Clinical trial results:
A Phase 1 / 2 Study of HKI-272 in combination With Paclitaxel in Subjects With Solid Tumors and Breast Cancer

Summary

EudraCT number	2006-006412-29
Trial protocol	BE
Global end of trial date	07 February 2018

Results information

Result version number	v1 (current)
This version publication date	24 February 2019
First version publication date	24 February 2019

Trial information

Trial identification

Sponsor protocol code	3144A1-203-WW

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00445458
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Puma Biotechnology, Inc.
Sponsor organisation address	10880 Wilshire Blvd, 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	07 February 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	07 February 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Part 1: The primary objectives of part 1 are to assess the safety and tolerability, and to define the maximum tolerated dose (MTD) of HKI-272 in combination with paclitaxel in subjects with advanced solid tumors
Part 2: The primary objective of part 2 of this study is to estimate the overall response rate (ORR) for subjects with HER2 positive breast cancer treated at the MTD of HKI-272 in combination with paclitaxel.

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) if patient required more than 2 dose reductions of neratinib, or if 120 mg of neratinib was not tolerable, or if the subject had not recovered from treatment-related toxicity after >3 weeks; disease progression, pregnancy, or patient request.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	11 September 2007
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	India: 13
Country: Number of subjects enrolled	Korea, Republic of: 6
Country: Number of subjects enrolled	Poland: 8
Country: Number of subjects enrolled	Ukraine: 11
Country: Number of subjects enrolled	United States: 9
Country: Number of subjects enrolled	Belgium: 4
Country: Number of subjects enrolled	Canada: 2
Country: Number of subjects enrolled	China: 42
Country: Number of subjects enrolled	Hong Kong: 15
Worldwide total number of subjects	110
EEA total number of subjects	12

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)	105
From 65 to 84 years	5
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Informed consent was obtained before any protocol required assessments were performed. Subjects who signed informed consent, but fail to meet inclusion/exclusion criteria or withdrew consent prior to receiving any study medication were considered screen failures.

Period 1

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

Arms

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

Arm description:

Neratinib 160 mg orally once daily every day, in combination with paclitaxel 80 mg/m^2 intravenous infusion on days 1, 8 and 15 of a 28-day cycle.

Arm type	Experimental
Investigational medicinal product name	Neratinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, Tablet
Routes of administration	Oral use

Dosage and administration details:

2 Neratinib 80-mg capsules or 4 40-mg tablets taken 1 daily, with food, preferably in the morning, during each 28-day cycle.

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

Dosage and administration details:

Within each 28-day cycle, paclitaxel (80 mg/m2) was to be intravenously infused (over approximately 1 hour) on Days 1, 8, and 15 (Table 8).

Arm title	Part 1 Ner240 + Paclitaxel

Arm description:

Neratinib 240 mg orally once daily every day, in combination with paclitaxel 80 mg/m^2 intravenous infusion on days 1, 8 and 15 of a 28-day cycle.

Arm type	Experimental
Investigational medicinal product name	Neratinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, Tablet
Routes of administration	Oral use

Dosage and administration details:

Neratinib capsules or tablets (80 mg and/or 40 mg, as appropriate) were taken orally once daily, with food, preferably in the morning during each 28-day cycle.

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

Dosage and administration details:

Within each 28-day cycle, paclitaxel (80 mg/m2) was to be intravenously infused (over approximately 1 hour) on Days 1, 8, and 15.

Arm title	Part 2 Ner240 + Paclitaxel ArmA

Arm description:

Neratinib (MTD, 240 mg) qd + Paclitaxel 80 mg/m2 on days 1, 8, and 15 of a 28 day cycle for subjects with not more than 1 prior cytotoxic chemotherapy treatment regimen for metastatic disease.

Arm type	Experimental
Investigational medicinal product name	Neratinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, Tablet
Routes of administration	Oral use

Dosage and administration details:

Neratinib capsules or tablets (80 mg and/or 40 mg, as appropriate) were taken orally once daily, with food, preferably in the morning during each 28-day cycle.

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

Dosage and administration details:

Within each 28-day cycle, paclitaxel (80 mg/m2) was to be intravenously infused (over approximately 1 hour) on Days 1, 8, and 15.

Arm title	Part 2 Ner240 + Paclitaxel ArmB

Arm description:

Neratinib (MTD, 240 mg) qd + Paclitaxel 80 mg/m2 on days 1, 8, and 15 of a 28 day cycle for subjects with not more than 3 prior cytotoxic chemotherapy treatment regimen for metastatic disease.

Arm type	Experimental
Investigational medicinal product name	Neratinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, Tablet
Routes of administration	Oral use

Dosage and administration details:

Neratinib capsules or tablets (80 mg and/or 40 mg, as appropriate) were taken orally once daily, with food, preferably in the morning during each 28-day cycle.

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

Dosage and administration details:

Within each 28-day cycle, paclitaxel (80 mg/m2) was to be intravenously infused (over approximately 1 hour) on Days 1, 8, and 15.

Number of subjects in period 1	Part 1 Ner160 + Paclitaxel	Part 1 Ner240 + Paclitaxel	Part 2 Ner240 + Paclitaxel ArmA
Started	3	5	71
Completed	0	0	0
Not completed	3	5	71
Adverse event, serious fatal	-	1	2
Physician decision	-	-	1
Consent withdrawn by subject	-	-	8
Surgical Procedure	-	-	1
Adverse event, non-fatal	-	-	4
Study Discontinued by Sponsor	-	-	1
Disease Progression	3	4	54

Number of subjects in period 1	Part 2 Ner240 + Paclitaxel ArmB
Started	31
Completed	0
Not completed	31
Adverse event, serious fatal	-
Physician decision	1
Consent withdrawn by subject	1
Surgical Procedure	-
Adverse event, non-fatal	-
Study Discontinued by Sponsor	1
Disease Progression	28

Baseline characteristics

Reporting groups

Reporting group title	Treatment Period

Reporting group description: -

Reporting group values	Treatment Period	Total	
Number of subjects	110	110	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	105	105	
From 65-84 years	5	5	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	50.6		
standard deviation	± 9.8	-	
Gender categorical Units: Subjects			
Female	105	105	
Male	5	5	

End points

End points reporting groups

Reporting group title	Part 1 Ner160 + Paclitaxel
Reporting group description:	
Neratinib 160 mg orally once daily every day, in combination with paclitaxel 80 mg/m^2 intravenous infusion on days 1, 8 and 15 of a 28-day cycle.	
Reporting group title	Part 1 Ner240 + Paclitaxel
Reporting group description:	
Neratinib 240 mg orally once daily every day, in combination with paclitaxel 80 mg/m^2 intravenous infusion on days 1, 8 and 15 of a 28-day cycle.	
Reporting group title	Part 2 Ner240 + Paclitaxel ArmA
Reporting group description:	
Neratinib (MTD, 240 mg) qd + Paclitaxel 80 mg/m2 on days 1, 8, and 15 of a 28 day cycle for subjects with not more than 1 prior cytotoxic chemotherapy treatment regimen for metastatic disease.	
Reporting group title	Part 2 Ner240 + Paclitaxel ArmB
Reporting group description:	
Neratinib (MTD, 240 mg) qd + Paclitaxel 80 mg/m2 on days 1, 8, and 15 of a 28 day cycle for subjects with not more than 3 prior cytotoxic chemotherapy treatment regimen for metastatic disease.	

Primary: Objective Response Rate. Part 2 of Study

End point title	Objective Response Rate. Part 2 of Study[1]
End point description:	
Subjects with partial response (PR) or complete response (CR) with ERBB2 positive breast cancer treated at the maximum tolerated dose (MTD) of neratinib in combination with paclitaxel, per Response Evaluation Criteria In Solid Tumors Criteria (RECIST) v.1.0: CR, disappearance of all target lesions; PR, >=30% decrease in the sum of the longest diameter of target lesions; and no progressive disease (PD) for non-target lesions, and no new lesions.	
End point type	Primary
End point timeframe:	
From first dose date to progression or last tumor assessment, up to 140 weeks	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There was no preplanned hypothesis testing. The objective of the study was to estimate the objective response rate within each arm.

End point values	Part 1 Ner160 + Paclitaxel	Part 1 Ner240 + Paclitaxel	Part 2 Ner240 + Paclitaxel ArmA	Part 2 Ner240 + Paclitaxel ArmB
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[2]	0[3]	68	31
Units: Percentage of Participants				
number (confidence interval 95%)	(to)	(to)	70.6 (58.3 to 81.0)	77.4 (58.9 to 90.4)

Notes:

[2] - Objective Response Rate was measured and assessed in Part 2 of the study only.

[3] - Objective Response Rate was measured and assessed in Part 2 of the study only.

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects with Dose Limiting Toxicities Part 1

End point title	Number of Subjects with Dose Limiting Toxicities Part 1[4]

End point description:

Dose Limiting Toxicity in subjects with solid tumors treated with neratinib, administered daily, in combination with paclitaxel 80 mg/m² IV on days 1, 8, and 15 of a 28 day cycle, for subjects in Part 1 of the study.

End point type	Primary

End point timeframe:

From first dose date through day 28.

Notes:

[4] - 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 objective of this endpoint was to assess the maximum tolerated dose (MTD) of neratinib. There was no preplanned hypothesis testing.

End point values	Part 1 Ner160 + Paclitaxel	Part 1 Ner240 + Paclitaxel	Part 2 Ner240 + Paclitaxel ArmA	Part 2 Ner240 + Paclitaxel ArmB
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	5	0[5]	0[6]
Units: Patients	0	0		

Notes:

[5] - DLTs were collected in Part 1 of the study only, in order to determine the Maximum Dose for Part 2.
[6] - DLTs were collected in Part 1 of the study only, in order to determine the Maximum Dose for Part 2.

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Concentration-time Curve 0-24

End point title	Area Under the Concentration-time Curve 0-24

End point description:

Area under the concentration-time curve of neratinib; after each dosing of neratinib on Cycle 1 of Day 15, blood samples taken at regular time points.

End point type	Secondary

End point timeframe:

Area under the concentration-time curve of neratinib; after each dosing of neratinib on Cycle 1 of Day 15, blood samples taken at regular time points.

End point values	Part 1 Ner160 + Paclitaxel	Part 1 Ner240 + Paclitaxel	Part 2 Ner240 + Paclitaxel ArmA	Part 2 Ner240 + Paclitaxel ArmB
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	4	63	27
Units: h*ng/mL				
geometric mean (geometric coefficient of variation)	684 (± 92)	1488 (± 29)	1239 (± 63)	1331 (± 61)

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Plasma Concentration of Neratinib

End point title	Maximum Plasma Concentration of Neratinib

End point description:

Maximum plasma concentration of neratinib; after each dosing of neratinib on Cycle 1 of Day 15, blood samples taken at regular time points.

End point type	Secondary

End point timeframe:

Samples taken at 0 hour and at 1, 2, 4, 6, 8, and 24 hours postdose on Day 15 of Cycle 1, and 1 predose sample on Day 1 in Cycle 1.

End point values	Part 1 Ner160 + Paclitaxel	Part 1 Ner240 + Paclitaxel	Part 2 Ner240 + Paclitaxel ArmA	Part 2 Ner240 + Paclitaxel ArmB
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	4	63	27
Units: ng/mL				
geometric mean (geometric coefficient of variation)	66.78 (± 25)	91.74 (± 41)	80.31 (± 55)	79.13 (± 61)

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	Part 1 Ner160 + Paclitaxel
Reporting group description: Neratinib 160 mg orally once daily every day, in combination with paclitaxel 80 mg/m^2 intravenous infusion on days 1, 8 and 15 of a 28-day cycle.	
Reporting group title	Part 1 Ner240 + Paclitaxel
Reporting group description: Neratinib 240 mg orally once daily every day, in combination with paclitaxel 80 mg/m^2 intravenous infusion on days 1, 8 and 15 of a 28-day cycle.	
Reporting group title	Part 2 Ner240 + Paclitaxel ArmA
Reporting group description: Neratinib (MTD) qd + Paclitaxel 80 mg/m2 on days 1, 8, and 15 of a 28 day cycle for subjects with not more than1 prior cytotoxic chemotherapy treatment regimen for metastatic disease	
Reporting group title	Part 2 Ner240 + Paclitaxel ArmB
Reporting group description: Neratinib 240 mg qd + Paclitaxel 80 mg/m2 on days 1, 8, and 15 of a 28 day cycle for subjects with not more than3 prior cytotoxic chemotherapy treatment regimen for metastatic disease.	

Serious adverse events	Part 1 Ner160 + Paclitaxel	Part 1 Ner240 + Paclitaxel	Part 2 Ner240 + Paclitaxel ArmA
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 3 (33.33%)	4 / 5 (80.00%)	27 / 71 (38.03%)
number of deaths (all causes)	0	1	5
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer metastatic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	4 / 71 (5.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to central nervous system			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	2 / 71 (2.82%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	1 / 71 (1.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gait disturbance			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	1 / 71 (1.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oedema peripheral			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 5 (20.00%)	1 / 71 (1.41%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 3 (0.00%)	1 / 5 (20.00%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	0 / 3 (0.00%)	1 / 5 (20.00%)	2 / 71 (2.82%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonitis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	1 / 71 (1.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			

subjects affected / exposed	0 / 3 (0.00%)	1 / 5 (20.00%)	1 / 71 (1.41%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	1 / 71 (1.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Ejection fraction decreased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	1 / 71 (1.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Electrocardiogram T wave inversion			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	1 / 71 (1.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	1 / 71 (1.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hip fracture			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	1 / 71 (1.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tibia fracture			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	1 / 71 (1.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Sinus tachycardia			

subjects affected / exposed	1 / 3 (33.33%)	0 / 5 (0.00%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Brain oedema			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dizziness			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	1 / 71 (1.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Loss of consciousness			
subjects affected / exposed	0 / 3 (0.00%)	1 / 5 (20.00%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 3 (0.00%)	2 / 5 (40.00%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	1 / 71 (1.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Leukopenia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	1 / 71 (1.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			

Cataract			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	1 / 3 (33.33%)	0 / 5 (0.00%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	1 / 3 (33.33%)	1 / 5 (20.00%)	6 / 71 (8.45%)
occurrences causally related to treatment / all	1 / 1	1 / 1	9 / 9
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	0 / 3 (0.00%)	1 / 5 (20.00%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 3 (0.00%)	1 / 5 (20.00%)	2 / 71 (2.82%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Ingrowing nail			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	1 / 71 (1.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Renal failure acute			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	1 / 71 (1.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Bone pain			

subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	1 / 71 (1.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain in extremity			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	1 / 71 (1.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Bacteraemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	1 / 71 (1.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	1 / 71 (1.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cystitis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	1 / 71 (1.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fungaemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	1 / 71 (1.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malaria			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	1 / 71 (1.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	2 / 71 (2.82%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			

subjects affected / exposed	0 / 3 (0.00%)	1 / 5 (20.00%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	2 / 71 (2.82%)
occurrences causally related to treatment / all	0 / 0	0 / 0	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoglycaemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	1 / 71 (1.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Part 2 Ner240 + Paclitaxel ArmB		
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 31 (12.90%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer metastatic			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metastases to central nervous system			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gait disturbance			

subjects affected / exposed	0 / 31 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Oedema peripheral				
subjects affected / exposed	1 / 31 (3.23%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pyrexia				
subjects affected / exposed	0 / 31 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Chronic obstructive pulmonary disease				
subjects affected / exposed	0 / 31 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Dyspnoea				
subjects affected / exposed	0 / 31 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonitis				
subjects affected / exposed	0 / 31 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pulmonary embolism				
subjects affected / exposed	0 / 31 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Psychiatric disorders				
Anxiety				
subjects affected / exposed	0 / 31 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Investigations			
Ejection fraction decreased			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Electrocardiogram T wave inversion			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hip fracture			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Tibia fracture			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Sinus tachycardia			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Brain oedema			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Dizziness			

subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Loss of consciousness			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Transient ischaemic attack			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Febrile neutropenia			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Leukopenia			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Cataract			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Diarrhoea				
subjects affected / exposed	0 / 31 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nausea				
subjects affected / exposed	0 / 31 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Vomiting				
subjects affected / exposed	0 / 31 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Skin and subcutaneous tissue disorders				
Ingrowing nail				
subjects affected / exposed	0 / 31 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Renal and urinary disorders				
Renal failure acute				
subjects affected / exposed	0 / 31 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal and connective tissue disorders				
Bone pain				
subjects affected / exposed	0 / 31 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pain in extremity				
subjects affected / exposed	0 / 31 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Bacteraemia				

subjects affected / exposed	0 / 31 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cellulitis				
subjects affected / exposed	0 / 31 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cystitis				
subjects affected / exposed	0 / 31 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Fungaemia				
subjects affected / exposed	0 / 31 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Malaria				
subjects affected / exposed	0 / 31 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	0 / 31 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Sepsis				
subjects affected / exposed	0 / 31 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
Dehydration				
subjects affected / exposed	0 / 31 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hypoglycaemia				

subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Part 1 Ner160 + Paclitaxel	Part 1 Ner240 + Paclitaxel	Part 2 Ner240 + Paclitaxel ArmA
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 3 (100.00%)	5 / 5 (100.00%)	70 / 71 (98.59%)
Vascular disorders			
Hot flush			
subjects affected / exposed	0 / 3 (0.00%)	1 / 5 (20.00%)	1 / 71 (1.41%)
occurrences (all)	0	2	1
Hypertension			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	5 / 71 (7.04%)
occurrences (all)	0	0	6
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	13 / 71 (18.31%)
occurrences (all)	0	0	21
Axillary pain			
subjects affected / exposed	0 / 3 (0.00%)	1 / 5 (20.00%)	0 / 71 (0.00%)
occurrences (all)	0	1	0
Fatigue			
subjects affected / exposed	1 / 3 (33.33%)	1 / 5 (20.00%)	16 / 71 (22.54%)
occurrences (all)	2	3	36
Generalised oedema			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	0 / 71 (0.00%)
occurrences (all)	0	0	0
Local swelling			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	1 / 71 (1.41%)
occurrences (all)	0	0	1
Malaise			
subjects affected / exposed	1 / 3 (33.33%)	2 / 5 (40.00%)	1 / 71 (1.41%)
occurrences (all)	1	4	3

Mucosal inflammation			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	6 / 71 (8.45%)
occurrences (all)	0	0	30
Oedema peripheral			
subjects affected / exposed	0 / 3 (0.00%)	2 / 5 (40.00%)	13 / 71 (18.31%)
occurrences (all)	0	2	20
Pain			
subjects affected / exposed	1 / 3 (33.33%)	0 / 5 (0.00%)	2 / 71 (2.82%)
occurrences (all)	1	0	2
Pyrexia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	18 / 71 (25.35%)
occurrences (all)	0	0	35
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	1 / 3 (33.33%)	2 / 5 (40.00%)	1 / 71 (1.41%)
occurrences (all)	2	3	1
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 3 (33.33%)	1 / 5 (20.00%)	16 / 71 (22.54%)
occurrences (all)	1	1	29
Dyspnoea			
subjects affected / exposed	1 / 3 (33.33%)	0 / 5 (0.00%)	9 / 71 (12.68%)
occurrences (all)	1	0	19
Epistaxis			
subjects affected / exposed	1 / 3 (33.33%)	1 / 5 (20.00%)	5 / 71 (7.04%)
occurrences (all)	2	1	5
Nasal inflammation			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	1 / 71 (1.41%)
occurrences (all)	0	0	1
Oropharyngeal pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	4 / 71 (5.63%)
occurrences (all)	0	0	5
Rhinorrhoea			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	3 / 71 (4.23%)
occurrences (all)	0	0	6
Psychiatric disorders			

Insomnia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	1 / 71 (1.41%)
occurrences (all)	0	0	3
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	10 / 71 (14.08%)
occurrences (all)	0	0	21
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	9 / 71 (12.68%)
occurrences (all)	0	0	18
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 3 (33.33%)	0 / 5 (0.00%)	0 / 71 (0.00%)
occurrences (all)	1	0	0
Blood urine present			
subjects affected / exposed	1 / 3 (33.33%)	0 / 5 (0.00%)	0 / 71 (0.00%)
occurrences (all)	1	0	0
Weight decreased			
subjects affected / exposed	0 / 3 (0.00%)	2 / 5 (40.00%)	10 / 71 (14.08%)
occurrences (all)	0	2	22
Cardiac disorders			
Arrhythmia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 5 (20.00%)	0 / 71 (0.00%)
occurrences (all)	0	1	0
Palpitations			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	4 / 71 (5.63%)
occurrences (all)	0	0	9
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	7 / 71 (9.86%)
occurrences (all)	0	0	9
Headache			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	10 / 71 (14.08%)
occurrences (all)	0	0	15
Peripheral sensory neuropathy			
subjects affected / exposed	2 / 3 (66.67%)	1 / 5 (20.00%)	36 / 71 (50.70%)
occurrences (all)	4	1	60

Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 3 (66.67%)	2 / 5 (40.00%)	24 / 71 (33.80%)
occurrences (all)	5	4	69
Leukopenia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	29 / 71 (40.85%)
occurrences (all)	0	0	166
Neutropenia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 5 (20.00%)	37 / 71 (52.11%)
occurrences (all)	0	2	143
Thrombocytopenia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	4 / 71 (5.63%)
occurrences (all)	0	0	6
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	0 / 71 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	3 / 71 (4.23%)
occurrences (all)	0	0	3
Abdominal distension			
subjects affected / exposed	1 / 3 (33.33%)	1 / 5 (20.00%)	5 / 71 (7.04%)
occurrences (all)	1	1	6
Abdominal pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	8 / 71 (11.27%)
occurrences (all)	0	0	11
Abdominal pain upper			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	10 / 71 (14.08%)
occurrences (all)	0	0	14
Constipation			
subjects affected / exposed	1 / 3 (33.33%)	0 / 5 (0.00%)	3 / 71 (4.23%)
occurrences (all)	2	0	3
Diarrhoea			
subjects affected / exposed	1 / 3 (33.33%)	5 / 5 (100.00%)	65 / 71 (91.55%)
occurrences (all)	12	13	389
Dry mouth			

subjects affected / exposed	0 / 3 (0.00%)	1 / 5 (20.00%)	4 / 71 (5.63%)
occurrences (all)	0	1	4
Dyspepsia			
subjects affected / exposed	0 / 3 (0.00%)	2 / 5 (40.00%)	8 / 71 (11.27%)
occurrences (all)	0	2	12
Dysphagia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 5 (20.00%)	1 / 71 (1.41%)
occurrences (all)	0	1	1
Gastritis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	5 / 71 (7.04%)
occurrences (all)	0	0	8
Gingival ulceration			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	2 / 71 (2.82%)
occurrences (all)	0	0	5
Mouth ulceration			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	5 / 71 (7.04%)
occurrences (all)	0	0	10
Nausea			
subjects affected / exposed	0 / 3 (0.00%)	4 / 5 (80.00%)	26 / 71 (36.62%)
occurrences (all)	0	6	83
Rectal haemorrhage			
subjects affected / exposed	0 / 3 (0.00%)	1 / 5 (20.00%)	0 / 71 (0.00%)
occurrences (all)	0	1	0
Stomatitis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 5 (20.00%)	13 / 71 (18.31%)
occurrences (all)	0	1	18
Vomiting			
subjects affected / exposed	0 / 3 (0.00%)	3 / 5 (60.00%)	20 / 71 (28.17%)
occurrences (all)	0	4	86
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	0 / 3 (0.00%)	2 / 5 (40.00%)	37 / 71 (52.11%)
occurrences (all)	0	2	40
Decubitus ulcer			
subjects affected / exposed	0 / 3 (0.00%)	1 / 5 (20.00%)	0 / 71 (0.00%)
occurrences (all)	0	1	0

Dermatitis acneiform			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	1 / 71 (1.41%)
occurrences (all)	0	0	1
Dry skin			
subjects affected / exposed	1 / 3 (33.33%)	0 / 5 (0.00%)	1 / 71 (1.41%)
occurrences (all)	2	0	1
Nail disorder			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	2 / 71 (2.82%)
occurrences (all)	0	0	4
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	2 / 71 (2.82%)
occurrences (all)	0	0	2
Pigmentation disorder			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	0 / 71 (0.00%)
occurrences (all)	0	0	0
Pruritus			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	7 / 71 (9.86%)
occurrences (all)	0	0	9
Rash			
subjects affected / exposed	1 / 3 (33.33%)	2 / 5 (40.00%)	21 / 71 (29.58%)
occurrences (all)	1	2	31
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	1 / 3 (33.33%)	0 / 5 (0.00%)	3 / 71 (4.23%)
occurrences (all)	1	0	3
Hydronephrosis			
subjects affected / exposed	1 / 3 (33.33%)	0 / 5 (0.00%)	0 / 71 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	6 / 71 (8.45%)
occurrences (all)	0	0	13
Back pain			
subjects affected / exposed	1 / 3 (33.33%)	0 / 5 (0.00%)	3 / 71 (4.23%)
occurrences (all)	1	0	4
Bone pain			

subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	5 / 71 (7.04%)
occurrences (all)	0	0	8
Muscle spasms			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	3 / 71 (4.23%)
occurrences (all)	0	0	3
Musculoskeletal chest pain			
subjects affected / exposed	0 / 3 (0.00%)	1 / 5 (20.00%)	1 / 71 (1.41%)
occurrences (all)	0	1	1
Myalgia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 5 (20.00%)	3 / 71 (4.23%)
occurrences (all)	0	2	7
Pain in extremity			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	8 / 71 (11.27%)
occurrences (all)	0	0	10
Infections and infestations			
Catheter site infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	0 / 71 (0.00%)
occurrences (all)	0	0	0
Gastroenteritis			
subjects affected / exposed	1 / 3 (33.33%)	0 / 5 (0.00%)	0 / 71 (0.00%)
occurrences (all)	1	0	0
Gingivitis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	4 / 71 (5.63%)
occurrences (all)	0	0	10
Influenza			
subjects affected / exposed	0 / 3 (0.00%)	1 / 5 (20.00%)	6 / 71 (8.45%)
occurrences (all)	0	1	7
Nasopharyngitis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 5 (20.00%)	7 / 71 (9.86%)
occurrences (all)	0	1	27
Oral herpes			
subjects affected / exposed	0 / 3 (0.00%)	1 / 5 (20.00%)	0 / 71 (0.00%)
occurrences (all)	0	1	0
Paronychia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	3 / 71 (4.23%)
occurrences (all)	0	0	3

Upper respiratory tract infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	9 / 71 (12.68%)
occurrences (all)	0	0	11
Urinary tract infection			
subjects affected / exposed	0 / 3 (0.00%)	1 / 5 (20.00%)	10 / 71 (14.08%)
occurrences (all)	0	2	17
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 3 (33.33%)	3 / 5 (60.00%)	16 / 71 (22.54%)
occurrences (all)	1	4	36
Hypocalcaemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	6 / 71 (8.45%)
occurrences (all)	0	0	8
Hypokalaemia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 5 (20.00%)	7 / 71 (9.86%)
occurrences (all)	0	1	33
Hypomagnesaemia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 5 (20.00%)	1 / 71 (1.41%)
occurrences (all)	0	1	1
Hypophagia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 5 (20.00%)	0 / 71 (0.00%)
occurrences (all)	0	1	0
Hypoproteinaemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 5 (0.00%)	0 / 71 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Part 2 Ner240 + Paclitaxel ArmB		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	31 / 31 (100.00%)		
Vascular disorders			
Hot flush			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences (all)	1		
Hypertension			
subjects affected / exposed	2 / 31 (6.45%)		
occurrences (all)	2		
General disorders and administration			

site conditions			
Asthenia			
subjects affected / exposed	7 / 31 (22.58%)		
occurrences (all)	13		
Axillary pain			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences (all)	0		
Fatigue			
subjects affected / exposed	6 / 31 (19.35%)		
occurrences (all)	11		
Generalised oedema			
subjects affected / exposed	2 / 31 (6.45%)		
occurrences (all)	3		
Local swelling			
subjects affected / exposed	2 / 31 (6.45%)		
occurrences (all)	4		
Malaise			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences (all)	0		
Mucosal inflammation			
subjects affected / exposed	2 / 31 (6.45%)		
occurrences (all)	4		
Oedema peripheral			
subjects affected / exposed	5 / 31 (16.13%)		
occurrences (all)	7		
Pain			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences (all)	1		
Pyrexia			
subjects affected / exposed	4 / 31 (12.90%)		
occurrences (all)	5		
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences (all)	0		
Respiratory, thoracic and mediastinal disorders			

Cough			
subjects affected / exposed	2 / 31 (6.45%)		
occurrences (all)	2		
Dyspnoea			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences (all)	1		
Epistaxis			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences (all)	1		
Nasal inflammation			
subjects affected / exposed	2 / 31 (6.45%)		
occurrences (all)	3		
Oropharyngeal pain			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences (all)	0		
Rhinorrhoea			
subjects affected / exposed	3 / 31 (9.68%)		
occurrences (all)	4		
Psychiatric disorders			
Insomnia			
subjects affected / exposed	2 / 31 (6.45%)		
occurrences (all)	2		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	6 / 31 (19.35%)		
occurrences (all)	10		
Aspartate aminotransferase increased			
subjects affected / exposed	4 / 31 (12.90%)		
occurrences (all)	6		
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences (all)	0		
Blood urine present			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences (all)	0		
Weight decreased			

subjects affected / exposed	2 / 31 (6.45%)		
occurrences (all)	2		
Cardiac disorders			
Arrhythmia			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences (all)	0		
Palpitations			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences (all)	0		
Nervous system disorders			
Dizziness			
subjects affected / exposed	4 / 31 (12.90%)		
occurrences (all)	5		
Headache			
subjects affected / exposed	5 / 31 (16.13%)		
occurrences (all)	11		
Peripheral sensory neuropathy			
subjects affected / exposed	17 / 31 (54.84%)		
occurrences (all)	27		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	12 / 31 (38.71%)		
occurrences (all)	50		
Leukopenia			
subjects affected / exposed	15 / 31 (48.39%)		
occurrences (all)	104		
Neutropenia			
subjects affected / exposed	17 / 31 (54.84%)		
occurrences (all)	96		
Thrombocytopenia			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences (all)	1		
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	2 / 31 (6.45%)		
occurrences (all)	2		
Gastrointestinal disorders			

Abdominal discomfort				
subjects affected / exposed	3 / 31 (9.68%)			
occurrences (all)	4			
Abdominal distension				
subjects affected / exposed	1 / 31 (3.23%)			
occurrences (all)	2			
Abdominal pain				
subjects affected / exposed	3 / 31 (9.68%)			
occurrences (all)	7			
Abdominal pain upper				
subjects affected / exposed	3 / 31 (9.68%)			
occurrences (all)	4			
Constipation				
subjects affected / exposed	1 / 31 (3.23%)			
occurrences (all)	1			
Diarrhoea				
subjects affected / exposed	29 / 31 (93.55%)			
occurrences (all)	190			
Dry mouth				
subjects affected / exposed	1 / 31 (3.23%)			
occurrences (all)	2			
Dyspepsia				
subjects affected / exposed	4 / 31 (12.90%)			
occurrences (all)	4			
Dysphagia				
subjects affected / exposed	0 / 31 (0.00%)			
occurrences (all)	0			
Gastritis				
subjects affected / exposed	3 / 31 (9.68%)			
occurrences (all)	3			
Gingival ulceration				
subjects affected / exposed	2 / 31 (6.45%)			
occurrences (all)	5			
Mouth ulceration				
subjects affected / exposed	0 / 31 (0.00%)			
occurrences (all)	0			

Nausea				
subjects affected / exposed	7 / 31 (22.58%)			
occurrences (all)	9			
Rectal haemorrhage				
subjects affected / exposed	0 / 31 (0.00%)			
occurrences (all)	0			
Stomatitis				
subjects affected / exposed	5 / 31 (16.13%)			
occurrences (all)	10			
Vomiting				
subjects affected / exposed	4 / 31 (12.90%)			
occurrences (all)	7			
Skin and subcutaneous tissue disorders				
Alopecia				
subjects affected / exposed	12 / 31 (38.71%)			
occurrences (all)	15			
Decubitus ulcer				
subjects affected / exposed	0 / 31 (0.00%)			
occurrences (all)	0			
Dermatitis acneiform				
subjects affected / exposed	2 / 31 (6.45%)			
occurrences (all)	9			
Dry skin				
subjects affected / exposed	0 / 31 (0.00%)			
occurrences (all)	0			
Nail disorder				
subjects affected / exposed	2 / 31 (6.45%)			
occurrences (all)	2			
Palmar-plantar erythrodysaesthesia syndrome				
subjects affected / exposed	3 / 31 (9.68%)			
occurrences (all)	5			
Pigmentation disorder				
subjects affected / exposed	2 / 31 (6.45%)			
occurrences (all)	2			
Pruritus				

subjects affected / exposed	3 / 31 (9.68%)		
occurrences (all)	5		
Rash			
subjects affected / exposed	8 / 31 (25.81%)		
occurrences (all)	15		
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences (all)	0		
Hydronephrosis			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences (all)	0		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences (all)	0		
Back pain			
subjects affected / exposed	5 / 31 (16.13%)		
occurrences (all)	6		
Bone pain			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences (all)	1		
Muscle spasms			
subjects affected / exposed	2 / 31 (6.45%)		
occurrences (all)	4		
Musculoskeletal chest pain			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences (all)	0		
Myalgia			
subjects affected / exposed	3 / 31 (9.68%)		
occurrences (all)	5		
Pain in extremity			
subjects affected / exposed	3 / 31 (9.68%)		
occurrences (all)	3		
Infections and infestations			

Catheter site infection			
subjects affected / exposed	2 / 31 (6.45%)		
occurrences (all)	4		
Gastroenteritis			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences (all)	0		
Gingivitis			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences (all)	1		
Influenza			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences (all)	1		
Nasopharyngitis			
subjects affected / exposed	2 / 31 (6.45%)		
occurrences (all)	10		
Oral herpes			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences (all)	0		
Paronychia			
subjects affected / exposed	2 / 31 (6.45%)		
occurrences (all)	2		
Upper respiratory tract infection			
subjects affected / exposed	2 / 31 (6.45%)		
occurrences (all)	3		
Urinary tract infection			
subjects affected / exposed	5 / 31 (16.13%)		
occurrences (all)	5		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	8 / 31 (25.81%)		
occurrences (all)	17		
Hypocalcaemia			
subjects affected / exposed	3 / 31 (9.68%)		
occurrences (all)	3		
Hypokalaemia			

subjects affected / exposed	3 / 31 (9.68%)		
occurrences (all)	4		
Hypomagnesaemia			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences (all)	0		
Hypophagia			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences (all)	0		
Hypoproteinaemia			
subjects affected / exposed	2 / 31 (6.45%)		
occurrences (all)	2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 June 2007	This protocol includes removal of lung and pancreatic cancer subjects and docetaxel treatment, addition of paclitaxel treatment, increased PK testing, additional secondary outcomes, expanded definition of dose limiting toxicity, change to number of subjects enrolled, eligibility criteria and other administrative updates.
12 December 2007	This protocol includes changes to exclusion criteria, study procedures, study drug administration, growth factor guidelines, PK testing, and other administrative updates.
18 March 2008	This protocol includes updates to study design, including addition of a second arm B (non-randomized) to Part 2, exclusion criterion changed to allow enrollment of subjects with prior lapatinib exposure in Arm B of Part 2. The sample size for Arm B of Part 2 included approximately 25 subjects, with a total number of 95 subjects enrolled in study. The number of sites increased to approximately 30. Temperature for storing PK samples was updated from -70°C to -20°C. Statistical considerations and study procedures and other administrative updates were also included.
08 February 2010	This protocol includes updates to the following sections: study rationale, length of treatment period, instructions for co-administration of neratinib and digoxin, additional blood chemistry and coagulation tests and other administrative updates.
05 April 2011	This protocol includes the addition of a treatment extension period and associated study procedures and other administrative updates.
22 March 2012	This protocol includes addition of a revised treatment extension period which decreases the efficacy assessments for those subjects that continue to receive clinical benefit, along with other administrative updates.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported