Year 5

End point description:

Invasive disease-free survival time is defined as the time from date of randomization until the first disease recurrence of the following events: invasive ipsilateral breast tumor recurrence, invasive contralateral breast cancer, local/regional invasive recurrence, distant recurrence and death from any cause.

End point type	Other pre-specified

End point timeframe:

From randomization until time of event up to 5 years

End point values	Neratinib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1420	1420		
Units: percent				
number (not applicable)	8.2	11.5		

Statistical analyses

Statistical analysis title	Invasive Disease-free Survival (iDFS)

Statistical analysis description:

The 2-sided P-value was based on stratified log-rank test (stratification factors: prior Trastuzumab (concurrent or sequential), nodal status (<=3 or >=4) and ER/PgR status (positive or negative). The hazard ratio and corresponding 95% CI from the stratified cox proportional hazard model were also presented.

Comparison groups	Neratinib v Placebo

Number of subjects included in analysis	2840
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.008
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.73
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.57
upper limit	0.92

Other pre-specified: Kaplan-Meier Estimates of Invasive Disease-free Survival (iDFS) at Year 5 by Treatment Arms

End point title	Kaplan-Meier Estimates of Invasive Disease-free Survival (iDFS) at Year 5 by Treatment Arms

End point description:

Invasive disease-free survival time is defined as the time from date of randomization until the first disease recurrence of the following events: invasive ipsilateral breast tumor recurrence, invasive contralateral breast cancer, local/regional invasive recurrence, distant recurrence and death from any cause.

End point type	Other pre-specified

End point timeframe:

From randomization until time of event up to 5 years

End point values	Neratinib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1420	1420		
Units: percent				
number (confidence interval 95%)	90.2 (88.3 to 91.8)	87.7 (85.7 to 89.4)		

Statistical analyses

Statistical analysis title	Invasive Disease-free Survival (iDFS)
Comparison groups	Neratinib v Placebo
Number of subjects included in analysis	2840
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.008
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.73

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.57
upper limit	0.92

Other pre-specified: Disease-free Survival Including Ductal Carcinoma in Situ (DFS-DCIS) in Neratinib Arm Compared to Placebo Arm at Year 5

End point title	Disease-free Survival Including Ductal Carcinoma in Situ (DFS-DCIS) in Neratinib Arm Compared to Placebo Arm at Year 5

End point description:

Disease-free survival including DCIS time is defined as the time from date of randomization until the first occurrence of DCIS or an iDFS event (an iDFS event including invasive ipsilateral breast tumor recurrence, invasive contralateral breast cancer, local/regional invasive recurrence, or distant recurrence and death from any cause.

End point type	Other pre-specified

End point timeframe:

From randomization until time of event up to 5 years.

End point values	Neratinib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1420	1420		
Units: percent				
number (not applicable)	8.5	12.3		

Statistical analyses

Statistical analysis title	DFS-DCIS

Statistical analysis description:

The hazard ratio is estimated by stratified Cox model. The Cox model is stratified by prior trastuzumab (concurrent or sequential), nodal status (<= 3 or >= 4) and ER/PgR status (positive or negative).

Comparison groups	Neratinib v Placebo
Number of subjects included in analysis	2840
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Hazard ratio (HR)
Point estimate	0.71
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.56
upper limit	0.89

Other pre-specified: Distant Disease-free Survival (DDFS) in Neratinib Arm Compared to Placebo Arm at Year 5

End point title	Distant Disease-free Survival (DDFS) in Neratinib Arm Compared to Placebo Arm at Year 5

End point description:

Distant disease-free survival time is defined as the time from date of randomization until the first occurrence of distant recurrence or death from any cause.

End point type	Other pre-specified

End point timeframe:

From randomization until time of event up to 5 years

End point values	Neratinib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1420	1420		
Units: percent				
number (not applicable)	7.0	9.2		

Statistical analyses

Statistical analysis title	DDFS

Statistical analysis description:

The hazard ratio is estimated by stratified Cox model. The Cox model is stratified by prior trastuzumab (concurrent or sequential), nodal status (<= 3 or >= 4) and ER/PgR status (positive or negative).

Comparison groups	Neratinib v Placebo
Number of subjects included in analysis	2840
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Hazard ratio (HR)
Point estimate	0.78
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.6
upper limit	1.01

Other pre-specified: Time to Distant Recurrence (TTDR) in Neratinib Arm Compared to Placebo Arm at Year 5

End point title	Time to Distant Recurrence (TTDR) in Neratinib Arm Compared to Placebo Arm at Year 5

End point description:

Time to distant recurrence is defined as the time from date of randomization until the first occurrence of distant recurrence or death from breast cancer.

End point type	Other pre-specified

End point timeframe:

From randomization until time of event up to 5 years.

End point values	Neratinib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1420	1420		
Units: percent				
number (not applicable)	6.8	8.9		

Statistical analyses

Statistical analysis title	TTDR

Statistical analysis description:

The hazard ratio is estimated by stratified Cox model. The Cox model is stratified by prior trastuzumab (concurrent or sequential), nodal status (<= 3 or >= 4) and ER/PgR status (positive or negative).

Comparison groups	Neratinib v Placebo
Number of subjects included in analysis	2840
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Hazard ratio (HR)
Point estimate	0.79
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.6
upper limit	1.03

Other pre-specified: Cumulative Incidence of Central Nervous System Recurrence (CNS) at Year 5

End point title	Cumulative Incidence of Central Nervous System Recurrence (CNS) at Year 5

End point description:

Cumulative incidence of CNS recurrence as a site of first distant recurrence is defined as time from randomization to CNS recurrence as first distant recurrence. Competing events include distant recurrence at other sites as first distant recurrence and death from any cause prior to distant recurrence.

End point type	Other pre-specified

End point timeframe:

From randomization until time of event up to 5 years.

End point values	Neratinib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1420	1420		
Units: percent				
number (confidence interval 95%)	1.3 (0.77 to 2.06)	1.82 (1.19 to 2.68)		

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	Placebo
Reporting group description: Placebo qd	
Reporting group title	Neratinib
Reporting group description: Neratinib 240 mg qd	

Serious adverse events	Placebo	Neratinib	
Total subjects affected by serious adverse events			
subjects affected / exposed	85 / 1408 (6.04%)	103 / 1408 (7.32%)	
number of deaths (all causes)	28	25	
number of deaths resulting from adverse events	1	2	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute myeloid leukaemia			
subjects affected / exposed	0 / 1408 (0.00%)	1 / 1408 (0.07%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Basal cell carcinoma			
subjects affected / exposed	2 / 1408 (0.14%)	2 / 1408 (0.14%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Benign breast neoplasm			
subjects affected / exposed	1 / 1408 (0.07%)	0 / 1408 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Benign female reproductive tract neoplasm			

subjects affected / exposed	0 / 1408 (0.00%)	1 / 1408 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cancer			
subjects affected / exposed	2 / 1408 (0.14%)	0 / 1408 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cancer metastatic			
subjects affected / exposed	0 / 1408 (0.00%)	1 / 1408 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Breast neoplasm			
subjects affected / exposed	1 / 1408 (0.07%)	0 / 1408 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cancer pain			
subjects affected / exposed	0 / 1408 (0.00%)	1 / 1408 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric cancer			
subjects affected / exposed	1 / 1408 (0.07%)	0 / 1408 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Glioblastoma			
subjects affected / exposed	0 / 1408 (0.00%)	1 / 1408 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Glioma			
subjects affected / exposed	0 / 1408 (0.00%)	1 / 1408 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung adenocarcinoma			

subjects affected / exposed	1 / 1408 (0.07%)	0 / 1408 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant melanoma			
subjects affected / exposed	0 / 1408 (0.00%)	1 / 1408 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant melanoma in situ			
subjects affected / exposed	0 / 1408 (0.00%)	1 / 1408 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant pleural effusion			
subjects affected / exposed	0 / 1408 (0.00%)	1 / 1408 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to eye			
subjects affected / exposed	1 / 1408 (0.07%)	0 / 1408 (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	0 / 1408 (0.00%)	1 / 1408 (0.07%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Sarcoma			
subjects affected / exposed	1 / 1408 (0.07%)	0 / 1408 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sarcoma uterus			
subjects affected / exposed	1 / 1408 (0.07%)	0 / 1408 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine leiomyoma			

subjects affected / exposed	1 / 1408 (0.07%)	0 / 1408 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular neoplasm			
subjects affected / exposed	1 / 1408 (0.07%)	0 / 1408 (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 / 1408 (0.07%)	0 / 1408 (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 / 1408 (0.07%)	0 / 1408 (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 / 1408 (0.00%)	1 / 1408 (0.07%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Hysterosalpingo-oophorectomy			
subjects affected / exposed	1 / 1408 (0.07%)	0 / 1408 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 1408 (0.00%)	1 / 1408 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	0 / 1408 (0.00%)	3 / 1408 (0.21%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	

Non-cardiac chest pain			
subjects affected / exposed	0 / 1408 (0.00%)	3 / 1408 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	1 / 1408 (0.07%)	2 / 1408 (0.14%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Food allergy			
subjects affected / exposed	1 / 1408 (0.07%)	0 / 1408 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Endometrial hyperplasia			
subjects affected / exposed	1 / 1408 (0.07%)	1 / 1408 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endometrial hypertrophy			
subjects affected / exposed	0 / 1408 (0.00%)	1 / 1408 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endometriosis			
subjects affected / exposed	0 / 1408 (0.00%)	1 / 1408 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metrorrhagia			
subjects affected / exposed	1 / 1408 (0.07%)	1 / 1408 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian cyst			
subjects affected / exposed	1 / 1408 (0.07%)	0 / 1408 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Uterine polyp			
subjects affected / exposed	1 / 1408 (0.07%)	0 / 1408 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vulval leukoplakia			
subjects affected / exposed	1 / 1408 (0.07%)	0 / 1408 (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			
Atelectasis			
subjects affected / exposed	0 / 1408 (0.00%)	1 / 1408 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	1 / 1408 (0.07%)	2 / 1408 (0.14%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 1408 (0.07%)	1 / 1408 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	1 / 1408 (0.07%)	0 / 1408 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	1 / 1408 (0.07%)	1 / 1408 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	3 / 1408 (0.21%)	3 / 1408 (0.21%)	
occurrences causally related to treatment / all	1 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	

Tachypnoea			
subjects affected / exposed	1 / 1408 (0.07%)	0 / 1408 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 1408 (0.07%)	0 / 1408 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
subjects affected / exposed	2 / 1408 (0.14%)	1 / 1408 (0.07%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental disorder			
subjects affected / exposed	1 / 1408 (0.07%)	0 / 1408 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental status changes			
subjects affected / exposed	0 / 1408 (0.00%)	2 / 1408 (0.14%)	
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	0 / 1408 (0.00%)	4 / 1408 (0.28%)	
occurrences causally related to treatment / all	0 / 0	5 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 1408 (0.00%)	4 / 1408 (0.28%)	
occurrences causally related to treatment / all	0 / 0	5 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood creatine increased			
subjects affected / exposed	0 / 1408 (0.00%)	1 / 1408 (0.07%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Blood thyroid stimulating hormone increased			
subjects affected / exposed	0 / 1408 (0.00%)	1 / 1408 (0.07%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ejection fraction decreased			
subjects affected / exposed	1 / 1408 (0.07%)	0 / 1408 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrocardiogram T wave inversion			
subjects affected / exposed	0 / 1408 (0.00%)	1 / 1408 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcus test positive			
subjects affected / exposed	0 / 1408 (0.00%)	1 / 1408 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	0 / 1408 (0.00%)	1 / 1408 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	1 / 1408 (0.07%)	0 / 1408 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fracture			
subjects affected / exposed	0 / 1408 (0.00%)	1 / 1408 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	1 / 1408 (0.07%)	0 / 1408 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Humerus fracture			
subjects affected / exposed	1 / 1408 (0.07%)	0 / 1408 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meniscus injury			
subjects affected / exposed	2 / 1408 (0.14%)	0 / 1408 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple injuries			
subjects affected / exposed	0 / 1408 (0.00%)	1 / 1408 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Patella fracture			
subjects affected / exposed	1 / 1408 (0.07%)	0 / 1408 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sternal fracture			
subjects affected / exposed	0 / 1408 (0.00%)	1 / 1408 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound dehiscence			
subjects affected / exposed	1 / 1408 (0.07%)	1 / 1408 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wrist fracture			
subjects affected / exposed	0 / 1408 (0.00%)	1 / 1408 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	0 / 1408 (0.00%)	1 / 1408 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			

subjects affected / exposed	1 / 1408 (0.07%)	0 / 1408 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	1 / 1408 (0.07%)	1 / 1408 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus tachycardia			
subjects affected / exposed	1 / 1408 (0.07%)	0 / 1408 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia			
subjects affected / exposed	1 / 1408 (0.07%)	0 / 1408 (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			
Ageusia			
subjects affected / exposed	0 / 1408 (0.00%)	1 / 1408 (0.07%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anosmia			
subjects affected / exposed	0 / 1408 (0.00%)	1 / 1408 (0.07%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain oedema			
subjects affected / exposed	1 / 1408 (0.07%)	0 / 1408 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carotid artery stenosis			
subjects affected / exposed	1 / 1408 (0.07%)	0 / 1408 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haemorrhage			

subjects affected / exposed	0 / 1408 (0.00%)	1 / 1408 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral infarction			
subjects affected / exposed	0 / 1408 (0.00%)	1 / 1408 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	1 / 1408 (0.07%)	0 / 1408 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	1 / 1408 (0.07%)	0 / 1408 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	1 / 1408 (0.07%)	0 / 1408 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intercostal neuralgia			
subjects affected / exposed	1 / 1408 (0.07%)	0 / 1408 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paresis			
subjects affected / exposed	0 / 1408 (0.00%)	1 / 1408 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Speech disorder			
subjects affected / exposed	1 / 1408 (0.07%)	0 / 1408 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			

subjects affected / exposed	2 / 1408 (0.14%)	3 / 1408 (0.21%)	
occurrences causally related to treatment / all	0 / 2	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	1 / 1408 (0.07%)	0 / 1408 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tremor			
subjects affected / exposed	1 / 1408 (0.07%)	0 / 1408 (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			
Anaemia			
subjects affected / exposed	1 / 1408 (0.07%)	1 / 1408 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 1408 (0.07%)	0 / 1408 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	1 / 1408 (0.07%)	0 / 1408 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	0 / 1408 (0.00%)	2 / 1408 (0.14%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	0 / 1408 (0.00%)	1 / 1408 (0.07%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Abdominal strangulated hernia			
subjects affected / exposed	0 / 1408 (0.00%)	1 / 1408 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	2 / 1408 (0.14%)	0 / 1408 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis ischaemic			
subjects affected / exposed	1 / 1408 (0.07%)	0 / 1408 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	1 / 1408 (0.07%)	0 / 1408 (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	1 / 1408 (0.07%)	22 / 1408 (1.56%)	
occurrences causally related to treatment / all	2 / 2	29 / 30	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocele			
subjects affected / exposed	0 / 1408 (0.00%)	1 / 1408 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	1 / 1408 (0.07%)	4 / 1408 (0.28%)	
occurrences causally related to treatment / all	1 / 1	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	1 / 1408 (0.07%)	2 / 1408 (0.14%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Periodontal disease			

subjects affected / exposed	0 / 1408 (0.00%)	1 / 1408 (0.07%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal cancer			
subjects affected / exposed	0 / 1408 (0.00%)	1 / 1408 (0.07%)	
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 / 1408 (0.07%)	12 / 1408 (0.85%)	
occurrences causally related to treatment / all	0 / 1	13 / 15	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 1408 (0.00%)	1 / 1408 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			
subjects affected / exposed	0 / 1408 (0.00%)	1 / 1408 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	0 / 1408 (0.00%)	2 / 1408 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic function abnormal			
subjects affected / exposed	1 / 1408 (0.07%)	0 / 1408 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertransaminasaemia			
subjects affected / exposed	1 / 1408 (0.07%)	0 / 1408 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaundice cholestatic			

subjects affected / exposed	1 / 1408 (0.07%)	0 / 1408 (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			
Dermatitis			
subjects affected / exposed	0 / 1408 (0.00%)	1 / 1408 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erythema			
subjects affected / exposed	0 / 1408 (0.00%)	1 / 1408 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin disorder			
subjects affected / exposed	1 / 1408 (0.07%)	0 / 1408 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin necrosis			
subjects affected / exposed	1 / 1408 (0.07%)	1 / 1408 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Bladder prolapse			
subjects affected / exposed	1 / 1408 (0.07%)	0 / 1408 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperuricosuria			
subjects affected / exposed	0 / 1408 (0.00%)	1 / 1408 (0.07%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal colic			
subjects affected / exposed	0 / 1408 (0.00%)	1 / 1408 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			

subjects affected / exposed	0 / 1408 (0.00%)	2 / 1408 (0.14%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure acute			
subjects affected / exposed	0 / 1408 (0.00%)	3 / 1408 (0.21%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Lumbar spinal stenosis			
subjects affected / exposed	1 / 1408 (0.07%)	0 / 1408 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscle spasms			
subjects affected / exposed	1 / 1408 (0.07%)	0 / 1408 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular weakness			
subjects affected / exposed	1 / 1408 (0.07%)	0 / 1408 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal chest pain			
subjects affected / exposed	1 / 1408 (0.07%)	0 / 1408 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	1 / 1408 (0.07%)	1 / 1408 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	1 / 1408 (0.07%)	0 / 1408 (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			

Abdominal wall abscess			
subjects affected / exposed	1 / 1408 (0.07%)	0 / 1408 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal abscess			
subjects affected / exposed	0 / 1408 (0.00%)	1 / 1408 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anorectal cellulitis			
subjects affected / exposed	0 / 1408 (0.00%)	1 / 1408 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	1 / 1408 (0.07%)	1 / 1408 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis perforated			
subjects affected / exposed	0 / 1408 (0.00%)	1 / 1408 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast abscess			
subjects affected / exposed	1 / 1408 (0.07%)	0 / 1408 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cellulitis			
subjects affected / exposed	1 / 1408 (0.07%)	1 / 1408 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	1 / 1408 (0.07%)	2 / 1408 (0.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			

subjects affected / exposed	4 / 1408 (0.28%)	6 / 1408 (0.43%)	
occurrences causally related to treatment / all	0 / 4	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis			
subjects affected / exposed	0 / 1408 (0.00%)	1 / 1408 (0.07%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	3 / 1408 (0.21%)	0 / 1408 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	1 / 1408 (0.07%)	0 / 1408 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	0 / 1408 (0.00%)	5 / 1408 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia urinary tract infection			
subjects affected / exposed	0 / 1408 (0.00%)	1 / 1408 (0.07%)	
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 / 1408 (0.00%)	1 / 1408 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis salmonella			
subjects affected / exposed	0 / 1408 (0.00%)	1 / 1408 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal viral infection			

subjects affected / exposed	0 / 1408 (0.00%)	1 / 1408 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	0 / 1408 (0.00%)	1 / 1408 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incision site cellulitis			
subjects affected / exposed	1 / 1408 (0.07%)	0 / 1408 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Localised infection			
subjects affected / exposed	0 / 1408 (0.00%)	1 / 1408 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mastitis			
subjects affected / exposed	1 / 1408 (0.07%)	0 / 1408 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ophthalmic herpes zoster			
subjects affected / exposed	0 / 1408 (0.00%)	1 / 1408 (0.07%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	4 / 1408 (0.28%)	1 / 1408 (0.07%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal abscess			
subjects affected / exposed	0 / 1408 (0.00%)	1 / 1408 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			

subjects affected / exposed	1 / 1408 (0.07%)	0 / 1408 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Streptococcal sepsis			
subjects affected / exposed	0 / 1408 (0.00%)	1 / 1408 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			
subjects affected / exposed	0 / 1408 (0.00%)	1 / 1408 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 1408 (0.07%)	9 / 1408 (0.64%)	
occurrences causally related to treatment / all	0 / 1	8 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrolyte imbalance			
subjects affected / exposed	1 / 1408 (0.07%)	0 / 1408 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	1 / 1408 (0.07%)	0 / 1408 (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 / 1408 (0.00%)	1 / 1408 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypomagnesaemia			
subjects affected / exposed	0 / 1408 (0.00%)	1 / 1408 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			

subjects affected / exposed	1 / 1408 (0.07%)	1 / 1408 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo	Neratinib	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1234 / 1408 (87.64%)	1386 / 1408 (98.44%)	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	45 / 1408 (3.20%)	118 / 1408 (8.38%)	
occurrences (all)	63	170	
Aspartate aminotransferase increased			
subjects affected / exposed	46 / 1408 (3.27%)	101 / 1408 (7.17%)	
occurrences (all)	65	152	
Electrocardiogram QT prolonged			
subjects affected / exposed	93 / 1408 (6.61%)	49 / 1408 (3.48%)	
occurrences (all)	128	64	
Vascular disorders			
Hot flush			
subjects affected / exposed	84 / 1408 (5.97%)	40 / 1408 (2.84%)	
occurrences (all)	109	49	
Nervous system disorders			
Dizziness			
subjects affected / exposed	127 / 1408 (9.02%)	146 / 1408 (10.37%)	
occurrences (all)	211	241	
Headache			
subjects affected / exposed	275 / 1408 (19.53%)	278 / 1408 (19.74%)	
occurrences (all)	764	707	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	110 / 1408 (7.81%)	107 / 1408 (7.60%)	
occurrences (all)	194	237	
Fatigue			

subjects affected / exposed	283 / 1408 (20.10%)	381 / 1408 (27.06%)	
occurrences (all)	490	805	
Pyrexia			
subjects affected / exposed	54 / 1408 (3.84%)	77 / 1408 (5.47%)	
occurrences (all)	73	95	
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	49 / 1408 (3.48%)	73 / 1408 (5.18%)	
occurrences (all)	79	160	
Abdominal pain			
subjects affected / exposed	144 / 1408 (10.23%)	339 / 1408 (24.08%)	
occurrences (all)	256	924	
Abdominal pain upper			
subjects affected / exposed	96 / 1408 (6.82%)	212 / 1408 (15.06%)	
occurrences (all)	195	607	
Constipation			
subjects affected / exposed	134 / 1408 (9.52%)	115 / 1408 (8.17%)	
occurrences (all)	290	245	
Diarrhoea			
subjects affected / exposed	499 / 1408 (35.44%)	1341 / 1408 (95.24%)	
occurrences (all)	3215	25625	
Dyspepsia			
subjects affected / exposed	59 / 1408 (4.19%)	139 / 1408 (9.87%)	
occurrences (all)	113	253	
Nausea			
subjects affected / exposed	303 / 1408 (21.52%)	605 / 1408 (42.97%)	
occurrences (all)	593	1377	
Stomatitis			
subjects affected / exposed	29 / 1408 (2.06%)	85 / 1408 (6.04%)	
occurrences (all)	62	151	
Vomiting			
subjects affected / exposed	113 / 1408 (8.03%)	364 / 1408 (25.85%)	
occurrences (all)	161	627	
Respiratory, thoracic and mediastinal disorders			

Cough			
subjects affected / exposed	92 / 1408 (6.53%)	69 / 1408 (4.90%)	
occurrences (all)	122	81	
Epistaxis			
subjects affected / exposed	18 / 1408 (1.28%)	71 / 1408 (5.04%)	
occurrences (all)	33	120	
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	33 / 1408 (2.34%)	85 / 1408 (6.04%)	
occurrences (all)	35	101	
Rash			
subjects affected / exposed	100 / 1408 (7.10%)	211 / 1408 (14.99%)	
occurrences (all)	142	369	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	73 / 1408 (5.18%)	44 / 1408 (3.13%)	
occurrences (all)	90	56	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	162 / 1408 (11.51%)	86 / 1408 (6.11%)	
occurrences (all)	240	123	
Back pain			
subjects affected / exposed	134 / 1408 (9.52%)	79 / 1408 (5.61%)	
occurrences (all)	168	127	
Muscle spasms			
subjects affected / exposed	44 / 1408 (3.13%)	159 / 1408 (11.29%)	
occurrences (all)	70	303	
Pain in extremity			
subjects affected / exposed	98 / 1408 (6.96%)	58 / 1408 (4.12%)	
occurrences (all)	159	108	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	126 / 1408 (8.95%)	84 / 1408 (5.97%)	
occurrences (all)	188	143	
Urinary tract infection			

subjects affected / exposed	23 / 1408 (1.63%)	72 / 1408 (5.11%)	
occurrences (all)	26	86	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	40 / 1408 (2.84%)	170 / 1408 (12.07%)	
occurrences (all)	51	226	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 February 2010	This amendment included the following updates: restricted eligibility criteria to only include patients with a higher risk of recurrence: node positive patients only, within 1 year from completion of prior trastuzumab therapy; excluded patients with prior neoadjuvant therapy if they achieved a pathologic complete response (pCR) in breast and/or axilla, or if they had only residual in situ disease; removed node-negative stratum, and revised randomization stratification to include the following factors: ER- and/or PR-positive versus ER- and PR-negative; nodal status (1-3 versus 4 or more); and trastuzumab given sequentially versus concurrently with chemotherapy; mandated the availability of an archived diagnostic tumor sample for central ERBB2 testing and the patient's written consent for this testing; revised dose adjustment guidelines for neratinib-related toxicities; revised guidelines for the management of asymptomatic LVEF declines; increased frequency of safety monitoring for hepatotoxicity and added guidelines for the management of changes in liver function tests; updated the statistical analysis section to reflect changes in trial design and underlying assumptions; allowed concomitant therapy with bisphosphonates at any time regardless of the indication; and other nonadministrative and administrative changes, including changing the sponsor due to the acquisition of Wyeth by Pfizer Inc.
14 June 2010	This amendment included the following updates: clarified eligibility criteria to state that patients who are node negative or have an unknown nodal status in the axilla after neoadjuvant therapy, but have residual invasive disease in the breast, are eligible. These patients must be stratified as "1-3" positive nodes, revised the definition of the amended intent-to-treat (aITT) population include patients who are node-negative or have an unknown nodal status after neoadjuvant therapy, but have residual disease in the breast; added additional complete blood count (CBC) collection time points at months 2 and 4.5 as a precaution per recommendation of the Independent Data Monitoring Committee (IDMC) after bone marrow suppression (resulting in neutropenia and thrombocytopenia, without any other clear cause) was reported in another neratinib trial in one patient who had taken neratinib monotherapy for 4 months; refined exclusion criterion number 17 to state "On treatment or in followup of any other neoadjuvant or adjuvant breast cancer trial with DFS as an endpoint"; and clarified that missed doses or underdosing of investigational product are not considered medication errors; updated blood volumes to be drawn from each patient; and specified acceptable fixation methods for tumor samples and the minimum number of slides required for central ERBB2 testing.

18 November 2010	This amendment included the following updates per recommendation of the independent monitoring committee. Additional measures were implemented and existing tools were modified to improve the monitoring and clinical management of diarrhea, the dominant adverse event (AE) seen in the study. The key changes were: Patients must have loperamide on hand when taking the first dose of investigational product (IP). Options included: dispense loperamide along with IP, the investigator provides a prescription for loperamide when dispensing IP on day 1, or the patient obtains loperamide over-the-counter. The following documents were implemented at each site: new investigator checklist for each patient prior to randomizing, modified patient instructions for the management of diarrhea, and modified patient diary for recording of IP intake, AEs (including diarrhea), number of daily stools, and the use of loperamide and/or other anti-diarrheals. The investigator/designee were to call the patient between days 3-5 to confirm that the patient has loperamide available; to inquire about the first dose of IP and any AEs, especially diarrhea; and to provide guidance for immediate medical management of the AEs, if any. Guidelines for diarrhea management with loperamide and for neratinib dose adjustment were revised and consolidated in one place in the protocol. Guidelines for unblinding were updated per recent administrative letter. Other administrative updates were made throughout the document due to the acquisition of Wyeth by Pfizer Inc. These changes included updates in contact information, a new global Serious AE reporting fax number, and removal of the Sponsor and investigator signature pages due to revised approval process.

14 October 2011	This amendment included the following updates due to changes in organizational strategy. Enrollment of new patients was stopped, and several study design changes were implemented, including reductions to the number of randomized patients, the duration of patient participation, study duration, follow-up period and the scope of exploratory objectives. Patient-reported outcome data (FACT-B, EQ-5D) and tumor samples for biomarker analysis were removed. Statistical assumptions were adjusted due to the reduction in sample size and shortened follow-up time; the prespecified total number of disease-free survival events required for final analysis and the previously-planned interim analyses were removed. Guidelines for the management of diarrhea were revised. Guidelines for the management of changes in liver function tests were revised. Option for dose re-escalation was removed globally. The mandate to discontinue study treatment after unblinding in case of a Suspected Unexpected Serious Adverse Reaction was removed. Adverse Event Reporting was adjusted to standard Legacy-Pfizer safety language, and a new SAE reporting form was adopted. Language providing an option for patients in the placebo arm to receive IP after study completion/termination was removed in anticipation that the reduced sample size will affect the ability to draw efficacy conclusions from the study. References to the 240-mg tablet were removed because the formulation had not been provided for the study. Storage conditions for the IP were clarified. The sponsorship of the study was transferred from Wyeth, a Pfizer Company, to Puma starting on 01-JAN-2012, following a development and commercialization agreement for the IP (neratinib) between Pfizer Inc. and Puma Biotechnology, Inc. on 05-OCT-2011.
21 March 2012	This amendment included the following updates: Safety reporting wording was updated to comply with the most recent Sponsor-approved safety language. The requirement to collect a PK sample in case of suspected severe hepatotoxicity was removed due to a very small number of suspected hepatotoxicities reported in the study to date (5 out of 2842 randomized patients). Synopsis, Flowchart, and other pertinent sections were updated to reflect changes made in the body of the protocol. Reference to the Academic Steering Committee was removed since the committee is no longer in place. Administrative changes were made due to the transfer of sponsorship from Wyeth, a Pfizer Company, to Puma, including revisions in the emergency contact information.

16 January 2014	The purpose of the Amendment was to obtain additional Disease Free Survival (DFS) and Overall Survival (OS) data in order to evaluate the long-term efficacy of neratinib in the adjuvant setting. The study follow-up (FU) period was extended to 5 years, and all randomized patients who had discontinued FU at 2 years will be re-consented to obtain survival data. All randomized patients will be included in the analysis of efficacy endpoints. The study design was revised to indicate how recurrent disease events and deaths will be ascertained for the Intent to Treat (ITT) population: Part A: Data collected during the FU period of 2 years post randomization will form the primary analysis. DFS and OS endpoints will be based upon the recurrent disease events and deaths that occurred during this 2-year period. Part B: The expanded FU period from years 2 through 5 years post randomization will evaluate the durability of the treatment effect on DFS and the impact on OS. Recurrent disease events and deaths will be ascertained from patients' medical records. Statistical evaluations for this part of the study will be considered sensitivity analyses. Part C: Long-term FU of OS will continue for patients who re-consented and will start from 5 years post randomization. Sensitivity analyses of DFS will be included on patient subsets according to the following criteria: Patients in the amended ITT population (aITT) consisting of all patients randomized under Amendment 3 or later, and all patients randomized prior to implementation of Amendment 3 if they had node-positive disease and were treated with trastuzumab ≤1 year prior to randomization; All randomized patients who had node-positive disease; All randomized patients who entered the trial within 1 year of completion of prior trastuzumab; All randomized patients who were ERBB2-positive by central testing. Statistical methods and considerations were revised and a description of the sensitivity analysis was added.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/31140297

http://www.ncbi.nlm.nih.gov/pubmed/30867034

http://www.ncbi.nlm.nih.gov/pubmed/30813966

http://www.ncbi.nlm.nih.gov/pubmed/30689703

http://www.ncbi.nlm.nih.gov/pubmed/29146401

http://www.ncbi.nlm.nih.gov/pubmed/26874901