Clinical trial results:
Randomised phase II study of afatinib alone or in combination with vinorelbine versus investigator's choice of treatment in patients with HER2-positive (HER2 = Human epidermal growth factor receptor) breast cancer with progressive brain metastases after trastuzumab or lapatinib based therapy.

Due to the EudraCT – Results system being out of service between 31 July 2015 and 12 January 2016, these results have been published in compliance with revised timelines.

Summary

EudraCT number	2010-021415-16
Trial protocol	FI ES DE IT
Global end of trial date	26 August 2014

Results information

Result version number	v1 (current)
This version publication date	06 April 2016
First version publication date	06 April 2016

Trial information

Trial identification

Sponsor protocol code	1200.67

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01441596
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Boehringer Ingelheim
Sponsor organisation address	Binger Strasse 173, Ingelheim am Rhein, Germany, 55216
Public contact	QRPE Processes and Systems Coordination Clinical Trial Information Disclosure, Boehringer Ingelheim , +1 800 243 0127, clintriage.rdg@boehringer-ingelheim.com
Scientific contact	QRPE Processes and Systems Coordination Clinical Trial Information Disclosure, Boehringer Ingelheim , +1 800 243 0127, clintriage.rdg@boehringer-ingelheim.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	27 November 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	11 February 2014
Global end of trial reached?	Yes
Global end of trial date	26 August 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To investigate the antitumour activity and safety of afatinib alone or in combination with vinorelbine versus investigator’s choice of treatment for the treatment of patients with HER2-positive breast cancer with progressive brain metastases after trastuzumab and/or lapatinib based therapy.

Protection of trial subjects:

Only subjects that met all the study inclusion and none of the exclusion criteria were to be entered in the study. All subjects were free to withdraw from the clinical trial at any time for any reason given. If a subject continued to take trial medication, close monitoring was adhered to and all adverse events recorded. Rules were implemented whereby doses would be reduced if required. Thereafter, if further events were reported, the subject would be withdrawn from the trial. Symptomatic treatment of tumour associated symptoms were allowed throughout. A Data Monitoring Committee (DMC) was appointed by the sponsor. The DMC represented an independent multidisciplinary group consisting of 3 members, including independent clinicians and an independent biostatistician. The DMC periodically assessed the trial data to ensure the overall safety and integrity of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	22 December 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 22
Country: Number of subjects enrolled	Finland: 9
Country: Number of subjects enrolled	France: 42
Country: Number of subjects enrolled	Germany: 16
Country: Number of subjects enrolled	Italy: 4
Country: Number of subjects enrolled	Canada: 4
Country: Number of subjects enrolled	Korea, Republic of: 23
Country: Number of subjects enrolled	United States: 12
Worldwide total number of subjects	132
EEA total number of subjects	93

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)	117
From 65 to 84 years	15
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

All subjects were screened for eligibility to participate in the trial. Subjects attended specialist sites which would then ensure that they (the subjects) met all strictly implemented inclusion/exclusion criteria. Subjects were not to be randomised to trial treatment if any one of the specific entry criteria were violated.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Afatinib mono

Arm description:

Afatinib monotherapy: starting dose 40 mg per day, continuous treatment in a 3-weekly course. If well tolerated, the dose may be escalated to 50 mg.

Arm type	Experimental
Investigational medicinal product name	Afatinib film-coated tablets
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

starting dose 40 mg once daily, continuous treatment in a 3-weekly course. If well tolerated, the dose may be escalated to 50 mg.

Arm title	Afatinib+Vino

Arm description:

Afatinib 40 mg per day, continuous treatment, in combination with weekly Vinorelbine 25 mg/m² on days 1, 8, 15 in a 3-weekly course.

Arm type	Experimental
Investigational medicinal product name	Afatinib film-coated tablets
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

40 mg once daily

Investigational medicinal product name	vinorelbine concentrate for intravenous (i.v.) infusion
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Intravenous infusion over approximately 10 minutes, 25 mg/m2 on Days 1, 8, 15 in a 3-weekly course.

Arm title	Investigator's Choice

Arm description:

Patients will receive, at the investigator's discretion, the most appropriate medical treatment consisting of single agent or combination regimen approved for the treatment of metastatic breast cancer, and according to patient status and local guidelines.

Arm type	Active comparator
Investigational medicinal product name	the most appropriate medical treatment
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, Infusion, Tablet
Routes of administration	Intravenous use, Oral use

Dosage and administration details:

Variable dose, depending on treatment regimen

Number of subjects in period 1[1]	Afatinib mono	Afatinib+Vino	Investigator's Choice
Started	40	38	43
Completed	36	35	39
Not completed	4	3	4
Consent withdrawn by subject	4	-	2
Other reason not defined below	-	2	1
Not treated	-	1	1

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Baseline characteristics are based on patients who were randomised after successfully completing the screening period and received at least one of the trial medication.

Baseline characteristics

Reporting groups	
Reporting group title	Afatinib mono
Reporting group description:	
Afatinib monotherapy: starting dose 40 mg per day, continuous treatment in a 3-weekly course. If well tolerated, the dose may be escalated to 50 mg.	
Reporting group title	Afatinib+Vino
Reporting group description:	
Afatinib 40 mg per day, continuous treatment, in combination with weekly Vinorelbine 25 mg/m² on days 1, 8, 15 in a 3-weekly course.	
Reporting group title	Investigator's Choice
Reporting group description:	
Patients will receive, at the investigator's discretion, the most appropriate medical treatment consisting of single agent or combination regimen approved for the treatment of metastatic breast cancer, and according to patient status and local guidelines.	

Reporting group values	Afatinib mono	Afatinib+Vino	Investigator's Choice
Number of subjects	40	38	43
Age categorical Units: Subjects			

Age Continuous |			
Randomised Set (RS): Includes all randomised patients, whether treated or not.			
Units: years			
arithmetic mean	51.5	51.2	52.6
standard deviation	± 10.3	± 10.6	± 10.3
Gender, Male/Female Units: participants			
Female	40	38	43
Male	0	0	0

Reporting group values	Total		
Number of subjects	121		
Age categorical Units: Subjects			

Age Continuous |			
Randomised Set (RS): Includes all randomised patients, whether treated or not.			
Units: years			
arithmetic mean			
standard deviation	-		
Gender, Male/Female Units: participants			
Female	121		
Male	0		

End points

End points reporting groups

Reporting group title	Afatinib mono
Reporting group description:	
Afatinib monotherapy: starting dose 40 mg per day, continuous treatment in a 3-weekly course. If well tolerated, the dose may be escalated to 50 mg.	
Reporting group title	Afatinib+Vino
Reporting group description:	
Afatinib 40 mg per day, continuous treatment, in combination with weekly Vinorelbine 25 mg/m² on days 1, 8, 15 in a 3-weekly course.	
Reporting group title	Investigator's Choice
Reporting group description:	
Patients will receive, at the investigator's discretion, the most appropriate medical treatment consisting of single agent or combination regimen approved for the treatment of metastatic breast cancer, and according to patient status and local guidelines.	

Primary: Patient benefit rate at 12 weeks

End point title	Patient benefit rate at 12 weeks[1]
End point description:	
Patient benefit was defined by the absence of central nervous system (CNS) disease progression according to Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1 in addition to no tumour-related worsening of the neurological signs and symptoms (NSS), no tumour-related increase in corticosteroid dosage and no progression of extra CNS disease according to RECIST 1.1 The randomised set included all randomised patients, whether treated or not.	
End point type	Primary
End point timeframe:	
at 12 weeks from randomisation	

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: This endpoint was evaluated only descriptively. Thus, no statistical hypothesis test were tested.

End point values	Afatinib mono	Afatinib+Vino	Investigator's Choice	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	40[2]	38[3]	43[4]	
Units: percentage of participants				
number (confidence interval 95%)	30 (16.6 to 46.5)	34.2 (19.6 to 51.4)	41.9 (27 to 57.9)	

Notes:

[2] - RS (Randomised set)

[3] - RS

[4] - RS

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-Free Survival

End point title	Progression-Free Survival

End point description:

Progression-Free Survival is defined as the time from the date of randomisation to the date of disease progression or death whichever came first. Disease progression was defined as either disease progression in CNS lesions (including worsening in NSS and use of corticosteroid) or disease progression in extra-CNS lesions according to RECIST 1.1.

End point type	Secondary

End point timeframe:

Up to 805 days (115 weeks)

End point values	Afatinib mono	Afatinib+Vino	Investigator's Choice	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	40[5]	38[6]	43[7]	
Units: weeks				
median (inter-quartile range (Q1-Q3))	11.9 (6.1 to 20.9)	12.3 (6.3 to 23.3)	18.4 (8.3 to 30.7)	

Notes:

[5] - RS

[6] - RS

[7] - RS

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival

End point title	Overall Survival

End point description:

Overall Survival is defined as time from randomisation to the date of death from any cause.

End point type	Secondary

End point timeframe:

Up to 805 days (115 weeks)

End point values	Afatinib mono	Afatinib+Vino	Investigator's Choice	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	40[8]	38[9]	43[10]	
Units: weeks				
median (inter-quartile range (Q1-Q3))	57.7 (34.1 to 81.3)	37.3 (21 to 66.7)	52.1 (29.1 to 122.6)	

Notes:

[8] - RS

[9] - RS

[10] - RS

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first drug administration until 28 days after end of treatment, up to 805 days.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	Afatinib Mono

Reporting group description:

Afatinib monotherapy administered orally: starting dose 40 mg per day, continuous treatment in a 3-weekly course. If well tolerated, the dose may be escalated to 50 mg.

Reporting group title	Afatinib+Vino

Reporting group description:

Afatinib 40 mg per day administered orally, continuous treatment, in combination with weekly Vinorelbine 25 mg/m² administered intravenously on days 1, 8, 15 in a 3-weekly course.

Reporting group title	Investigator's Choice

Reporting group description:

Patients will receive, at the investigator's discretion, the most appropriate medical treatment consisting of single agent or combination regimen approved for the treatment of metastatic breast cancer, and according to patient status and local guidelines.

Serious adverse events	Afatinib Mono	Afatinib+Vino	Investigator's Choice
Total subjects affected by serious adverse events			
subjects affected / exposed	18 / 40 (45.00%)	24 / 37 (64.86%)	22 / 42 (52.38%)
number of deaths (all causes)	3	7	5
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant neoplasm progression			
subjects affected / exposed	1 / 40 (2.50%)	0 / 37 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Metastases to liver			
subjects affected / exposed	1 / 40 (2.50%)	0 / 37 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to meninges			

subjects affected / exposed	0 / 40 (0.00%)	0 / 37 (0.00%)	2 / 42 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastatic neoplasm			
subjects affected / exposed	0 / 40 (0.00%)	1 / 37 (2.70%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Neoplasm progression			
subjects affected / exposed	0 / 40 (0.00%)	1 / 37 (2.70%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Vascular disorders			
Orthostatic hypotension			
subjects affected / exposed	0 / 40 (0.00%)	0 / 37 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 40 (0.00%)	2 / 37 (5.41%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chest discomfort			
subjects affected / exposed	0 / 40 (0.00%)	1 / 37 (2.70%)	0 / 42 (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
Concomitant disease progression			
subjects affected / exposed	0 / 40 (0.00%)	1 / 37 (2.70%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Death			
subjects affected / exposed	0 / 40 (0.00%)	0 / 37 (0.00%)	2 / 42 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 2

General physical health deterioration			
subjects affected / exposed	4 / 40 (10.00%)	6 / 37 (16.22%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	1 / 4	0 / 6	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 3	0 / 1
Generalised oedema			
subjects affected / exposed	0 / 40 (0.00%)	0 / 37 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mucosal inflammation			
subjects affected / exposed	0 / 40 (0.00%)	1 / 37 (2.70%)	0 / 42 (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
Pyrexia			
subjects affected / exposed	1 / 40 (2.50%)	1 / 37 (2.70%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pleural effusion			
subjects affected / exposed	0 / 40 (0.00%)	0 / 37 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed	0 / 40 (0.00%)	0 / 37 (0.00%)	1 / 42 (2.38%)
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 congestion			
subjects affected / exposed	0 / 40 (0.00%)	1 / 37 (2.70%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Respiratory distress			
subjects affected / exposed	0 / 40 (0.00%)	1 / 37 (2.70%)	0 / 42 (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

Psychiatric disorders			
Confusional state			
subjects affected / exposed	0 / 40 (0.00%)	0 / 37 (0.00%)	2 / 42 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mood altered			
subjects affected / exposed	0 / 40 (0.00%)	0 / 37 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
CSF protein increased			
subjects affected / exposed	0 / 40 (0.00%)	0 / 37 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oxygen saturation decreased			
subjects affected / exposed	0 / 40 (0.00%)	1 / 37 (2.70%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Injury, poisoning and procedural complications			
Brain herniation			
subjects affected / exposed	0 / 40 (0.00%)	1 / 37 (2.70%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Fall			
subjects affected / exposed	0 / 40 (0.00%)	1 / 37 (2.70%)	0 / 42 (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
Femoral neck fracture			
subjects affected / exposed	0 / 40 (0.00%)	2 / 37 (5.41%)	0 / 42 (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
Hip fracture			

subjects affected / exposed	0 / 40 (0.00%)	0 / 37 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pelvic fracture			
subjects affected / exposed	1 / 40 (2.50%)	0 / 37 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Procedural complication			
subjects affected / exposed	0 / 40 (0.00%)	0 / 37 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Congenital, familial and genetic disorders			
Progressive cerebellar degeneration			
subjects affected / exposed	0 / 40 (0.00%)	0 / 37 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Carotid artery stenosis			
subjects affected / exposed	0 / 40 (0.00%)	0 / 37 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cognitive disorder			
subjects affected / exposed	0 / 40 (0.00%)	0 / 37 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Convulsion			
subjects affected / exposed	2 / 40 (5.00%)	3 / 37 (8.11%)	3 / 42 (7.14%)
occurrences causally related to treatment / all	0 / 3	0 / 4	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dizziness			
subjects affected / exposed	1 / 40 (2.50%)	2 / 37 (5.41%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 1	1 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Epilepsy			
subjects affected / exposed	2 / 40 (5.00%)	1 / 37 (2.70%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			
subjects affected / exposed	0 / 40 (0.00%)	3 / 37 (8.11%)	2 / 42 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hemiparesis			
subjects affected / exposed	0 / 40 (0.00%)	1 / 37 (2.70%)	0 / 42 (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
Hemiplegia			
subjects affected / exposed	0 / 40 (0.00%)	0 / 37 (0.00%)	1 / 42 (2.38%)
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 / 40 (0.00%)	1 / 37 (2.70%)	0 / 42 (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
Motor dysfunction			
subjects affected / exposed	0 / 40 (0.00%)	0 / 37 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Motor neurone disease			
subjects affected / exposed	1 / 40 (2.50%)	0 / 37 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neurological symptom			
subjects affected / exposed	0 / 40 (0.00%)	1 / 37 (2.70%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Partial seizures			

subjects affected / exposed	1 / 40 (2.50%)	1 / 37 (2.70%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Presyncope			
subjects affected / exposed	0 / 40 (0.00%)	1 / 37 (2.70%)	0 / 42 (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
Somnolence			
subjects affected / exposed	0 / 40 (0.00%)	0 / 37 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	1 / 40 (2.50%)	0 / 37 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tremor			
subjects affected / exposed	1 / 40 (2.50%)	0 / 37 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 1	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 / 40 (0.00%)	1 / 37 (2.70%)	0 / 42 (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
Febrile neutropenia			
subjects affected / exposed	0 / 40 (0.00%)	3 / 37 (8.11%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	2 / 3	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 40 (0.00%)	0 / 37 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			

Diarrhoea			
subjects affected / exposed	3 / 40 (7.50%)	5 / 37 (13.51%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	3 / 3	5 / 5	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysphagia			
subjects affected / exposed	0 / 40 (0.00%)	1 / 37 (2.70%)	0 / 42 (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
Enteritis			
subjects affected / exposed	0 / 40 (0.00%)	1 / 37 (2.70%)	0 / 42 (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
Ileus			
subjects affected / exposed	0 / 40 (0.00%)	1 / 37 (2.70%)	0 / 42 (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
Intestinal obstruction			
subjects affected / exposed	0 / 40 (0.00%)	1 / 37 (2.70%)	0 / 42 (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
Nausea			
subjects affected / exposed	1 / 40 (2.50%)	0 / 37 (0.00%)	0 / 42 (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
Stomatitis			
subjects affected / exposed	1 / 40 (2.50%)	1 / 37 (2.70%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subileus			
subjects affected / exposed	0 / 40 (0.00%)	1 / 37 (2.70%)	0 / 42 (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
Vomiting			

subjects affected / exposed	3 / 40 (7.50%)	2 / 37 (5.41%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	2 / 3	1 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 40 (0.00%)	1 / 37 (2.70%)	0 / 42 (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
Renal and urinary disorders			
Renal failure acute			
subjects affected / exposed	1 / 40 (2.50%)	1 / 37 (2.70%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Hypercreatinaemia			
subjects affected / exposed	1 / 40 (2.50%)	0 / 37 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain in extremity			
subjects affected / exposed	0 / 40 (0.00%)	0 / 37 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal pain			
subjects affected / exposed	0 / 40 (0.00%)	0 / 37 (0.00%)	1 / 42 (2.38%)
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			
Device related infection			
subjects affected / exposed	0 / 40 (0.00%)	2 / 37 (5.41%)	0 / 42 (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
Erysipelas			

subjects affected / exposed	0 / 40 (0.00%)	0 / 37 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection			
subjects affected / exposed	1 / 40 (2.50%)	0 / 37 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung infection			
subjects affected / exposed	1 / 40 (2.50%)	3 / 37 (8.11%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 1	2 / 3	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 40 (0.00%)	1 / 37 (2.70%)	0 / 42 (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
Pyelonephritis acute			
subjects affected / exposed	0 / 40 (0.00%)	1 / 37 (2.70%)	0 / 42 (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
Sepsis			
subjects affected / exposed	0 / 40 (0.00%)	1 / 37 (2.70%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	0 / 40 (0.00%)	2 / 37 (5.41%)	0 / 42 (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
Urinary tract infection			
subjects affected / exposed	1 / 40 (2.50%)	0 / 37 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			

subjects affected / exposed	0 / 40 (0.00%)	1 / 37 (2.70%)	0 / 42 (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
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 40 (2.50%)	0 / 37 (0.00%)	0 / 42 (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
Dehydration			
subjects affected / exposed	1 / 40 (2.50%)	1 / 37 (2.70%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypocalcaemia			
subjects affected / exposed	1 / 40 (2.50%)	0 / 37 (0.00%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalaemia			
subjects affected / exposed	1 / 40 (2.50%)	1 / 37 (2.70%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Afatinib Mono	Afatinib+Vino	Investigator's Choice
Total subjects affected by non-serious adverse events			
subjects affected / exposed	39 / 40 (97.50%)	37 / 37 (100.00%)	40 / 42 (95.24%)
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	8 / 40 (20.00%)	11 / 37 (29.73%)	3 / 42 (7.14%)
occurrences (all)	9	20	3
Asthenia			
subjects affected / exposed	11 / 40 (27.50%)	9 / 37 (24.32%)	14 / 42 (33.33%)
occurrences (all)	11	13	17
Gait disturbance			

subjects affected / exposed	2 / 40 (5.00%)	3 / 37 (8.11%)	1 / 42 (2.38%)
occurrences (all)	3	4	1
Malaise			
subjects affected / exposed	0 / 40 (0.00%)	2 / 37 (5.41%)	0 / 42 (0.00%)
occurrences (all)	0	2	0
Mucosal inflammation			
subjects affected / exposed	8 / 40 (20.00%)	11 / 37 (29.73%)	6 / 42 (14.29%)
occurrences (all)	11	16	11
Oedema peripheral			
subjects affected / exposed	4 / 40 (10.00%)	2 / 37 (5.41%)	5 / 42 (11.90%)
occurrences (all)	4	2	6
Pain			
subjects affected / exposed	1 / 40 (2.50%)	3 / 37 (8.11%)	2 / 42 (4.76%)
occurrences (all)	1	5	2
Pyrexia			
subjects affected / exposed	0 / 40 (0.00%)	2 / 37 (5.41%)	3 / 42 (7.14%)
occurrences (all)	0	3	4
Xerosis			
subjects affected / exposed	0 / 40 (0.00%)	2 / 37 (5.41%)	0 / 42 (0.00%)
occurrences (all)	0	2	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	3 / 40 (7.50%)	4 / 37 (10.81%)	2 / 42 (4.76%)
occurrences (all)	4	4	2
Dyspnoea			
subjects affected / exposed	2 / 40 (5.00%)	3 / 37 (8.11%)	4 / 42 (9.52%)
occurrences (all)	4	3	4
Epistaxis			
subjects affected / exposed	5 / 40 (12.50%)	7 / 37 (18.92%)	3 / 42 (7.14%)
occurrences (all)	5	7	3
Rhinorrhoea			
subjects affected / exposed	2 / 40 (5.00%)	3 / 37 (8.11%)	3 / 42 (7.14%)
occurrences (all)	2	3	3
Psychiatric disorders			

Anxiety			
subjects affected / exposed	2 / 40 (5.00%)	2 / 37 (5.41%)	2 / 42 (4.76%)
occurrences (all)	3	2	2
Depression			
subjects affected / exposed	1 / 40 (2.50%)	2 / 37 (5.41%)	1 / 42 (2.38%)
occurrences (all)	1	2	1
Insomnia			
subjects affected / exposed	6 / 40 (15.00%)	5 / 37 (13.51%)	4 / 42 (9.52%)
occurrences (all)	6	7	4
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 40 (2.50%)	3 / 37 (8.11%)	1 / 42 (2.38%)
occurrences (all)	1	3	1
Aspartate aminotransferase increased			
subjects affected / exposed	2 / 40 (5.00%)	2 / 37 (5.41%)	0 / 42 (0.00%)
occurrences (all)	2	3	0
Weight decreased			
subjects affected / exposed	2 / 40 (5.00%)	3 / 37 (8.11%)	1 / 42 (2.38%)
occurrences (all)	2	3	1
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	3 / 40 (7.50%)	1 / 37 (2.70%)	3 / 42 (7.14%)
occurrences (all)	3	1	5
Nervous system disorders			
Aphasia			
subjects affected / exposed	1 / 40 (2.50%)	3 / 37 (8.11%)	3 / 42 (7.14%)
occurrences (all)	1	3	4
Ataxia			
subjects affected / exposed	2 / 40 (5.00%)	3 / 37 (8.11%)	4 / 42 (9.52%)
occurrences (all)	2	4	4
Balance disorder			
subjects affected / exposed	1 / 40 (2.50%)	2 / 37 (5.41%)	2 / 42 (4.76%)
occurrences (all)	1	2	2
Brain oedema			
subjects affected / exposed	0 / 40 (0.00%)	2 / 37 (5.41%)	0 / 42 (0.00%)
occurrences (all)	0	2	0

Dizziness			
subjects affected / exposed	8 / 40 (20.00%)	9 / 37 (24.32%)	12 / 42 (28.57%)
occurrences (all)	8	10	13
Dysarthria			
subjects affected / exposed	1 / 40 (2.50%)	3 / 37 (8.11%)	1 / 42 (2.38%)
occurrences (all)	1	3	1
Headache			
subjects affected / exposed	11 / 40 (27.50%)	12 / 37 (32.43%)	16 / 42 (38.10%)
occurrences (all)	14	21	23
Neuropathy peripheral			
subjects affected / exposed	0 / 40 (0.00%)	0 / 37 (0.00%)	4 / 42 (9.52%)
occurrences (all)	0	0	4
Neurotoxicity			
subjects affected / exposed	3 / 40 (7.50%)	0 / 37 (0.00%)	1 / 42 (2.38%)
occurrences (all)	3	0	1
Paraesthesia			
subjects affected / exposed	0 / 40 (0.00%)	0 / 37 (0.00%)	3 / 42 (7.14%)
occurrences (all)	0	0	3
Peripheral sensory neuropathy			
subjects affected / exposed	1 / 40 (2.50%)	2 / 37 (5.41%)	3 / 42 (7.14%)
occurrences (all)	1	3	6
Somnolence			
subjects affected / exposed	3 / 40 (7.50%)	3 / 37 (8.11%)	1 / 42 (2.38%)
occurrences (all)	4	3	1
Tremor			
subjects affected / exposed	0 / 40 (0.00%)	1 / 37 (2.70%)	3 / 42 (7.14%)
occurrences (all)	0	2	3
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 40 (2.50%)	12 / 37 (32.43%)	6 / 42 (14.29%)
occurrences (all)	1	14	6
Leukopenia			
subjects affected / exposed	0 / 40 (0.00%)	3 / 37 (8.11%)	5 / 42 (11.90%)
occurrences (all)	0	17	8
Lymphopenia			

subjects affected / exposed	1 / 40 (2.50%)	3 / 37 (8.11%)	1 / 42 (2.38%)
occurrences (all)	1	13	4
Neutropenia			
subjects affected / exposed	0 / 40 (0.00%)	23 / 37 (62.16%)	11 / 42 (26.19%)
occurrences (all)	0	79	27
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 40 (2.50%)	6 / 37 (16.22%)	9 / 42 (21.43%)
occurrences (all)	1	7	9
Eye disorders			
Conjunctivitis			
subjects affected / exposed	4 / 40 (10.00%)	2 / 37 (5.41%)	0 / 42 (0.00%)
occurrences (all)	4	3	0
Diplopia			
subjects affected / exposed	0 / 40 (0.00%)	0 / 37 (0.00%)	5 / 42 (11.90%)
occurrences (all)	0	0	5
Dry eye			
subjects affected / exposed	1 / 40 (2.50%)	4 / 37 (10.81%)	3 / 42 (7.14%)
occurrences (all)	1	4	5
Vision blurred			
subjects affected / exposed	3 / 40 (7.50%)	4 / 37 (10.81%)	4 / 42 (9.52%)
occurrences (all)	3	5	4
Visual impairment			
subjects affected / exposed	3 / 40 (7.50%)	5 / 37 (13.51%)	5 / 42 (11.90%)
occurrences (all)	4	5	5
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	2 / 40 (5.00%)	2 / 37 (5.41%)	0 / 42 (0.00%)
occurrences (all)	2	2	0
Abdominal pain			
subjects affected / exposed	2 / 40 (5.00%)	6 / 37 (16.22%)	7 / 42 (16.67%)
occurrences (all)	3	12	11
Abdominal pain upper			
subjects affected / exposed	3 / 40 (7.50%)	2 / 37 (5.41%)	1 / 42 (2.38%)
occurrences (all)	3	2	1
Constipation			

subjects affected / exposed	8 / 40 (20.00%)	10 / 37 (27.03%)	14 / 42 (33.33%)
occurrences (all)	8	12	20
Diarrhoea			
subjects affected / exposed	36 / 40 (90.00%)	31 / 37 (83.78%)	16 / 42 (38.10%)
occurrences (all)	62	69	32
Dry mouth			
subjects affected / exposed	2 / 40 (5.00%)	4 / 37 (10.81%)	0 / 42 (0.00%)
occurrences (all)	2	5	0
Dyspepsia			
subjects affected / exposed	5 / 40 (12.50%)	2 / 37 (5.41%)	2 / 42 (4.76%)
occurrences (all)	5	3	2
Gastritis			
subjects affected / exposed	0 / 40 (0.00%)	3 / 37 (8.11%)	0 / 42 (0.00%)
occurrences (all)	0	3	0
Haemorrhoids			
subjects affected / exposed	4 / 40 (10.00%)	1 / 37 (2.70%)	0 / 42 (0.00%)
occurrences (all)	4	1	0
Nausea			
subjects affected / exposed	10 / 40 (25.00%)	13 / 37 (35.14%)	15 / 42 (35.71%)
occurrences (all)	12	17	18
Stomatitis			
subjects affected / exposed	5 / 40 (12.50%)	13 / 37 (35.14%)	6 / 42 (14.29%)
occurrences (all)	5	16	8
Vomiting			
subjects affected / exposed	7 / 40 (17.50%)	9 / 37 (24.32%)	11 / 42 (26.19%)
occurrences (all)	9	14	15
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	0 / 40 (0.00%)	3 / 37 (8.11%)	8 / 42 (19.05%)
occurrences (all)	0	3	8
Dermatitis acneiform			
subjects affected / exposed	8 / 40 (20.00%)	2 / 37 (5.41%)	0 / 42 (0.00%)
occurrences (all)	9	3	0
Dry skin			
subjects affected / exposed	8 / 40 (20.00%)	5 / 37 (13.51%)	1 / 42 (2.38%)
occurrences (all)	9	7	1

Nail disorder			
subjects affected / exposed	2 / 40 (5.00%)	2 / 37 (5.41%)	2 / 42 (4.76%)
occurrences (all)	2	3	2
Nail dystrophy			
subjects affected / exposed	0 / 40 (0.00%)	2 / 37 (5.41%)	1 / 42 (2.38%)
occurrences (all)	0	2	1
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	6 / 40 (15.00%)	0 / 37 (0.00%)	7 / 42 (16.67%)
occurrences (all)	7	0	8
Pruritus			
subjects affected / exposed	3 / 40 (7.50%)	1 / 37 (2.70%)	1 / 42 (2.38%)
occurrences (all)	3	2	1
Rash			
subjects affected / exposed	15 / 40 (37.50%)	20 / 37 (54.05%)	4 / 42 (9.52%)
occurrences (all)	21	25	4
Skin lesion			
subjects affected / exposed	3 / 40 (7.50%)	0 / 37 (0.00%)	0 / 42 (0.00%)
occurrences (all)	3	0	0
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	1 / 40 (2.50%)	3 / 37 (8.11%)	1 / 42 (2.38%)
occurrences (all)	1	3	1
Urinary incontinence			
subjects affected / exposed	0 / 40 (0.00%)	2 / 37 (5.41%)	0 / 42 (0.00%)
occurrences (all)	0	2	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 40 (0.00%)	3 / 37 (8.11%)	3 / 42 (7.14%)
occurrences (all)	0	3	4
Back pain			
subjects affected / exposed	1 / 40 (2.50%)	6 / 37 (16.22%)	6 / 42 (14.29%)
occurrences (all)	1	7	7
Muscle spasms			
subjects affected / exposed	4 / 40 (10.00%)	3 / 37 (8.11%)	0 / 42 (0.00%)
occurrences (all)	4	3	0
Muscular weakness			

subjects affected / exposed	1 / 40 (2.50%)	1 / 37 (2.70%)	3 / 42 (7.14%)
occurrences (all)	1	1	3
Musculoskeletal chest pain			
subjects affected / exposed	0 / 40 (0.00%)	2 / 37 (5.41%)	2 / 42 (4.76%)
occurrences (all)	0	2	2
Myalgia			
subjects affected / exposed	1 / 40 (2.50%)	4 / 37 (10.81%)	6 / 42 (14.29%)
occurrences (all)	1	6	6
Pain in extremity			
subjects affected / exposed	1 / 40 (2.50%)	4 / 37 (10.81%)	2 / 42 (4.76%)
occurrences (all)	1	4	2
Infections and infestations			
Bronchitis			
subjects affected / exposed	3 / 40 (7.50%)	1 / 37 (2.70%)	1 / 42 (2.38%)
occurrences (all)	3	1	1
Cystitis			
subjects affected / exposed	0 / 40 (0.00%)	3 / 37 (8.11%)	2 / 42 (4.76%)
occurrences (all)	0	4	3
Paronychia			
subjects affected / exposed	5 / 40 (12.50%)	6 / 37 (16.22%)	1 / 42 (2.38%)
occurrences (all)	6	8	1
Rhinitis			
subjects affected / exposed	1 / 40 (2.50%)	2 / 37 (5.41%)	0 / 42 (0.00%)
occurrences (all)	1	2	0
Urinary tract infection			
subjects affected / exposed	2 / 40 (5.00%)	8 / 37 (21.62%)	6 / 42 (14.29%)
occurrences (all)	2	8	9
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	9 / 40 (22.50%)	9 / 37 (24.32%)	10 / 42 (23.81%)
occurrences (all)	12	9	13
Hypoalbuminaemia			
subjects affected / exposed	2 / 40 (5.00%)	3 / 37 (8.11%)	1 / 42 (2.38%)
occurrences (all)	2	3	1
Hypokalaemia			

subjects affected / exposed occurrences (all)	4 / 40 (10.00%) 6	7 / 37 (18.92%) 12	2 / 42 (4.76%) 4

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 December 2011	"LUX-Breast 3" was added to the title of the Clinical Trial Protocol (CTP) to indicate that this trial is part of the LUX-Breast programme. The study title and inclusion criterion 6 were corrected to allow recruitment of patients with CNS progression during or after both trastuzumab and lapatinib. "Targeted treatment other than trastuzumab" was deleted from exclusion criterion 1 to allow recruitment of patients who had received other anti-HER2 monoclonal antibodies in addition to trastuzumab. A statement on vinorelbine dose adjustment was added to allow patients who benefited from vinorelbine therapy to continue treatment on a regular dosing schedule. A description of the clinical evaluation and reporting of Drug-induced liver injury (DILI) was added at the request of the Regulatory Authority. The reporting requirements for worsening of underlying disease or other pre-existing conditions, and changes in vital signs, Electrocardiogram (ECG), physical examination and laboratory tests results were modified at the request of the Regulatory Authority. Information on the DMC was added to ensure blinding of the trial to the study team. The number of patient's characteristics to be collected at baseline was reduced because it was non-pertinent data. The NSS worksheet had been omitted from the original protocol and was added in an appendix. Other changes were made to clarify the study procedures or to update the information in the CTP.
12 September 2012	It was originally planned that the DMC meeting would be held when 20 patients had been treated for at least 12 weeks in each treatment arm (or progressed before Week 12). However, there was a risk that recruitment into the trial would be complete before the benefit-risk analysis was performed and so the analysis was performed on the first 60 patients treated, regardless of treatment duration. A caution was added if afatinib was to be combined with potent P-glycoprotein modulators as exposure to afatinib could be decreased. However, it ceased to be a requirement to discontinue a patient from the trial if they required concurrent therapy. Information was added on the potential adverse effects of keratitis and ulcerative keratitis, which have been added to the class labelling for Epidermal growth factor receptor (EGFR) inhibitors. It was clarified that afatinib could be paused for up to 7 days but dose reductions of afatinib were not to be performed in the event of AEs or SAEs that were notm treatment-related. The threshold for withholding vinorelbine infusion on the basis of platelet counts was increased from <75 to <100 x 109/L. The dose of vinorelbine could be reduced to 20 mg/m2 in patients with severe hepatic impairment. A patient diary was added for optional use during the trial to collect information on the time of study treatment, food intake, and occurrence of acute side effects. It ceased to be necessary to repeat the tumour assessment at the Screening Visit if valid results were available from routine clinical practice within 28 days prior to start of treatment. Minor errors were corrected and inconsistencies clarified.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported