Clinical trial results:
A Phase 2 Study of Neratinib and Neratinib Plus Temsirolimus in Patients with Non-Small Cell Lung Cancer Carrying Known HER2 Activating Mutations

Summary

EudraCT number	2012-004743-68
Trial protocol	FR
Global end of trial date	03 October 2017

Results information

Result version number	v1 (current)
This version publication date	19 October 2018
First version publication date	19 October 2018

Trial information

Trial identification

Sponsor protocol code	PUMA-NER-4201

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01827267
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 April 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	20 September 2016
Global end of trial reached?	Yes
Global end of trial date	03 October 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This is a Phase 2, therapeutic-exploratory, adaptive design, open-label, multicenter, multinational study evaluating neratinib monotherapy and neratinib plus temsirolimus combination therapy in patients with non-small cell lung cancer (NSCLC) who have documented somatic HER2 mutations.

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 investigational product(s) (IP) in the following circumstances: unacceptable toxicity, if patient required more than 2 dose reductions of neratinib, disease progression on combination therapy, initiation of alternative anti-cancer therapy, including chemotherapy, radiotherapy, and cancer-related surgery, pregnancy, or patient request.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 May 2013
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	United States: 34
Country: Number of subjects enrolled	France: 28
Worldwide total number of subjects	62
EEA total number of subjects	28

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	30
From 65 to 84 years	31
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

This is a Phase 2, therapeutic-exploratory, adaptive design, open-label, multicenter, multinational study evaluating neratinib monotherapy and neratinib plus temsirolimus combination therapy in patients with NSCLC who have documented somatic HER2 mutations and who have received at least one prior cytotoxic chemotherapy regimen.

Pre-assignment

Screening details:

A total of 62 patients were randomised: 18 to Neratinib arm and 44 to Neratinib + Temsirolimus arm. Two patients were randomised but did not receive investigational product and are not included in the Safety Population or in the Efficacy Evaluable Population.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Neratinib

Arm description:

Neratinib 240 mg

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 40 mg tablets (total daily dose 240 mg) orally, once daily with food, preferably in the morning, continuously in 21-day cycles.

Arm title	Neratinib+Temsirolimus

Arm description:

Neratinib 240 mg + Temsirolimus 8 mg.

Arm type	Experimental
Investigational medicinal product name	Neratinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Oral use

Dosage and administration details:

Six neratinib 40 mg tablets (total daily dose 240 mg) orally, once daily with food, preferably in the morning, continuously in 21-day cycles, plus temsirolimus 8 mg weekly by IV infusion. All patients on combination therapy may be dose-escalated with respect to temsirolimus dose to 15 mg/week at the end of first cycle of treatment with the combination, if well tolerated and at the physician's discretion. In the event that the neratinib 240 mg/day plus temsirolimus 15 mg/week dose is not well tolerated, the patient will be subsequently dose reduced back to neratinib 240 mg/day plus temsirolimus 8 mg/week

Number of subjects in period 1	Neratinib	Neratinib+Temsirolimus
Started	18	44
Completed	17	43
Not completed	1	1
Adverse event, serious fatal	1	-
Physician decision	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Neratinib
Reporting group description: Neratinib 240 mg	
Reporting group title	Neratinib+Temsirolimus
Reporting group description: Neratinib 240 mg + Temsirolimus 8 mg.	

Reporting group values	Neratinib	Neratinib+Temsirolimus	Total
Number of subjects	18	44	62
Age categorical Units: Subjects			
Adults (18-64 years)	11	19	30
From 65-84 years	7	24	31
85 years and over	0	1	1
Gender categorical Units: Subjects			
Female	9	33	42
Male	9	11	20

End points

End points reporting groups

Reporting group title	Neratinib
Reporting group description: Neratinib 240 mg	
Reporting group title	Neratinib+Temsirolimus
Reporting group description: Neratinib 240 mg + Temsirolimus 8 mg.	

Primary: Objective Response Rate (ORR)

End point title	Objective Response Rate (ORR)[1]

End point description:

ORR is defined as proportion of subjects who achieved confirmed complete response (CR) or partial response (PR) per RECIST v1.1. A complete or partial response must be confirmed no less than 4-weeks after the criteria for response are initially met.

End point type	Primary

End point timeframe:

From randomisation to disease progression or last tumor assessment.

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: No formal comparisons between treatment groups were specified by the protocol. Descriptive statistics only are provided.

End point values	Neratinib	Neratinib+Temsirolimus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	43		
Units: Percentage of overall population				
number (confidence interval 95%)	0 (0 to 19.51)	13.95 (5.3 to 27.93)		

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Benefit Rate (CBR)

End point title	Clinical Benefit Rate (CBR)

End point description:

CBR is defined as the proportion of patients who achieved objective response (CR or PR) or SD for at least 12 weeks.

End point type	Secondary

End point timeframe:

From randomisation to disease progression or death.

End point values	Neratinib	Neratinib+Temsirolimus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	43		
Units: percentage of overall population				
number (confidence interval 95%)	35.29 (14.21 to 61.67)	48.84 (33.31 to 65.54)		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival (PFS)

End point title	Progression Free Survival (PFS)

End point description:

PFS is defined as the interval from the date of randomisation to date of first documented disease progression (per RECIST v1.1) or death due to any cause, whichever comes first.

End point type	Secondary

End point timeframe:

From randomisation to first documented disease progression, death or end of long term follow-up.

End point values	Neratinib	Neratinib+Temsirolimus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	43		
Units: months				
median (confidence interval 95%)	2.9 (1.4 to 9.8)	4 (2.9 to 5.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR)

End point title	Duration of Response (DOR)

End point description:

For subjects who achieved a response. Measured from the time at which measurement criteria were first met for CR or PR (whichever status was recorded first), until the date of first recurrence, PD, or death was objectively documented, taking as a reference for PD the smallest measurements recorded since enrollment, per RECIST (v1.1) criteria.

End point type	Secondary

End point timeframe:

From first response to first PD or death.

End point values	Neratinib	Neratinib+Temsirolimus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[2]	6[3]		
Units: Percentage of overall population				
number (not applicable)				
Less than 3 months		2		
3 to less than 6 months		2		
6 to less than 12 months		0		
Greater than 12 months		2		

Notes:

[2] - No subjects achieved a response in this arm.

[3] - 6 subjects achieved response in the Neratinib + Temsirolimus arm.

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

Overall survival is defined as time from randomisation to death due to any cause.

End point type	Secondary

End point timeframe:

From randomisation to death or end of long term follow-up.

End point values	Neratinib	Neratinib+Temsirolimus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	43		
Units: months				
median (confidence interval 95%)	10 (4.9 to 18.9)	15.1 (10.8 to 17.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Safety Adverse Events and Serious Adverse Events [SAEs])

End point title	Safety Adverse Events and Serious Adverse Events [SAEs])

End point description:

The percent of patients with a adverse events or serious adverse event (SAE) reported during the study.

End point type	Secondary

End point timeframe:

Estimated 6 months

End point values	Neratinib	Neratinib+Temsirolimus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	43		
Units: Percentage of Patients				
number (not applicable)				
Adverse Events	100	100		
Serious Adverse Events	41.2	37.2		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: First dose through 28 days after last dose	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	17.0
Reporting groups	
Reporting group title	Neratinib + Temsirolimus
Reporting group description: Neratinib + Temsirolimus	
Reporting group title	Neratinib
Reporting group description: Neratinib	

Serious adverse events	Neratinib + Temsirolimus	Neratinib	
Total subjects affected by serious adverse events			
subjects affected / exposed	16 / 43 (37.21%)	11 / 17 (64.71%)	
number of deaths (all causes)	32	13	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant pleural effusion			
subjects affected / exposed	1 / 43 (2.33%)	0 / 17 (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	0 / 43 (0.00%)	1 / 17 (5.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Embolism			
subjects affected / exposed	1 / 43 (2.33%)	0 / 17 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			

Asthenia			
subjects affected / exposed	1 / 43 (2.33%)	1 / 17 (5.88%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	0 / 43 (0.00%)	2 / 17 (11.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pyrexia			
subjects affected / exposed	2 / 43 (4.65%)	0 / 17 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Anaphylactic shock			
subjects affected / exposed	1 / 43 (2.33%)	0 / 17 (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			
Pelvic pain			
subjects affected / exposed	0 / 43 (0.00%)	1 / 17 (5.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	3 / 43 (6.98%)	0 / 17 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Lung disorder			
subjects affected / exposed	0 / 43 (0.00%)	1 / 17 (5.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pleural effusion			

subjects affected / exposed	1 / 43 (2.33%)	3 / 17 (17.65%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	0 / 43 (0.00%)	1 / 17 (5.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pulmonary embolism			
subjects affected / exposed	1 / 43 (2.33%)	1 / 17 (5.88%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory distress			
subjects affected / exposed	1 / 43 (2.33%)	0 / 17 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Psychiatric disorders			
Delirium			
subjects affected / exposed	0 / 43 (0.00%)	1 / 17 (5.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood uric acid increased			
subjects affected / exposed	0 / 43 (0.00%)	1 / 17 (5.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical condition abnormal			
subjects affected / exposed	1 / 43 (2.33%)	1 / 17 (5.88%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	1 / 43 (2.33%)	0 / 17 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Infusion related reaction			
subjects affected / exposed	1 / 43 (2.33%)	0 / 17 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardio-respiratory arrest			
subjects affected / exposed	0 / 43 (0.00%)	1 / 17 (5.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia			
subjects affected / exposed	0 / 43 (0.00%)	1 / 17 (5.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	0 / 43 (0.00%)	1 / 17 (5.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	1 / 43 (2.33%)	0 / 17 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Monoparesis			
subjects affected / exposed	1 / 43 (2.33%)	0 / 17 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorder			
subjects affected / exposed	0 / 43 (0.00%)	1 / 17 (5.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuropathy peripheral			
subjects affected / exposed	0 / 43 (0.00%)	1 / 17 (5.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pachymeningitis			
subjects affected / exposed	0 / 43 (0.00%)	1 / 17 (5.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Somnolence			
subjects affected / exposed	1 / 43 (2.33%)	0 / 17 (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	0 / 43 (0.00%)	1 / 17 (5.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 43 (2.33%)	0 / 17 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	4 / 43 (9.30%)	2 / 17 (11.76%)	
occurrences causally related to treatment / all	4 / 4	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	0 / 43 (0.00%)	1 / 17 (5.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	2 / 43 (4.65%)	1 / 17 (5.88%)	
occurrences causally related to treatment / all	2 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	2 / 43 (4.65%)	0 / 17 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Renal and urinary disorders			
Urinary retention			
subjects affected / exposed	0 / 43 (0.00%)	1 / 17 (5.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 43 (0.00%)	1 / 17 (5.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neck pain			
subjects affected / exposed	0 / 43 (0.00%)	1 / 17 (5.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Infection			
subjects affected / exposed	0 / 43 (0.00%)	1 / 17 (5.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parainfluenzae virus infection			
subjects affected / exposed	0 / 43 (0.00%)	1 / 17 (5.88%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	2 / 43 (4.65%)	0 / 17 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia bacterial			
subjects affected / exposed	0 / 43 (0.00%)	1 / 17 (5.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			

subjects affected / exposed	0 / 43 (0.00%)	1 / 17 (5.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 43 (2.33%)	0 / 17 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	1 / 43 (2.33%)	2 / 17 (11.76%)	
occurrences causally related to treatment / all	1 / 1	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	0 / 43 (0.00%)	1 / 17 (5.88%)	
occurrences causally related to treatment / all	0 / 0	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	Neratinib + Temsirolimus	Neratinib	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	43 / 43 (100.00%)	17 / 17 (100.00%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Metastases to liver			
subjects affected / exposed	0 / 43 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	12 / 43 (27.91%)	6 / 17 (35.29%)	
occurrences (all)	22	8	
Catheter site erythema			
subjects affected / exposed	0 / 43 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Catheter site related reaction			

subjects affected / exposed	0 / 43 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Chest discomfort			
subjects affected / exposed	2 / 43 (4.65%)	1 / 17 (5.88%)	
occurrences (all)	5	1	
Chills			
subjects affected / exposed	5 / 43 (11.63%)	4 / 17 (23.53%)	
occurrences (all)	6	4	
Fatigue			
subjects affected / exposed	17 / 43 (39.53%)	4 / 17 (23.53%)	
occurrences (all)	35	10	
Gait disturbance			
subjects affected / exposed	0 / 43 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Influenza like illness			
subjects affected / exposed	1 / 43 (2.33%)	1 / 17 (5.88%)	
occurrences (all)	1	1	
Local swelling			
subjects affected / exposed	0 / 43 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Malaise			
subjects affected / exposed	1 / 43 (2.33%)	2 / 17 (11.76%)	
occurrences (all)	1	2	
Nodule			
subjects affected / exposed	0 / 43 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	2	
Non-cardiac chest pain			
subjects affected / exposed	1 / 43 (2.33%)	1 / 17 (5.88%)	
occurrences (all)	1	1	
Oedema			
subjects affected / exposed	1 / 43 (2.33%)	1 / 17 (5.88%)	
occurrences (all)	1	1	
Oedema peripheral			
subjects affected / exposed	7 / 43 (16.28%)	0 / 17 (0.00%)	
occurrences (all)	13	0	
Pain			

subjects affected / exposed	0 / 43 (0.00%)	2 / 17 (11.76%)	
occurrences (all)	0	2	
Pyrexia			
subjects affected / exposed	4 / 43 (9.30%)	3 / 17 (17.65%)	
occurrences (all)	5	17	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 43 (2.33%)	1 / 17 (5.88%)	
occurrences (all)	1	2	
Reproductive system and breast disorders			
Pelvic pain			
subjects affected / exposed	0 / 43 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	10 / 43 (23.26%)	2 / 17 (11.76%)	
occurrences (all)	12	2	
Dysphonia			
subjects affected / exposed	2 / 43 (4.65%)	1 / 17 (5.88%)	
occurrences (all)	2	1	
Dyspnoea			
subjects affected / exposed	14 / 43 (32.56%)	5 / 17 (29.41%)	
occurrences (all)	14	7	
Dyspnoea exertional			
subjects affected / exposed	2 / 43 (4.65%)	2 / 17 (11.76%)	
occurrences (all)	2	5	
Epistaxis			
subjects affected / exposed	12 / 43 (27.91%)	3 / 17 (17.65%)	
occurrences (all)	19	3	
Haemoptysis			
subjects affected / exposed	0 / 43 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Lung consolidation			
subjects affected / exposed	0 / 43 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Oropharyngeal pain			

subjects affected / exposed	5 / 43 (11.63%)	2 / 17 (11.76%)	
occurrences (all)	5	2	
Pleural effusion			
subjects affected / exposed	0 / 43 (0.00%)	2 / 17 (11.76%)	
occurrences (all)	0	2	
Productive cough			
subjects affected / exposed	1 / 43 (2.33%)	1 / 17 (5.88%)	
occurrences (all)	1	1	
Pulmonary embolism			
subjects affected / exposed	0 / 43 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	3 / 43 (6.98%)	3 / 17 (17.65%)	
occurrences (all)	3	3	
Insomnia			
subjects affected / exposed	7 / 43 (16.28%)	2 / 17 (11.76%)	
occurrences (all)	8	2	
Investigations			
Activated partial thromboplastin time prolonged			
subjects affected / exposed	3 / 43 (6.98%)	0 / 17 (0.00%)	
occurrences (all)	4	0	
Alanine aminotransferase increased			
subjects affected / exposed	10 / 43 (23.26%)	1 / 17 (5.88%)	
occurrences (all)	18	1	
Amylase increased			
subjects affected / exposed	4 / 43 (9.30%)	2 / 17 (11.76%)	
occurrences (all)	21	2	
Aspartate aminotransferase increased			
subjects affected / exposed	10 / 43 (23.26%)	2 / 17 (11.76%)	
occurrences (all)	14	2	
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 43 (2.33%)	1 / 17 (5.88%)	
occurrences (all)	3	1	
Blood calcium decreased			

subjects affected / exposed	0 / 43 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Blood creatine phosphokinase increased			
subjects affected / exposed	2 / 43 (4.65%)	1 / 17 (5.88%)	
occurrences (all)	2	2	
Blood creatinine increased			
subjects affected / exposed	4 / 43 (9.30%)	1 / 17 (5.88%)	
occurrences (all)	21	2	
Blood lactate dehydrogenase increased			
subjects affected / exposed	3 / 43 (6.98%)	3 / 17 (17.65%)	
occurrences (all)	3	3	
Blood phosphorus increased			
subjects affected / exposed	0 / 43 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Blood triglycerides increased			
subjects affected / exposed	3 / 43 (6.98%)	0 / 17 (0.00%)	
occurrences (all)	3	0	
Electrocardiogram QT prolonged			
subjects affected / exposed	1 / 43 (2.33%)	1 / 17 (5.88%)	
occurrences (all)	1	1	
Gamma-glutamyltransferase increased			
subjects affected / exposed	5 / 43 (11.63%)	3 / 17 (17.65%)	
occurrences (all)	5	3	
International normalised ratio increased			
subjects affected / exposed	0 / 43 (0.00%)	2 / 17 (11.76%)	
occurrences (all)	0	2	
Lymphocyte count decreased			
subjects affected / exposed	3 / 43 (6.98%)	0 / 17 (0.00%)	
occurrences (all)	19	0	
Neutrophil count increased			
subjects affected / exposed	0 / 43 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Prothrombin time prolonged			

subjects affected / exposed	0 / 43 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Weight decreased			
subjects affected / exposed	10 / 43 (23.26%)	3 / 17 (17.65%)	
occurrences (all)	20	3	
White blood cell count decreased			
subjects affected / exposed	5 / 43 (11.63%)	1 / 17 (5.88%)	
occurrences (all)	17	1	
White blood cell count increased			
subjects affected / exposed	0 / 43 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
Fracture			
subjects affected / exposed	0 / 43 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Cardiac disorders			
Arrhythmia			
subjects affected / exposed	0 / 43 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Atrial fibrillation			
subjects affected / exposed	0 / 43 (0.00%)	2 / 17 (11.76%)	
occurrences (all)	0	3	
Left atrial dilatation			
subjects affected / exposed	0 / 43 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Tachycardia			
subjects affected / exposed	1 / 43 (2.33%)	2 / 17 (11.76%)	
occurrences (all)	2	2	
Nervous system disorders			
Dizziness			
subjects affected / exposed	8 / 43 (18.60%)	2 / 17 (11.76%)	
occurrences (all)	14	2	
Dysaesthesia			
subjects affected / exposed	0 / 43 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Dysgeusia			

subjects affected / exposed	13 / 43 (30.23%)	1 / 17 (5.88%)	
occurrences (all)	16	1	
Headache			
subjects affected / exposed	10 / 43 (23.26%)	2 / 17 (11.76%)	
occurrences (all)	15	3	
Hypoaesthesia			
subjects affected / exposed	0 / 43 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Neuropathy peripheral			
subjects affected / exposed	1 / 43 (2.33%)	1 / 17 (5.88%)	
occurrences (all)	1	1	
Somnolence			
subjects affected / exposed	1 / 43 (2.33%)	1 / 17 (5.88%)	
occurrences (all)	1	1	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	18 / 43 (41.86%)	8 / 17 (47.06%)	
occurrences (all)	32	14	
Lymphopenia			
subjects affected / exposed	4 / 43 (9.30%)	0 / 17 (0.00%)	
occurrences (all)	8	0	
Neutropenia			
subjects affected / exposed	4 / 43 (9.30%)	0 / 17 (0.00%)	
occurrences (all)	8	0	
Thrombocytopenia			
subjects affected / exposed	2 / 43 (4.65%)	1 / 17 (5.88%)	
occurrences (all)	2	1	
Thrombocytosis			
subjects affected / exposed	0 / 43 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Eye disorders			
Vision blurred			
subjects affected / exposed	3 / 43 (6.98%)	0 / 17 (0.00%)	
occurrences (all)	4	0	
Gastrointestinal disorders			

Abdominal distension			
subjects affected / exposed	2 / 43 (4.65%)	2 / 17 (11.76%)	
occurrences (all)	2	4	
Abdominal pain			
subjects affected / exposed	8 / 43 (18.60%)	6 / 17 (35.29%)	
occurrences (all)	13	7	
Abdominal pain upper			
subjects affected / exposed	2 / 43 (4.65%)	4 / 17 (23.53%)	
occurrences (all)	3	4	
Aphthous stomatitis			
subjects affected / exposed	1 / 43 (2.33%)	1 / 17 (5.88%)	
occurrences (all)	3	1	
Cheilosis			
subjects affected / exposed	0 / 43 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Constipation			
subjects affected / exposed	18 / 43 (41.86%)	7 / 17 (41.18%)	
occurrences (all)	24	9	
Diarrhoea			
subjects affected / exposed	37 / 43 (86.05%)	14 / 17 (82.35%)	
occurrences (all)	189	82	
Dry mouth			
subjects affected / exposed	3 / 43 (6.98%)	0 / 17 (0.00%)	
occurrences (all)	3	0	
Dyspepsia			
subjects affected / exposed	2 / 43 (4.65%)	2 / 17 (11.76%)	
occurrences (all)	2	2	
Dysphagia			
subjects affected / exposed	4 / 43 (9.30%)	1 / 17 (5.88%)	
occurrences (all)	5	1	
Flatulence			
subjects affected / exposed	3 / 43 (6.98%)	2 / 17 (11.76%)	
occurrences (all)	5	2	
Gastrointestinal hypermotility			
subjects affected / exposed	0 / 43 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	

Gastrooesophageal reflux disease			
subjects affected / exposed	2 / 43 (4.65%)	1 / 17 (5.88%)	
occurrences (all)	2	1	
Haemorrhoids			
subjects affected / exposed	1 / 43 (2.33%)	1 / 17 (5.88%)	
occurrences (all)	2	1	
Mouth haemorrhage			
subjects affected / exposed	0 / 43 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Nausea			
subjects affected / exposed	24 / 43 (55.81%)	7 / 17 (41.18%)	
occurrences (all)	51	9	
Oesophageal fistula			
subjects affected / exposed	0 / 43 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Stomatitis			
subjects affected / exposed	21 / 43 (48.84%)	3 / 17 (17.65%)	
occurrences (all)	41	4	
Vomiting			
subjects affected / exposed	14 / 43 (32.56%)	6 / 17 (35.29%)	
occurrences (all)	31	11	
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	1 / 43 (2.33%)	1 / 17 (5.88%)	
occurrences (all)	4	2	
Alopecia			
subjects affected / exposed	2 / 43 (4.65%)	1 / 17 (5.88%)	
occurrences (all)	2	1	
Dermatitis contact			
subjects affected / exposed	0 / 43 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Dry skin			
subjects affected / exposed	10 / 43 (23.26%)	1 / 17 (5.88%)	
occurrences (all)	11	1	
Erythema			

subjects affected / exposed	5 / 43 (11.63%)	1 / 17 (5.88%)	
occurrences (all)	8	2	
Hyperhidrosis			
subjects affected / exposed	0 / 43 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Nail toxicity			
subjects affected / exposed	1 / 43 (2.33%)	1 / 17 (5.88%)	
occurrences (all)	1	2	
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	2 / 43 (4.65%)	1 / 17 (5.88%)	
occurrences (all)	2	1	
Pruritus			
subjects affected / exposed	4 / 43 (9.30%)	0 / 17 (0.00%)	
occurrences (all)	11	0	
Rash			
subjects affected / exposed	12 / 43 (27.91%)	4 / 17 (23.53%)	
occurrences (all)	16	6	
Rash maculo-papular			
subjects affected / exposed	5 / 43 (11.63%)	0 / 17 (0.00%)	
occurrences (all)	5	0	
Skin toxicity			
subjects affected / exposed	0 / 43 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	3	
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	1 / 43 (2.33%)	1 / 17 (5.88%)	
occurrences (all)	1	1	
Haematuria			
subjects affected / exposed	6 / 43 (13.95%)	1 / 17 (5.88%)	
occurrences (all)	6	1	
Nocturia			
subjects affected / exposed	0 / 43 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Proteinuria			

subjects affected / exposed	4 / 43 (9.30%)	3 / 17 (17.65%)	
occurrences (all)	5	3	
Renal failure			
subjects affected / exposed	0 / 43 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	2	
Renal failure acute			
subjects affected / exposed	1 / 43 (2.33%)	1 / 17 (5.88%)	
occurrences (all)	1	1	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	5 / 43 (11.63%)	0 / 17 (0.00%)	
occurrences (all)	7	0	
Arthritis			
subjects affected / exposed	0 / 43 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	6	
Back pain			
subjects affected / exposed	3 / 43 (6.98%)	1 / 17 (5.88%)	
occurrences (all)	3	1	
Bone pain			
subjects affected / exposed	1 / 43 (2.33%)	1 / 17 (5.88%)	
occurrences (all)	1	1	
Clubbing			
subjects affected / exposed	0 / 43 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Muscle spasms			
subjects affected / exposed	2 / 43 (4.65%)	1 / 17 (5.88%)	
occurrences (all)	7	1	
Musculoskeletal chest pain			
subjects affected / exposed	3 / 43 (6.98%)	2 / 17 (11.76%)	
occurrences (all)	3	3	
Musculoskeletal pain			
subjects affected / exposed	4 / 43 (9.30%)	0 / 17 (0.00%)	
occurrences (all)	4	0	
Pain in extremity			

subjects affected / exposed	5 / 43 (11.63%)	1 / 17 (5.88%)	
occurrences (all)	6	1	
Pain in jaw			
subjects affected / exposed	0 / 43 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Sensation of heaviness			
subjects affected / exposed	0 / 43 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	2	
Spinal pain			
subjects affected / exposed	0 / 43 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 43 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Cystitis			
subjects affected / exposed	1 / 43 (2.33%)	1 / 17 (5.88%)	
occurrences (all)	1	1	
Endocarditis			
subjects affected / exposed	0 / 43 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Escherichia urinary tract infection			
subjects affected / exposed	0 / 43 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Herpes zoster			
subjects affected / exposed	0 / 43 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Lung abscess			
subjects affected / exposed	0 / 43 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Lung infection			
subjects affected / exposed	0 / 43 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Paronychia			
subjects affected / exposed	3 / 43 (6.98%)	2 / 17 (11.76%)	
occurrences (all)	4	2	

Pneumonia			
subjects affected / exposed	2 / 43 (4.65%)	1 / 17 (5.88%)	
occurrences (all)	2	1	
Pyelonephritis			
subjects affected / exposed	0 / 43 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Rash pustular			
subjects affected / exposed	2 / 43 (4.65%)	1 / 17 (5.88%)	
occurrences (all)	2	1	
Rhinitis			
subjects affected / exposed	4 / 43 (9.30%)	0 / 17 (0.00%)	
occurrences (all)	4	0	
Sinusitis			
subjects affected / exposed	0 / 43 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Upper respiratory tract infection			
subjects affected / exposed	2 / 43 (4.65%)	1 / 17 (5.88%)	
occurrences (all)	2	1	
Urinary tract infection			
subjects affected / exposed	4 / 43 (9.30%)	2 / 17 (11.76%)	
occurrences (all)	5	2	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	23 / 43 (53.49%)	5 / 17 (29.41%)	
occurrences (all)	42	7	
Dehydration			
subjects affected / exposed	4 / 43 (9.30%)	1 / 17 (5.88%)	
occurrences (all)	4	1	
Hypercholesterolaemia			
subjects affected / exposed	2 / 43 (4.65%)	2 / 17 (11.76%)	
occurrences (all)	2	2	
Hyperglycaemia			
subjects affected / exposed	4 / 43 (9.30%)	2 / 17 (11.76%)	
occurrences (all)	11	2	
Hypernatraemia			

subjects affected / exposed	0 / 43 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Hypertriglyceridaemia			
subjects affected / exposed	6 / 43 (13.95%)	1 / 17 (5.88%)	
occurrences (all)	15	1	
Hyperuricaemia			
subjects affected / exposed	1 / 43 (2.33%)	1 / 17 (5.88%)	
occurrences (all)	2	1	
Hypoalbuminaemia			
subjects affected / exposed	7 / 43 (16.28%)	4 / 17 (23.53%)	
occurrences (all)	14	4	
Hypocalcaemia			
subjects affected / exposed	1 / 43 (2.33%)	1 / 17 (5.88%)	
occurrences (all)	1	1	
Hypokalaemia			
subjects affected / exposed	13 / 43 (30.23%)	0 / 17 (0.00%)	
occurrences (all)	18	0	
Hyponatraemia			
subjects affected / exposed	4 / 43 (9.30%)	0 / 17 (0.00%)	
occurrences (all)	5	0	
Hypophosphataemia			
subjects affected / exposed	4 / 43 (9.30%)	2 / 17 (11.76%)	
occurrences (all)	10	2	
Malnutrition			
subjects affected / exposed	0 / 43 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 July 2013	• Removed the study enrollment requirement of at least one prior chemotherapy regimen or withdrawal from a prior chemotherapy treatment regimen due to toxicity. • Revised condition of dose-escalation of temsirolimus; • Changed the requirement of the time interval of prior exposure to other investigational agent from ≤30 days to ≤14 days before start of study therapy. • Added gender-specific limits of exclusion for QTc for more precise gender-specific QTc measurements. • Removed the entry criterion that excluded patients with prior therapy with tyrosine kinase inhibitor (TKI) class except prior therapy with neratinib • Clarified/corrected the units for absolute neutrophil and platelet counts and revise exclusionary limit for neutrophil count. • Removed the requirement to calculate corrected serum calcium. Correction for albumin binding will be performed programmatically. • Refined the description of the statistical analysis to better describe sample size determination and correct the sample size calculation accordingly. • Clarified the time points for some study assessments and pharmacokinetic (PK) blood sample collections and add timing tolerance windows for the assessments to facilitate better scheduling. • Clarified instructions for better management of diarrhea. • Added instructions for dose reductions for general toxicities related to neratinib and temsirolimus to clarify how these toxicities are to be managed. • Applied other administrative changes/corrections (stylistic, typographical, or grammatical errors) throughout as needed.
19 July 2016	• Added Treatment Extension Period (TEP) to the study design in order to allow patients who continue to derive benefit from study participation (after the main efficacy assessment phase of the study has concluded) to continue to receive investigational product (IP) with a reduced number of protocol-required assessments; visits will occur approximately annually. • Clarified and updated sections of protocol Amendment 1 affected by the addition of the TEP or that potentially could have been affected by the addition of the TEP, including timing of the final study analysis, the long-term follow-up phase of the study, definition of end of study, and other sections. • Applied minor corrections and clarifications throughout.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported