Clinical trial results:
Estudio de Fase I/II de HKI-272 en combinación con trastuzumab (Herceptin) en sujetos con cáncer de mama avanzado.

A Phase I/II Study of HKI-272 in Combination With Trastuzumab (Herceptin) in Subjects With Advanced Breast Cancer.

Summary

EudraCT number	2006-003215-52
Trial protocol	ES FR
Global end of trial date	23 May 2018
Results information	
Result version number	v2 (current)
This version publication date	22 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.
Summary attachment (see zip file)	3144A1-202 PDS (3144A1-202 (B1891013) Public Disclosure Synopsis .doc.pdf)

Trial information

Trial identification	
Sponsor protocol code	3144A1-202-WW
Additional study identifiers	
ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00398567
WHO universal trial number (UTN)	-

Notes:

Sponsors	
Sponsor organisation name	Puma Biotechnology, Inc.
Sponsor organisation address	10880 Wilshire Blvd, Suite 2100, 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	23 May 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	23 May 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Primary objectives:

Part 1: To assess the safety and tolerability, and to define the MTD of orally administered HKI-272 in combination with trastuzumab in subjects with advanced breast cancer.
Part 2: To determine the 16 week progression free survival (PFS) rate for subjects with advanced breast cancer treated at the MTD with HKI-272 and 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 active treatment phase of the study for any of the following reasons, but not limited to: documented disease progression, adverse event, symptomatic deterioration, subject request, investigator request (with detailed documentation of reasoning), protocol violation, discontinuation of the study by the sponsor, lost to follow-up, or death. Subjects were discontinued or withdrawn from the study for any of the following reasons: subject request, lost to follow up, protocol violation, discontinuation of the study by the sponsor, or death.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 February 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	France: 5
Country: Number of subjects enrolled	United States: 16
Country: Number of subjects enrolled	Switzerland: 4
Country: Number of subjects enrolled	China: 20
Worldwide total number of subjects	45
EEA total number of subjects	5

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)	39
From 65 to 84 years	6
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

All advertising, recruitment, and other written information provided to the subject had to have been approved by the IRB/IEC.

Pre-assignment

Screening details:

Patients were screened to evaluate any inclusion/exclusion criteria and were assigned to receive trastuzumab in combination Neratinib 160 mg or 240 mg in Part 1, and then the maximum tolerated dose, as determined in Part 1 of the study, in Part 2.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Part 1 Ner160 + Trastuzumab

Arm description:

Part 1, dose-escalation phase. Neratinib 160 mg in combination with trastuzumab 4 mg/kg loading and then 2 mg/kg every week after.

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 160 mg was administered orally, preferably with a meal and in the morning. On the days when both neratinib and trastuzumab were administered, neratinib was taken within 30 minutes after the end of the trastuzumab infusion.

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

Dosage and administration details:

Trastuzumab was administered as an IV infusion over 90 minutes at the dose of 4 mg/kg, followed by a weekly dose of 2 mg/kg administered over 30 minutes.

Arm title	Part 1 Ner240 + Trastuzumab

Arm description:

Part 1, dose-escalation phase. Neratinib 240 mg in combination with trastuzumab 4 mg/kg loading and then 2 mg/kg every week after.

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 240 mg was administered orally, preferably with a meal and in the morning. On the days when both neratinib and trastuzumab were administered, neratinib was taken within 30 minutes after the end of the trastuzumab infusion.

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

Dosage and administration details:

Trastuzumab was administered as an IV infusion over 90 minutes at the dose of 4 mg/kg, followed by a weekly dose of 2 mg/kg administered over 30 minutes.

Arm title	Part 2 Ner240 + Trastuzumab

Arm description:

Part 2 of study. Neratinib 240 mg in combination with Trastuzumab.

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 240 mg was administered orally, preferably with a meal and in the morning. On the days when both neratinib and trastuzumab were administered, neratinib was taken within 30 minutes after the end of the trastuzumab infusion.

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

Dosage and administration details:

Trastuzumab was administered as an IV infusion over 90 minutes at the dose of 4 mg/kg, followed by a weekly dose of 2 mg/kg administered over 30 minutes.

Number of subjects in period 1	Part 1 Ner160 + Trastuzumab	Part 1 Ner240 + Trastuzumab	Part 2 Ner240 + Trastuzumab
Started	4	4	37
Completed	0	0	0
Not completed	4	4	37
Consent withdrawn by subject	1	-	4
Adverse event, non-fatal	-	-	2
Study discontinuation by sponsor	-	-	1
Lost to follow-up	-	-	2
Disease Progression	3	4	27
Protocol deviation	-	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Part 1 Ner160 + Trastuzumab
Reporting group description:	
Part 1, dose-escalation phase. Neratinib 160 mg in combination with trastuzumab 4 mg/kg loading and then 2 mg/kg every week after.	
Reporting group title	Part 1 Ner240 + Trastuzumab
Reporting group description:	
Part 1, dose-escalation phase. Neratinib 240 mg in combination with trastuzumab 4 mg/kg loading and then 2 mg/kg every week after.	
Reporting group title	Part 2 Ner240 + Trastuzumab
Reporting group description:	
Part 2 of study. Neratinib 240 mg in combination with Trastuzumab.	

Reporting group values	Part 1 Ner160 + Trastuzumab	Part 1 Ner240 + Trastuzumab	Part 2 Ner240 + Trastuzumab
Number of subjects	4	4	37
Age categorical Units: Subjects			
Adults (18-64 years)	4	3	32
From 65-84 years	0	1	5
Gender categorical Units: Subjects			
Female	4	4	37

Reporting group values	Total		
Number of subjects	45		
Age categorical Units: Subjects			
Adults (18-64 years)	39		
From 65-84 years	6		
Gender categorical Units: Subjects			
Female	45		

End points

End points reporting groups

Reporting group title	Part 1 Ner160 + Trastuzumab
Reporting group description:	
Part 1, dose-escalation phase. Neratinib 160 mg in combination with trastuzumab 4 mg/kg loading and then 2 mg/kg every week after.	
Reporting group title	Part 1 Ner240 + Trastuzumab
Reporting group description:	
Part 1, dose-escalation phase. Neratinib 240 mg in combination with trastuzumab 4 mg/kg loading and then 2 mg/kg every week after.	
Reporting group title	Part 2 Ner240 + Trastuzumab
Reporting group description:	
Part 2 of study. Neratinib 240 mg in combination with Trastuzumab.	

Primary: Number of Patients with Dose Limiting Toxicity

End point title	Number of Patients with Dose Limiting Toxicity[1][2]
End point description:	
In part 1, the dose-escalation phase, 3 to 6 subjects were to be enrolled in each dose group. Enrollment at the next dose level began when all evaluable subjects at the first dose level were evaluated for 21 days after the first dose of test article. Additional subjects could be included at any dose level to further assess the safety and tolerability at that dose level. In part 1, subjects who withdrew from the study and were not considered evaluable could be replaced. DLTs were assessed from the administration of the first dose of test article through day 21, and were defined as any test article-related grade 2 or grade 3 diarrhea lasting >2 days despite optimal medical therapy, or diarrhea associated with fever or dehydration, grade 3 or grade 4 nonhematologic toxicity, grade 4 hematologic toxicity, or symptomatic congestive heart failure (CHF), confirmed by a cardiology assessment.	
End point type	Primary
End point timeframe:	
From first dose date through 21 days after dose.	

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 number of patients with Dose Limiting Toxicity were analyzed in each of the two arms in Part 1 of the study and they were analyzed separated. There were no comparisons or analyses to be made between the two arms.
[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Number of Patients with Dose Limiting Toxicity was analyzed only in Part 1 of the study.

End point values	Part 1 Ner160 + Trastuzumab	Part 1 Ner240 + Trastuzumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	4		
Units: Patients				
number (not applicable)	0	0		

Statistical analyses

No statistical analyses for this end point

Primary: 16-Week Progression-Free Survival Rate

End point title	16-Week Progression-Free Survival Rate[3][4]

End point description:

Sixteen (16) week PFS rate: the estimated proportion of evaluable subjects who are alive and progression-free 16 weeks after the first dose of test article. The evaluable population was defined as the subjects who met the eligibility criteria for study enrollment, received at least 1 week of neratinib and at least 2 doses of trastuzumab, and had a baseline tumor assessment and at least 1 follow-up tumor assessment approximately 8 weeks after starting test article administration.

End point type	Primary

End point timeframe:

From the date of first dose through Week 16.

Notes:

[3] - 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: This 16-Week Progression-Free Survival Rate was computed for Part 2 of the study and there were no comparisons to be made. The rate and the corresponding 95% CI were estimated using the Kaplan-Meier method.
[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: 16-Week Progression-Free Survival Rate was analyzed only in Part 2 of the study.

End point values	Part 2 Ner240 + Trastuzumab			
Subject group type	Reporting group			
Number of subjects analysed	28			
Units: percent				
number (confidence interval 95%)	44.8 (25.9 to 62.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-Free Survival

End point title	Progression-Free Survival[5]

End point description:

The time to tumor progression is the interval from the date of the first dose of test article to the first date on which any of the following criteria are met: 1. Documented PD per modified RECIST criteria as described above. 2. Early determination of PD status in the opinion of the investigator, in the absence of measurement data. 3. Discontinuation of test article due to symptomatic deterioration, or death due to any cause. The date of the last dose of test article will be considered the date of progression. Subjects who do not meet the above criteria for progression will be censored at the last valid post-screening tumor assessment. Valid tumor assessment is defined as an assessment where overall response includes either CR or PR or SD. Subjects who do not have a post-screening tumor assessment will be censored at the date of first dose of test article. Median PFS estimated by Kaplan-Meier method is reported.

End point type	Secondary

End point timeframe:

Interval from the first dose date of test article until the first date on which recurrence or progression, or death due to any cause, is documented, censored at the last tumor assessment date.

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Progression-Free Survival was analyzed only in Part 2 of the study.

End point values	Part 2 Ner240 + Trastuzumab			
Subject group type	Reporting group			
Number of subjects analysed	28			
Units: Weeks				
number (confidence interval 95%)	15.9 (15.1 to 31.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Objective Response Rate

End point title	Objective Response Rate[6]

End point description:

Percent of subjects achieving a complete or partial response. Complete and partial responses must be confirmed by 2 observations not less than 4 weeks apart.

End point type	Secondary

End point timeframe:

From Day 1 of study through the last assessment.

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Objective Response Rate was analyzed only in Part 2 of the study.

End point values	Part 2 Ner240 + Trastuzumab			
Subject group type	Reporting group			
Number of subjects analysed	28			
Units: Percentage				
number (confidence interval 95%)	28.6 (13.2 to 48.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Benefit Rate

End point title	Clinical Benefit Rate[7]

End point description:

Proportion of subjects demonstrating CR, PR, or duration of SD for at least 24 weeks

End point type	Secondary

End point timeframe:

From first dose to last tumor assessment.

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Clinical Benefit Rate was analyzed only in Part 2 of the study.

End point values	Part 2 Ner240 + Trastuzumab			
Subject group type	Reporting group			
Number of subjects analysed	28			
Units: Percentage				
number (confidence interval 95%)	35.7 (18.6 to 55.9)			

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	NER160 + TRAST, PART 1
Reporting group description: Neratinib 160 mg qd + Trastuzumab IV weekly at 4 mg/kg or 2 mg/kg, Part 1	
Reporting group title	NER240 + TRAST, PART 1
Reporting group description: Neratinib 240 mg qd + Trastuzumab IV weekly at 4 mg/kg or 2 mg/kg, Part 1	
Reporting group title	NER240 + TRAST, PART 2
Reporting group description: Neratinib MTD (240) mg qd + Trastuzumab IV weekly at 4 mg/kg or 2 mg/kg, Part 2	

Serious adverse events	NER160 + TRAST, PART 1	NER240 + TRAST, PART 1	NER240 + TRAST, PART 2
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	8 / 37 (21.62%)
number of deaths (all causes)	0	0	3
number of deaths resulting from adverse events	0	0	1
Injury, poisoning and procedural complications			
Lumbar vertebral fracture			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Ataxia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Disease progression			

subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal adhesions			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal distension			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	2 / 37 (5.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal			

disorders			
Dyspnoea			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Influenza			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nasopharyngitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hyponatraemia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	NER160 + TRAST, PART 1	NER240 + TRAST, PART 1	NER240 + TRAST, PART 2
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 4 (100.00%)	4 / 4 (100.00%)	37 / 37 (100.00%)
Vascular disorders			
Hot flush			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	1 / 37 (2.70%)
occurrences (all)	0	1	1
Hypotension			

subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 37 (0.00%)
occurrences (all)	0	1	0
Lymphoedema			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	2 / 37 (5.41%)
occurrences (all)	0	1	4
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	14 / 37 (37.84%)
occurrences (all)	0	0	27
Catheter site pain			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 37 (0.00%)
occurrences (all)	0	1	0
Chills			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	1 / 37 (2.70%)
occurrences (all)	0	1	1
Crying			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 37 (0.00%)
occurrences (all)	0	1	0
Fatigue			
subjects affected / exposed	1 / 4 (25.00%)	2 / 4 (50.00%)	6 / 37 (16.22%)
occurrences (all)	1	3	8
Irritability			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 37 (0.00%)
occurrences (all)	0	1	0
Non-cardiac chest pain			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 37 (0.00%)
occurrences (all)	1	0	0
Oedema peripheral			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	2 / 37 (5.41%)
occurrences (all)	0	1	2
Pyrexia			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	4 / 37 (10.81%)
occurrences (all)	1	0	8
Reproductive system and breast disorders			

Vulvovaginal pruritus			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 37 (0.00%)
occurrences (all)	1	0	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	4 / 37 (10.81%)
occurrences (all)	0	1	13
Dry throat			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 37 (0.00%)
occurrences (all)	0	1	0
Dysphonia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	1 / 37 (2.70%)
occurrences (all)	0	1	1
Dyspnoea			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	4 / 37 (10.81%)
occurrences (all)	0	0	7
Epistaxis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	1 / 37 (2.70%)
occurrences (all)	0	2	1
Nasal congestion			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 37 (0.00%)
occurrences (all)	0	2	0
Oropharyngeal pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	3 / 37 (8.11%)
occurrences (all)	0	0	3
Rhinorrhoea			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	3 / 37 (8.11%)
occurrences (all)	0	0	4
Upper-airway cough syndrome			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	2 / 37 (5.41%)
occurrences (all)	0	0	2
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 37 (0.00%)
occurrences (all)	0	1	0
Insomnia			

subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	4 / 37 (10.81%)
occurrences (all)	0	0	4
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	4 / 37 (10.81%)
occurrences (all)	0	0	6
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	5 / 37 (13.51%)
occurrences (all)	0	0	10
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	2 / 37 (5.41%)
occurrences (all)	0	0	3
Blood lactate dehydrogenase increased			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 37 (0.00%)
occurrences (all)	1	0	0
Ejection fraction decreased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	3 / 37 (8.11%)
occurrences (all)	0	0	4
Haemoglobin decreased			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	4 / 37 (10.81%)
occurrences (all)	0	3	6
Hepatic enzyme increased			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 37 (0.00%)
occurrences (all)	1	0	0
Weight decreased			
subjects affected / exposed	0 / 4 (0.00%)	2 / 4 (50.00%)	7 / 37 (18.92%)
occurrences (all)	0	3	11
Weight increased			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 37 (0.00%)
occurrences (all)	0	1	0
White blood cell count decreased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	2 / 37 (5.41%)
occurrences (all)	0	0	5
Cardiac disorders			

Palpitations			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 37 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			
Balance disorder			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 37 (0.00%)
occurrences (all)	0	1	0
Dizziness			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	5 / 37 (13.51%)
occurrences (all)	0	0	5
Dysgeusia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	2 / 37 (5.41%)
occurrences (all)	0	1	2
Headache			
subjects affected / exposed	2 / 4 (50.00%)	1 / 4 (25.00%)	5 / 37 (13.51%)
occurrences (all)	2	1	5
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 4 (25.00%)	1 / 4 (25.00%)	2 / 37 (5.41%)
occurrences (all)	2	1	3
Leukopenia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	2 / 37 (5.41%)
occurrences (all)	0	0	3
Neutropenia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	2 / 37 (5.41%)
occurrences (all)	0	0	4
Neutrophilia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	2 / 37 (5.41%)
occurrences (all)	0	0	3
Thrombocytopenia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	2 / 37 (5.41%)
occurrences (all)	0	0	2
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	2 / 37 (5.41%)
occurrences (all)	0	0	2
Eye disorders			

Conjunctivitis			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	1 / 37 (2.70%)
occurrences (all)	2	0	1
Dry eye			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	2 / 37 (5.41%)
occurrences (all)	0	0	2
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	3 / 37 (8.11%)
occurrences (all)	0	0	4
Abdominal pain			
subjects affected / exposed	1 / 4 (25.00%)	1 / 4 (25.00%)	6 / 37 (16.22%)
occurrences (all)	1	1	7
Abdominal pain upper			
subjects affected / exposed	2 / 4 (50.00%)	0 / 4 (0.00%)	2 / 37 (5.41%)
occurrences (all)	2	0	2
Constipation			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	1 / 37 (2.70%)
occurrences (all)	0	1	1
Diarrhoea			
subjects affected / exposed	4 / 4 (100.00%)	4 / 4 (100.00%)	34 / 37 (91.89%)
occurrences (all)	27	41	135
Dyspepsia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	4 / 37 (10.81%)
occurrences (all)	0	0	5
Dysphagia			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	1 / 37 (2.70%)
occurrences (all)	1	0	1
Haemorrhoids			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	2 / 37 (5.41%)
occurrences (all)	0	0	2
Nausea			
subjects affected / exposed	3 / 4 (75.00%)	3 / 4 (75.00%)	17 / 37 (45.95%)
occurrences (all)	5	7	32
Stomatitis			

subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	2 / 37 (5.41%)
occurrences (all)	0	0	2
Vomiting			
subjects affected / exposed	2 / 4 (50.00%)	2 / 4 (50.00%)	14 / 37 (37.84%)
occurrences (all)	2	4	28
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	2 / 37 (5.41%)
occurrences (all)	0	0	3
Alopecia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	2 / 37 (5.41%)
occurrences (all)	0	0	2
Dermatitis acneiform			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	2 / 37 (5.41%)
occurrences (all)	0	0	2
Dry skin			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	4 / 37 (10.81%)
occurrences (all)	1	0	5
Erythema			
subjects affected / exposed	2 / 4 (50.00%)	1 / 4 (25.00%)	2 / 37 (5.41%)
occurrences (all)	3	1	4
Exfoliative rash			
subjects affected / exposed	1 / 4 (25.00%)	1 / 4 (25.00%)	0 / 37 (0.00%)
occurrences (all)	1	1	0
Nail disorder			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	2 / 37 (5.41%)
occurrences (all)	0	0	4
Pruritus			
subjects affected / exposed	0 / 4 (0.00%)	2 / 4 (50.00%)	2 / 37 (5.41%)
occurrences (all)	0	2	6
Rash			
subjects affected / exposed	1 / 4 (25.00%)	1 / 4 (25.00%)	8 / 37 (21.62%)
occurrences (all)	5	1	13
Skin exfoliation			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	2 / 37 (5.41%)
occurrences (all)	0	0	3

Skin lesion			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	2 / 37 (5.41%)
occurrences (all)	0	0	2
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	4 / 37 (10.81%)
occurrences (all)	0	1	4
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	2 / 37 (5.41%)
occurrences (all)	0	2	3
Back pain			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	2 / 37 (5.41%)
occurrences (all)	0	2	2
Bone pain			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 37 (0.00%)
occurrences (all)	1	0	0
Muscle spasms			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	4 / 37 (10.81%)
occurrences (all)	0	0	12
Muscular weakness			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	3 / 37 (8.11%)
occurrences (all)	0	0	5
Pain in extremity			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	1 / 37 (2.70%)
occurrences (all)	0	1	1
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	2 / 37 (5.41%)
occurrences (all)	0	0	3
Lymphangitis			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 37 (0.00%)
occurrences (all)	1	0	0
Nasopharyngitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	2 / 37 (5.41%)
occurrences (all)	0	0	2

Paronychia			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	1 / 37 (2.70%)
occurrences (all)	2	0	1
Pharyngitis			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	1 / 37 (2.70%)
occurrences (all)	1	0	1
Rhinitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	3 / 37 (8.11%)
occurrences (all)	0	0	4
Upper respiratory tract infection			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	4 / 37 (10.81%)
occurrences (all)	0	1	4
Urinary tract infection			
subjects affected / exposed	0 / 4 (0.00%)	2 / 4 (50.00%)	3 / 37 (8.11%)
occurrences (all)	0	3	4
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 4 (25.00%)	2 / 4 (50.00%)	19 / 37 (51.35%)
occurrences (all)	1	2	26
Dehydration			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	2 / 37 (5.41%)
occurrences (all)	0	1	3
Hypocalcaemia			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	1 / 37 (2.70%)
occurrences (all)	1	0	1
Hypokalaemia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	3 / 37 (8.11%)
occurrences (all)	0	0	3

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 June 2007	This amendment included a smaller part 2, with 30 subjects enrolled at maximum tolerated dose, and updates to the eligibility criteria.
13 September 2007	This amendment clarified that certain standard procedures do not need to be repeated for the purposes of determining eligibility if done within the screening window, and that for final visit, if LVEF was assessed within the previous 8 weeks, it does not need to be repeated at the final visit.
19 May 2008	This amendment specified that subjects may receive more than 12 months of treatment if treatment was well tolerated, if the disease has not progressed, if the subject is clinically stable, and if the subject has received the overall benefit from the treatment according to the investigator's judgement. Subject continuation will be discussed with the Sponsor. Study procedures for any visits beyond 12 months will be the same as months 3-12 with the exception of pharmacokinetics.
22 March 2012	This amendment changed the Sponsor to Puma and included a Treatment Extension Period, which allowed patients who still derived benefit from study participation to remain on the study and enabled the Sponsor to continue to provide investigational product (IP) to the 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 documented, but no efficacy data were collected.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

Data reported in Addendum and Final Report for 3 patients followed after database lock are consistent with safety conclusions presented in iCSR and ISR and do not impact known safety profile of neratinib in combination with trastuzumab.

Notes: