Clinical trial results:
A Phase II, Randomised, Multi-Centre Study Evaluating Lapatinib in Combination with Vinorelbine or Capecitabine in Women with ErbB2-Overexpressing Metastatic Breast Cancer

Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate representation of the clinical trial results. Please use https://www.novctrd.com/CtrdWeb/home.novfor complete trial results.

Summary

EudraCT number	2009-009885-15
Trial protocol	DE FR ES IT GR BG
Global end of trial date	01 March 2016

Results information

Result version number	v1 (current)
This version publication date	21 July 2018
First version publication date	21 July 2018

Trial information

Trial identification

Sponsor protocol code	LAP016A2205 (NVS)/LAP112620 (GSK)

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01013740
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharmaceuticals
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111,
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111,

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	01 March 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	01 March 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to evaluate the progression-free survival in women with HER2-overexpressing metastatic breast cancer treated with lapatinib in combination with vinorelbine or capecitabine, who had received no more than 1 prior chemotherapeutic regimen in the metastatic setting;

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	25 November 2009
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	Bulgaria: 8
Country: Number of subjects enrolled	Chile: 6
Country: Number of subjects enrolled	France: 6
Country: Number of subjects enrolled	Germany: 17
Country: Number of subjects enrolled	Greece: 18
Country: Number of subjects enrolled	Italy: 7
Country: Number of subjects enrolled	Poland: 39
Country: Number of subjects enrolled	Serbia: 2
Country: Number of subjects enrolled	Spain: 9
Worldwide total number of subjects	112
EEA total number of subjects	104

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)	84
From 65 to 84 years	28
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

In the Randomized Phase (RP), participants were treated until disease progression (PD) or discontinuation of treatment due to unacceptable toxicity, withdrawal of consent, lost to follow-up, or death. After PD in the RP, participants were given the option of crossing over to the alternative treatment arm in a post-progression Cross-over Phase (CP).

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Lapatinib + capecitabine in RP; lapatinib + vinorelbine in CP

Arm description:

Participants received a daily dose of 5 tablets of lapatinib (1250 milligrams [mg]) continuously at approximately the same time every day, either 1 hour (or more) before food or 1 hour (or more) after food. Participants also received capecitabine 2000 mg per meters squared (mg/m^2) per day, divided and administered orally twice daily, 12 hours apart, for 14 days, every 21 days. Capecitabine was taken with food or within 30 minutes after food with approximately 200 milliliters (mL) of water. After disease progression in the Randomized Phase (in which participants received lapatinib plus vinorelbine), participants were given the option of crossing over to the alternative treatment arm (lapatinib plus capecitabine), and continuing in a post-progression Cross-over Phase.

Arm type	Experimental
Investigational medicinal product name	Lapatinib
Investigational medicinal product code	LAP016
Other name	LAP112620
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

LAPATINIB 1250 mg orally once daily

Investigational medicinal product name	capecitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

2000 mg/m2/day orally in 2 doses 12 hours apart on Days 1 to 14 every third week

Arm title	Lapatinib + vinorelbine in RP; lapatinib + capecitabine in CP

Arm description:

Participants received a daily dose of 5 tablets of lapatinib (1250 mg) at approximately the same time every day, either 1 hour (or more) before food or 1 hour (or more) after food. Participants also received an intravenous (IV) infusion of vinorelbine 20 mg/m^2 over the course of 5 to 10 minutes on Days 1 and 8 of a 21-day treatment cycle. After disease progression in the Randomized Phase (in which participants received lapatinib plus capecitabine), participants were given the option of crossing over to the alternative treatment arm (lapatinib plus vinorelbine), and continuing in a post-progression Cross-over Phase.

Arm type	Experimental

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

Dosage and administration details:

20 mg/m2 IV on Day 1 and 8, every third week

Investigational medicinal product name	Lapatinib
Investigational medicinal product code	LAP016
Other name	LAP112620
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

LAPATINIB 1250 mg orally once daily

Number of subjects in period 1	Lapatinib + capecitabine in RP; lapatinib + vinorelbine in CP	Lapatinib + vinorelbine in RP; lapatinib + capecitabine in CP
Started	37	75
Completed	26	56
Not completed	11	19
Physician decision	2	-
Consent withdrawn by subject	2	10
Ongoing: Study records not completed	-	2
study close / terminated : done in error	2	1
Lost to follow-up	3	5
Missing	2	1

Baseline characteristics

Reporting groups

Reporting group title	Lapatinib + capecitabine in RP; lapatinib + vinorelbine in CP

Reporting group description:

Participants received a daily dose of 5 tablets of lapatinib (1250 milligrams [mg]) continuously at approximately the same time every day, either 1 hour (or more) before food or 1 hour (or more) after food. Participants also received capecitabine 2000 mg per meters squared (mg/m^2) per day, divided and administered orally twice daily, 12 hours apart, for 14 days, every 21 days. Capecitabine was taken with food or within 30 minutes after food with approximately 200 milliliters (mL) of water. After disease progression in the Randomized Phase (in which participants received lapatinib plus vinorelbine), participants were given the option of crossing over to the alternative treatment arm (lapatinib plus capecitabine), and continuing in a post-progression Cross-over Phase.

Reporting group title	Lapatinib + vinorelbine in RP; lapatinib + capecitabine in CP

Reporting group description:

Participants received a daily dose of 5 tablets of lapatinib (1250 mg) at approximately the same time every day, either 1 hour (or more) before food or 1 hour (or more) after food. Participants also received an intravenous (IV) infusion of vinorelbine 20 mg/m^2 over the course of 5 to 10 minutes on Days 1 and 8 of a 21-day treatment cycle. After disease progression in the Randomized Phase (in which participants received lapatinib plus capecitabine), participants were given the option of crossing over to the alternative treatment arm (lapatinib plus vinorelbine), and continuing in a post-progression Cross-over Phase.

Reporting group values	Lapatinib + capecitabine in RP; lapatinib + vinorelbine in CP	Lapatinib + vinorelbine in RP; lapatinib + capecitabine in CP	Total
Number of subjects	37	75	112
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	27	57	84
From 65-84 years	10	18	28
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	37	75	112
Male	0	0	0
AgeContinuous | Units: Years			
arithmetic mean	57.5	57.7	
standard deviation	± 10.9	± 10.23	-

End points

End points reporting groups

Reporting group title	Lapatinib + capecitabine in RP; lapatinib + vinorelbine in CP

Reporting group description:

Participants received a daily dose of 5 tablets of lapatinib (1250 milligrams [mg]) continuously at approximately the same time every day, either 1 hour (or more) before food or 1 hour (or more) after food. Participants also received capecitabine 2000 mg per meters squared (mg/m^2) per day, divided and administered orally twice daily, 12 hours apart, for 14 days, every 21 days. Capecitabine was taken with food or within 30 minutes after food with approximately 200 milliliters (mL) of water. After disease progression in the Randomized Phase (in which participants received lapatinib plus vinorelbine), participants were given the option of crossing over to the alternative treatment arm (lapatinib plus capecitabine), and continuing in a post-progression Cross-over Phase.

Reporting group title	Lapatinib + vinorelbine in RP; lapatinib + capecitabine in CP

Reporting group description:

Participants received a daily dose of 5 tablets of lapatinib (1250 mg) at approximately the same time every day, either 1 hour (or more) before food or 1 hour (or more) after food. Participants also received an intravenous (IV) infusion of vinorelbine 20 mg/m^2 over the course of 5 to 10 minutes on Days 1 and 8 of a 21-day treatment cycle. After disease progression in the Randomized Phase (in which participants received lapatinib plus capecitabine), participants were given the option of crossing over to the alternative treatment arm (lapatinib plus vinorelbine), and continuing in a post-progression Cross-over Phase.

Subject analysis set title	Lapatinib plus capecitabine
Subject analysis set type	Full analysis

Subject analysis set description:

Participants received a daily dose of 5 tablets of lapatinib (1250 milligrams [mg]) continuously at approximately the same time every day, either 1 hour (or more) before food or 1 hour (or more) after food. Participants also received capecitabine 2000 mg per meters squared (mg/m^2) per day, divided and administered orally twice daily, 12 hours apart, for 14 days, every 21 days. Capecitabine was taken with food or within 30 minutes after food with approximately 200 milliliters (mL) of water.

Subject analysis set title	Lapatinib plus vinorelbine
Subject analysis set type	Full analysis

Subject analysis set description:

Participants received a daily dose of 5 tablets of lapatinib (1250 mg) at approximately the same time every day, either 1 hour (or more) before food or 1 hour (or more) after food. Participants also received an intravenous (IV) infusion of vinorelbine 20 mg/m^2 over the course of 5 to 10 minutes on Days 1 and 8 of a 21-day treatment cycle.

Subject analysis set title	Lapatinib plus Capecitabine
Subject analysis set type	Full analysis

Subject analysis set description:

Participants received a daily dose of 5 tablets of lapatinib (1250 milligrams [mg]) continuously at approximately the same time every day, either 1 hour (or more) before food or 1 hour (or more) after food. Participants also received capecitabine 2000 mg per meters squared (mg/m^2) per day, divided and administered orally twice daily, 12 hours apart, for 14 days, every 21 days. Capecitabine was taken with food or within 30 minutes after food with approximately 200 milliliters (mL) of water.

Subject analysis set title	Lapatinib plus Vinorelbine
Subject analysis set type	Full analysis

Subject analysis set description:

Participants received a daily dose of 5 tablets of lapatinib (1250 mg) at approximately the same time every day, either 1 hour (or more) before food or 1 hour (or more) after food. Participants also received an intravenous (IV) infusion of vinorelbine 20 mg/m^2 over the course of 5 to 10 minutes on Days 1 and 8 of a 21-day treatment cycle.

Subject analysis set title	Lapatinib plus Capecitabine
Subject analysis set type	Per protocol

Subject analysis set description:

Participants received a daily dose of 5 tablets of lapatinib (1250 milligrams [mg]) continuously at approximately the same time every day, either 1 hour (or more) before food or 1 hour (or more) after food. Participants also received capecitabine 2000 mg per meters squared (mg/m^2) per day, divided and administered orally twice daily, 12 hours apart, for 14 days, every 21 days. Capecitabine was taken

with food or within 30 minutes after food with approximately 200 milliliters (mL) of water.

Subject analysis set title	Lapatinib plus Vinorelbine
Subject analysis set type	Per protocol

Subject analysis set description:

Participants received a daily dose of 5 tablets of lapatinib (1250 mg) at approximately the same time every day, either 1 hour (or more) before food or 1 hour (or more) after food. Participants also received an intravenous (IV) infusion of vinorelbine 20 mg/m^2 over the course of 5 to 10 minutes on Days 1 and 8 of a 21-day treatment cycle.

Subject analysis set title	Lapatinib plus Capecitabine
Subject analysis set type	Full analysis

Subject analysis set description:

Participants received a daily dose of 5 tablets of lapatinib (1250 milligrams [mg]) continuously at approximately the same time every day, either 1 hour (or more) before food or 1 hour (or more) after food. Participants also received capecitabine 2000 mg per meters squared (mg/m^2) per day, divided and administered orally twice daily, 12 hours apart, for 14 days, every 21 days. Capecitabine was taken with food or within 30 minutes after food with approximately 200 milliliters (mL) of water.

Subject analysis set title	Lapatinib plus Vinorelbine
Subject analysis set type	Full analysis

Subject analysis set description:

Participants received a daily dose of 5 tablets of lapatinib (1250 mg) at approximately the same time every day, either 1 hour (or more) before food or 1 hour (or more) after food. Participants also received an intravenous (IV) infusion of vinorelbine 20 mg/m^2 over the course of 5 to 10 minutes on Days 1 and 8 of a 21-day treatment cycle.

Primary: Progression Free Survival (PFS) in the Randomized Phase

End point title	Progression Free Survival (PFS) in the Randomized Phase

End point description:

PFS is defined as the time from randomization until the earliest date of disease progression (PD) or death due to any cause, if sooner. PD is defined as at least a 20 % increase in the sum of the longest diameter (LD) of target lesions, taking as a reference the smallest sum LD recorded since the treatment started or the appearance of >=1 new lesion.

End point type	Primary

End point timeframe:

From randomization until disease progression, death, or discontinuation from the study (average of 27 study weeks)

End point values	Lapatinib plus capecitabine	Lapatinib plus vinorelbine		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	37	75		
Units: months				
median (confidence interval 95%)	6.2 (4.4 to 8.3)	6.2 (4.2 to 8.8)		

Statistical analyses

Statistical analysis title	Analysis of PFS L+C vs L+ V
Comparison groups	Lapatinib plus capecitabine v Lapatinib plus vinorelbine

Number of subjects included in analysis	112
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Hazard ratio (HR)
Point estimate	0.84
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.53
upper limit	1.35

Secondary: Number of participants with Overall Response (OR), as assessed by the investigator in the Randomized Phase

End point title	Number of participants with Overall Response (OR), as assessed by the investigator in the Randomized Phase

End point description:

OR is defined as the number of participants achieving either a confirmed complete response (CR: the disappearance of all target lesions [TLs]) or partial response (PR: a >=30% decrease in the sum of the longest diameter [LD] of the TLs, taking as reference the baseline sum LD) as assessed by the investigator as the best OR.

End point type	Secondary

End point timeframe:

From randomization until disease progression, death, or discontinuation from the study (average of 27 study weeks)

End point values	Lapatinib plus Capecitabine	Lapatinib plus Vinorelbine		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	37	75		
Units: participants	13	15		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

OS is defined as the time from randomization to the date of death due to any cause. Participants who had not died were censored at the date of the last adequate tumor assessment at the time of the cut-off.

End point type	Secondary

End point timeframe:

From the date of randomization until death (average of 55 study weeks)

End point values	Lapatinib plus Capecitabine	Lapatinib plus Vinorelbine		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	37	75		
Units: months				
median (confidence interval 95%)	19.4 (16.4 to 27.2)	24.3 (16.4 to 9999999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of response (DOR) in the Randomized Phase

End point title	Duration of response (DOR) in the Randomized Phase

End point description:

DOR is defined as the time from the first documented evidence of response (CR or PR) until the first documented sign of disease progression (a >=20% increase in the sum of the LD of TLs, taking as reference the smallest sum LD recorded since the treatment started or the appearance of >=1 new lesion) or death, if sooner. CR=the disappearance of all TLs. PR=a >=30% decrease in the sum of the LD of target lesions, taking as a reference the Baseline sum LD.

End point type	Secondary

End point timeframe:

From the time of the first documented confirmed complete or partial response until disease progression or death, if sooner (average of 27 study weeks)

End point values	Lapatinib plus Capecitabine	Lapatinib plus Vinorelbine		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	13	15		
Units: months				
median (confidence interval 95%)	10.8 (4.3 to 9999)	6.7 (4.6 to 8.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to response in the Randomized Phase

End point title	Time to response in the Randomized Phase

End point description:

Time to response is defined as the time from randomization until the first documented evidence of CR (the disappearance of all TLs) or PR (a >=30% decrease in the sum of the LD of the TLs, taking as a reference the basline sum LD) (whichever status is recorded first). When tumor response was confirmed at a repeat assessment, the time to response was taken to be the first time that the response was

observed.

End point type	Secondary

End point timeframe:

From randomization until the time of the first documented confirmed CR or PR (average of 27 study weeks)

End point values	Lapatinib plus Capecitabine	Lapatinib plus Vinorelbine		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	13	15		
Units: weeks				
median (confidence interval 95%)	9.3 (9.1 to 10)	9.4 (9 to 10.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with clinical benefit (CB) in the Randomized Phase

End point title	Number of participants with clinical benefit (CB) in the Randomized Phase

End point description:

CB is defined as the the number of participants achieving either a confirmed CR or PR or having stable disease (SD) for at least 24 weeks (i.e., approximately 6 months). CR=the disappearance of all TLs. PR=a >=30% decrease in the sum of the LD of TLs, taking as a reference the Baseline sum LD. SD is defined as neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease (PD=at least a 20% increase in the sum of the LD of target lesions, taking as a reference the smallest sum LD recorded since the treatment started or the appearance of >=1 new lesion). Participants with unknown or missing responses were treated as non-responders.

End point type	Secondary

End point timeframe:

From randomization until disease progression, death, or discontinuation from the study (average of 27 study weeks)

End point values	Lapatinib plus Capecitabine	Lapatinib plus Vinorelbine		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	37	75		
Units: participants	18	29		

Statistical analyses

No statistical analyses for this end point

Secondary: Area under the concentration-time curve over the dosing interval (AUC-tau) for vinorelbine

End point title	Area under the concentration-time curve over the dosing interval (AUC-tau) for vinorelbine

End point description:

AUC-tau is defined as the area under the concentration-time curve over a dosing interval at steady state, where tau is the length of the dosing interval. The AUC is of particular use in estimating the bioavailability of drugs, by measuring the extent of absorption. Pharmacokinetic (PK) parameters were to be assessed in an optional sub-study. No participants were enrolled in this optional sub-study; thus, no PK data are available.

End point type	Secondary

End point timeframe:

Days 1 and 8; 0 to 24 hours post-dose

End point values	Lapatinib plus Capecitabine	Lapatinib plus Vinorelbine		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	0[1]	0[2]		
Units: nanograms*hour/milliliter				

Notes:

[1] - No participants were enrolled in this optional sub-study; thus, no PK data are available.

[2] - No participants were enrolled in this optional sub-study; thus, no PK data are available.

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum concentration (Cmax) for vinorelbine

End point title	Maximum concentration (Cmax) for vinorelbine

End point description:

Cmax is defined as the maximum observed plasma or serum concentration after administration of the drug. PK parameters were to be assessed in an optional sub-study. No participants were enrolled in this optional sub-study; thus, no PK data are available.

End point type	Secondary

End point timeframe:

Days 1 and 8; 0 to 24 hours post-dose

End point values	Lapatinib plus Capecitabine	Lapatinib plus Vinorelbine		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	0[3]	0[4]		
Units: nanograms per milliliter				
number (not applicable)				

Notes:

[3] - No participants were enrolled in this optional sub-study; thus, no PK data are available.

[4] - No participants were enrolled in this optional sub-study; thus, no PK data are available.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with Grade 4 and Grade 5 adverse events (AE)

End point title	Number of participants with Grade 4 and Grade 5 adverse events (AE)

End point description:

An AE is defined as any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. AEs were graded using the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0. Grades: 0 = no AE or within normal limits; 1 = mild AE; 2 = moderate AE; 3 = severe and undesirable AE; 4 = life-threatening or disabling AE; 5 = death related to AE.

End point type	Secondary

End point timeframe:

From randomization until disease progression, death, or discontinuation from the study (average of 55 study weeks)

End point values	Lapatinib plus Capecitabine	Lapatinib plus Vinorelbine		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	37	75		
Units: participants				
Helicobacter gastritis, Grade 4	1	0		
Neutropenia, Grade 4	0	9		
Leukopenia, Grade 4	0	1		
Febrile neutropenia, Grade 4	0	1		
Mucosal inflammation, Grade 4	0	1		
Pulmonary embolism, Grade 4	0	1		
Intestinal obstruction, Grade 5	0	1		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Serious Adverse Events are monitored from date of First Subject First Visit (FSFV) until Last Subject Last Visit (LSLV). All other adverse events are monitored from First Subject First Treatment until LSLV.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	Randomized phase Lapatinib 1250mg QD + Capecitabine 2000mg/m2

Reporting group description:

Randomized phase Lapatinib 1250mg QD + Capecitabine 2000mg/m2

Reporting group title	Randomized phase Lapatinib 1250mg QD + Vinorelbine 20mg/m2

Reporting group description:

Randomized phase Lapatinib 1250mg QD + Vinorelbine 20mg/m2

Reporting group title	Crossover phase Lapatinib 1250mg QD + Capecitabine 2000mg/m2

Reporting group description:

Crossover phase Lapatinib 1250mg QD + Capecitabine 2000mg/m2

Reporting group title	Crossover phase Lapatinib 1250mg QD + Vinorelbine 20mg/m2

Reporting group description:

Crossover phase Lapatinib 1250mg QD + Vinorelbine 20mg/m2

Serious adverse events	Randomized phase Lapatinib 1250mg QD + Capecitabine 2000mg/m2	Randomized phase Lapatinib 1250mg QD + Vinorelbine 20mg/m2	Crossover phase Lapatinib 1250mg QD + Capecitabine 2000mg/m2
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 37 (10.81%)	25 / 75 (33.33%)	3 / 37 (8.11%)
number of deaths (all causes)	1	3	4
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Metastases to central nervous system			
subjects affected / exposed	0 / 37 (0.00%)	1 / 75 (1.33%)	0 / 37 (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
Vascular disorders			
Lymphoedema			

subjects affected / exposed	0 / 37 (0.00%)	1 / 75 (1.33%)	0 / 37 (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
Thrombosis			
subjects affected / exposed	1 / 37 (2.70%)	0 / 75 (0.00%)	0 / 37 (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
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 37 (0.00%)	1 / 75 (1.33%)	0 / 37 (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
Pyrexia			
subjects affected / exposed	0 / 37 (0.00%)	2 / 75 (2.67%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 37 (0.00%)	1 / 75 (1.33%)	0 / 37 (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
Pulmonary embolism			
subjects affected / exposed	0 / 37 (0.00%)	1 / 75 (1.33%)	0 / 37 (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
Product issues			
Device leakage			
subjects affected / exposed	0 / 37 (0.00%)	1 / 75 (1.33%)	0 / 37 (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
Investigations			
Ejection fraction decreased			

subjects affected / exposed	0 / 37 (0.00%)	1 / 75 (1.33%)	0 / 37 (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
Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	0 / 37 (0.00%)	1 / 75 (1.33%)	0 / 37 (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
Cardiac disorders			
Arrhythmia			
subjects affected / exposed	0 / 37 (0.00%)	1 / 75 (1.33%)	0 / 37 (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
Nervous system disorders			
Paraplegia			
subjects affected / exposed	0 / 37 (0.00%)	1 / 75 (1.33%)	0 / 37 (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
Peripheral motor neuropathy			
subjects affected / exposed	0 / 37 (0.00%)	1 / 75 (1.33%)	0 / 37 (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
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 37 (0.00%)	1 / 75 (1.33%)	0 / 37 (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
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 37 (0.00%)	2 / 75 (2.67%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	4 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			

subjects affected / exposed	0 / 37 (0.00%)	2 / 75 (2.67%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Leukopenia			
subjects affected / exposed	0 / 37 (0.00%)	1 / 75 (1.33%)	0 / 37 (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
Neutropenia			
subjects affected / exposed	0 / 37 (0.00%)	10 / 75 (13.33%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	11 / 11	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 37 (2.70%)	0 / 75 (0.00%)	0 / 37 (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
Diarrhoea			
subjects affected / exposed	1 / 37 (2.70%)	0 / 75 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	3 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal obstruction			
subjects affected / exposed	0 / 37 (0.00%)	1 / 75 (1.33%)	0 / 37 (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
Vomiting			
subjects affected / exposed	0 / 37 (0.00%)	1 / 75 (1.33%)	0 / 37 (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
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	0 / 37 (0.00%)	1 / 75 (1.33%)	0 / 37 (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
Cholestasis			

subjects affected / exposed	0 / 37 (0.00%)	0 / 75 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Liver injury			
subjects affected / exposed	0 / 37 (0.00%)	0 / 75 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Infections and infestations			
Helicobacter gastritis			
subjects affected / exposed	1 / 37 (2.70%)	0 / 75 (0.00%)	0 / 37 (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
Herpes zoster			
subjects affected / exposed	0 / 37 (0.00%)	1 / 75 (1.33%)	0 / 37 (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
Infection			
subjects affected / exposed	0 / 37 (0.00%)	1 / 75 (1.33%)	0 / 37 (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
Lymphangitis			
subjects affected / exposed	0 / 37 (0.00%)	1 / 75 (1.33%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection			
subjects affected / exposed	0 / 37 (0.00%)	1 / 75 (1.33%)	0 / 37 (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
Urinary tract infection			
subjects affected / exposed	0 / 37 (0.00%)	1 / 75 (1.33%)	0 / 37 (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

Serious adverse events	Crossover phase		

	Lapatinib 1250mg QD + Vinorelbine 20mg/m2		
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 17 (23.53%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Metastases to central nervous system			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Lymphoedema			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Thrombosis			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pyrexia			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Pulmonary embolism			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Product issues			
Device leakage			
subjects affected / exposed	0 / 17 (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 / 17 (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 / 17 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Arrhythmia			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Paraplegia			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Peripheral motor neuropathy			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Peripheral sensory neuropathy			

subjects affected / exposed	0 / 17 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Febrile neutropenia			
subjects affected / exposed	2 / 17 (11.76%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Leukopenia			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Neutropenia			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Intestinal obstruction			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vomiting			

subjects affected / exposed	0 / 17 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cholestasis			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Liver injury			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Helicobacter gastritis			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Herpes zoster			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infection			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Lymphangitis			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory tract infection			

subjects affected / exposed	0 / 17 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
subjects affected / exposed	0 / 17 (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	Randomized phase Lapatinib 1250mg QD + Capecitabine 2000mg/m2	Randomized phase Lapatinib 1250mg QD + Vinorelbine 20mg/m2	Crossover phase Lapatinib 1250mg QD + Capecitabine 2000mg/m2
Total subjects affected by non-serious adverse events			
subjects affected / exposed	32 / 37 (86.49%)	72 / 75 (96.00%)	27 / 37 (72.97%)
Vascular disorders			
Hot flush			
subjects affected / exposed	0 / 37 (0.00%)	2 / 75 (2.67%)	0 / 37 (0.00%)
occurrences (all)	0	3	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	5 / 37 (13.51%)	10 / 75 (13.33%)	3 / 37 (8.11%)
occurrences (all)	5	12	3
Axillary pain			
subjects affected / exposed	0 / 37 (0.00%)	0 / 75 (0.00%)	0 / 37 (0.00%)
occurrences (all)	0	0	0
Fatigue			
subjects affected / exposed	3 / 37 (8.11%)	17 / 75 (22.67%)	1 / 37 (2.70%)
occurrences (all)	4	19	1
Inflammation			
subjects affected / exposed	0 / 37 (0.00%)	1 / 75 (1.33%)	0 / 37 (0.00%)
occurrences (all)	0	1	0
Influenza like illness			
subjects affected / exposed	0 / 37 (0.00%)	2 / 75 (2.67%)	0 / 37 (0.00%)
occurrences (all)	0	2	0
Injection site reaction			

subjects affected / exposed	0 / 37 (0.00%)	0 / 75 (0.00%)	0 / 37 (0.00%)
occurrences (all)	0	0	0
Mucosal inflammation			
subjects affected / exposed	0 / 37 (0.00%)	9 / 75 (12.00%)	1 / 37 (2.70%)
occurrences (all)	0	11	1
Oedema peripheral			
subjects affected / exposed	1 / 37 (2.70%)	7 / 75 (9.33%)	0 / 37 (0.00%)
occurrences (all)	2	7	0
Peripheral swelling			
subjects affected / exposed	0 / 37 (0.00%)	0 / 75 (0.00%)	1 / 37 (2.70%)
occurrences (all)	0	0	1
Pyrexia			
subjects affected / exposed	1 / 37 (2.70%)	10 / 75 (13.33%)	2 / 37 (5.41%)
occurrences (all)	1	12	2
Reproductive system and breast disorders			
Vaginal inflammation			
subjects affected / exposed	2 / 37 (5.41%)	0 / 75 (0.00%)	0 / 37 (0.00%)
occurrences (all)	2	0	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 37 (2.70%)	9 / 75 (12.00%)	0 / 37 (0.00%)
occurrences (all)	1	10	0
Dyspnoea			
subjects affected / exposed	3 / 37 (8.11%)	4 / 75 (5.33%)	2 / 37 (5.41%)
occurrences (all)	3	5	2
Epistaxis			
subjects affected / exposed	2 / 37 (5.41%)	3 / 75 (4.00%)	1 / 37 (2.70%)
occurrences (all)	2	8	2
Haemoptysis			
subjects affected / exposed	0 / 37 (0.00%)	0 / 75 (0.00%)	1 / 37 (2.70%)
occurrences (all)	0	0	1
Oropharyngeal pain			
subjects affected / exposed	2 / 37 (5.41%)	0 / 75 (0.00%)	0 / 37 (0.00%)
occurrences (all)	3	0	0
Psychiatric disorders			

Insomnia			
subjects affected / exposed	2 / 37 (5.41%)	4 / 75 (5.33%)	0 / 37 (0.00%)
occurrences (all)	2	4	0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	3 / 37 (8.11%)	8 / 75 (10.67%)	4 / 37 (10.81%)
occurrences (all)	4	12	5
Aspartate aminotransferase increased			
subjects affected / exposed	4 / 37 (10.81%)	8 / 75 (10.67%)	5 / 37 (13.51%)
occurrences (all)	4	12	6
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 37 (2.70%)	4 / 75 (5.33%)	3 / 37 (8.11%)
occurrences (all)	1	6	3
Blood bilirubin increased			
subjects affected / exposed	4 / 37 (10.81%)	0 / 75 (0.00%)	1 / 37 (2.70%)
occurrences (all)	7	0	1
Blood calcium increased			
subjects affected / exposed	0 / 37 (0.00%)	0 / 75 (0.00%)	0 / 37 (0.00%)
occurrences (all)	0	0	0
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 37 (0.00%)	5 / 75 (6.67%)	0 / 37 (0.00%)
occurrences (all)	0	5	0
Weight decreased			
subjects affected / exposed	2 / 37 (5.41%)	4 / 75 (5.33%)	1 / 37 (2.70%)
occurrences (all)	3	9	1
Cardiac disorders			
Tachycardia			
subjects affected / exposed	2 / 37 (5.41%)	1 / 75 (1.33%)	0 / 37 (0.00%)
occurrences (all)	3	1	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 37 (0.00%)	5 / 75 (6.67%)	2 / 37 (5.41%)
occurrences (all)	0	5	2
Headache			
subjects affected / exposed	2 / 37 (5.41%)	8 / 75 (10.67%)	2 / 37 (5.41%)
occurrences (all)	2	10	4

Neuropathy peripheral			
subjects affected / exposed	0 / 37 (0.00%)	5 / 75 (6.67%)	2 / 37 (5.41%)
occurrences (all)	0	5	3
Paraesthesia			
subjects affected / exposed	2 / 37 (5.41%)	2 / 75 (2.67%)	0 / 37 (0.00%)
occurrences (all)	2	2	0
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 37 (0.00%)	8 / 75 (10.67%)	0 / 37 (0.00%)
occurrences (all)	0	13	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 37 (5.41%)	13 / 75 (17.33%)	2 / 37 (5.41%)
occurrences (all)	4	19	2
Febrile neutropenia			
subjects affected / exposed	0 / 37 (0.00%)	0 / 75 (0.00%)	0 / 37 (0.00%)
occurrences (all)	0	0	0
Leukopenia			
subjects affected / exposed	3 / 37 (8.11%)	11 / 75 (14.67%)	1 / 37 (2.70%)
occurrences (all)	3	40	1
Neutropenia			
subjects affected / exposed	3 / 37 (8.11%)	34 / 75 (45.33%)	2 / 37 (5.41%)
occurrences (all)	4	117	4
Thrombocytopenia			
subjects affected / exposed	0 / 37 (0.00%)	3 / 75 (4.00%)	2 / 37 (5.41%)
occurrences (all)	0	3	2
Eye disorders			
Ophthalmoplegia			
subjects affected / exposed	0 / 37 (0.00%)	0 / 75 (0.00%)	0 / 37 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 37 (5.41%)	7 / 75 (9.33%)	1 / 37 (2.70%)
occurrences (all)	3	7	1
Abdominal pain upper			
subjects affected / exposed	1 / 37 (2.70%)	6 / 75 (8.00%)	0 / 37 (0.00%)
occurrences (all)	1	6	0
Constipation			

subjects affected / exposed	2 / 37 (5.41%)	6 / 75 (8.00%)	0 / 37 (0.00%)
occurrences (all)	3	6	0
Diarrhoea			
subjects affected / exposed	21 / 37 (56.76%)	35 / 75 (46.67%)	7 / 37 (18.92%)
occurrences (all)	39	65	11
Dyspepsia			
subjects affected / exposed	0 / 37 (0.00%)	6 / 75 (8.00%)	1 / 37 (2.70%)
occurrences (all)	0	6	1
Flatulence			
subjects affected / exposed	1 / 37 (2.70%)	0 / 75 (0.00%)	0 / 37 (0.00%)
occurrences (all)	1	0	0
Mouth ulceration			
subjects affected / exposed	0 / 37 (0.00%)	0 / 75 (0.00%)	0 / 37 (0.00%)
occurrences (all)	0	0	0
Nausea			
subjects affected / exposed	3 / 37 (8.11%)	20 / 75 (26.67%)	6 / 37 (16.22%)
occurrences (all)	3	31	9
Stomatitis			
subjects affected / exposed	0 / 37 (0.00%)	1 / 75 (1.33%)	1 / 37 (2.70%)
occurrences (all)	0	2	1
Vomiting			
subjects affected / exposed	4 / 37 (10.81%)	13 / 75 (17.33%)	0 / 37 (0.00%)
occurrences (all)	4	20	0
Hepatobiliary disorders			
Hepatotoxicity			
subjects affected / exposed	0 / 37 (0.00%)	0 / 75 (0.00%)	1 / 37 (2.70%)
occurrences (all)	0	0	1
Hyperbilirubinaemia			
subjects affected / exposed	6 / 37 (16.22%)	1 / 75 (1.33%)	0 / 37 (0.00%)
occurrences (all)	49	1	0
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	1 / 37 (2.70%)	6 / 75 (8.00%)	0 / 37 (0.00%)
occurrences (all)	1	6	0
Erythema			

subjects affected / exposed	2 / 37 (5.41%)	1 / 75 (1.33%)	1 / 37 (2.70%)
occurrences (all)	2	1	1
Nail disorder			
subjects affected / exposed	4 / 37 (10.81%)	2 / 75 (2.67%)	1 / 37 (2.70%)
occurrences (all)	4	2	1
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	24 / 37 (64.86%)	6 / 75 (8.00%)	18 / 37 (48.65%)
occurrences (all)	32	6	23
Rash			
subjects affected / exposed	5 / 37 (13.51%)	15 / 75 (20.00%)	2 / 37 (5.41%)
occurrences (all)	6	19	2
Skin fissures			
subjects affected / exposed	2 / 37 (5.41%)	2 / 75 (2.67%)	0 / 37 (0.00%)
occurrences (all)	2	2	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	3 / 37 (8.11%)	9 / 75 (12.00%)	1 / 37 (2.70%)
occurrences (all)	3	16	3
Back pain			
subjects affected / exposed	1 / 37 (2.70%)	7 / 75 (9.33%)	0 / 37 (0.00%)
occurrences (all)	1	11	0
Bone pain			
subjects affected / exposed	2 / 37 (5.41%)	7 / 75 (9.33%)	0 / 37 (0.00%)
occurrences (all)	2	7	0
Myalgia			
subjects affected / exposed	0 / 37 (0.00%)	5 / 75 (6.67%)	2 / 37 (5.41%)
occurrences (all)	0	8	4
Neck pain			
subjects affected / exposed	2 / 37 (5.41%)	1 / 75 (1.33%)	0 / 37 (0.00%)
occurrences (all)	2	1	0
Pain in extremity			
subjects affected / exposed	3 / 37 (8.11%)	8 / 75 (10.67%)	4 / 37 (10.81%)
occurrences (all)	3	8	4
Infections and infestations			

Abscess			
subjects affected / exposed	0 / 37 (0.00%)	0 / 75 (0.00%)	0 / 37 (0.00%)
occurrences (all)	0	0	0
Bronchitis			
subjects affected / exposed	1 / 37 (2.70%)	4 / 75 (5.33%)	0 / 37 (0.00%)
occurrences (all)	1	4	0
Cystitis			
subjects affected / exposed	1 / 37 (2.70%)	2 / 75 (2.67%)	1 / 37 (2.70%)
occurrences (all)	1	3	1
Herpes zoster			
subjects affected / exposed	1 / 37 (2.70%)	0 / 75 (0.00%)	0 / 37 (0.00%)
occurrences (all)	1	0	0
Nasopharyngitis			
subjects affected / exposed	1 / 37 (2.70%)	4 / 75 (5.33%)	1 / 37 (2.70%)
occurrences (all)	1	7	1
Oral herpes			
subjects affected / exposed	0 / 37 (0.00%)	0 / 75 (0.00%)	0 / 37 (0.00%)
occurrences (all)	0	0	0
Paronychia			
subjects affected / exposed	5 / 37 (13.51%)	2 / 75 (2.67%)	2 / 37 (5.41%)
occurrences (all)	7	2	3
Pharyngitis			
subjects affected / exposed	1 / 37 (2.70%)	1 / 75 (1.33%)	0 / 37 (0.00%)
occurrences (all)	2	1	0
Sinusitis			
subjects affected / exposed	0 / 37 (0.00%)	0 / 75 (0.00%)	0 / 37 (0.00%)
occurrences (all)	0	0	0
Subcutaneous abscess			
subjects affected / exposed	0 / 37 (0.00%)	0 / 75 (0.00%)	0 / 37 (0.00%)
occurrences (all)	0	0	0
Upper respiratory tract infection			
subjects affected / exposed	2 / 37 (5.41%)	5 / 75 (6.67%)	1 / 37 (2.70%)
occurrences (all)	2	6	1
Metabolism and nutrition disorders			
Decreased appetite			

subjects affected / exposed	2 / 37 (5.41%)	12 / 75 (16.00%)	2 / 37 (5.41%)
occurrences (all)	2	14	2
Hypercalcaemia			
subjects affected / exposed	0 / 37 (0.00%)	1 / 75 (1.33%)	0 / 37 (0.00%)
occurrences (all)	0	1	0
Hypoalbuminaemia			
subjects affected / exposed	0 / 37 (0.00%)	4 / 75 (5.33%)	0 / 37 (0.00%)
occurrences (all)	0	4	0
Hypocalcaemia			
subjects affected / exposed	2 / 37 (5.41%)	1 / 75 (1.33%)	0 / 37 (0.00%)
occurrences (all)	2	1	0
Hypochloraemia			
subjects affected / exposed	0 / 37 (0.00%)	0 / 75 (0.00%)	0 / 37 (0.00%)
occurrences (all)	0	0	0
Hypokalaemia			
subjects affected / exposed	1 / 37 (2.70%)	0 / 75 (0.00%)	0 / 37 (0.00%)
occurrences (all)	1	0	0

Non-serious adverse events	Crossover phase Lapatinib 1250mg QD + Vinorelbine 20mg/m2		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	15 / 17 (88.24%)		
Vascular disorders			
Hot flush			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Axillary pain			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Fatigue			
subjects affected / exposed	2 / 17 (11.76%)		
occurrences (all)	2		

Inflammation			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Influenza like illness			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Injection site reaction			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Mucosal inflammation			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Oedema peripheral			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Peripheral swelling			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Pyrexia			
subjects affected / exposed	2 / 17 (11.76%)		
occurrences (all)	5		
Reproductive system and breast disorders			
Vaginal inflammation			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 17 (11.76%)		
occurrences (all)	3		
Dyspnoea			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Epistaxis			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Haemoptysis			

subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Oropharyngeal pain			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Psychiatric disorders			
Insomnia			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	2 / 17 (11.76%)		
occurrences (all)	7		
Aspartate aminotransferase increased			
subjects affected / exposed	2 / 17 (11.76%)		
occurrences (all)	9		
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Blood bilirubin increased			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Blood calcium increased			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Weight decreased			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Cardiac disorders			
Tachycardia			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Nervous system disorders			

Dizziness subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0		
Headache subjects affected / exposed occurrences (all)	2 / 17 (11.76%) 2		
Neuropathy peripheral subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0		
Paraesthesia subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0		
Peripheral sensory neuropathy subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	2 / 17 (11.76%) 2		
Febrile neutropenia subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1		
Leukopenia subjects affected / exposed occurrences (all)	2 / 17 (11.76%) 2		
Neutropenia subjects affected / exposed occurrences (all)	7 / 17 (41.18%) 29		
Thrombocytopenia subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 3		
Eye disorders Ophthalmoplegia subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1		
Gastrointestinal disorders			

Abdominal pain			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Abdominal pain upper			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Constipation			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Diarrhoea			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Dyspepsia			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Flatulence			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Mouth ulceration			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Nausea			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Stomatitis			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Vomiting			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Hepatobiliary disorders			
Hepatotoxicity			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	5		
Hyperbilirubinaemia			

subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Erythema			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Nail disorder			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Rash			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Skin fissures			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Back pain			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Bone pain			
subjects affected / exposed	3 / 17 (17.65%)		
occurrences (all)	3		
Myalgia			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Neck pain			

subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Pain in extremity			
subjects affected / exposed	2 / 17 (11.76%)		
occurrences (all)	2		
Infections and infestations			
Abscess			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Bronchitis			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Cystitis			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Herpes zoster			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Nasopharyngitis			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Oral herpes			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Paronychia			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Pharyngitis			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Sinusitis			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Subcutaneous abscess			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		

Upper respiratory tract infection subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0		
Hypercalcaemia subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 6		
Hypoalbuminaemia subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0		
Hypocalcaemia subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0		
Hypochloraemia subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1		
Hypokalaemia subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 March 2015	Following analysis and reporting of the study primary efficacy and safety data and of updated overall survival rates, further collection and analysis of study efficacy and safety data is unlikely to change the overall outcome of the study or interpretation of the primary analysis of the study data. This amendment will discontinue collection of many study-specific assessments while allowing subjects currently on active study treatment to have continued access to treatment until the occurrence of unacceptable toxicity or disease progression (as determined by the investigator) or permanent withdrawal from treatment for any reason. Subjects who have completed study treatment and are in the follow up phase will be withdrawn from the study with no further follow up.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate representation of the clinical trial results. Please use https://www.novctrd.com/CtrdWeb/home.novfor complete trial results.

Notes: