Clinical trial results:
A Randomized, Multicentre, Open-Label, Phase III Study of Lapatinib plus Capecitabine versus Trastuzumab plus Capecitabine in Subjects with Anthracycline- or Taxane-Exposed ErbB2-Positive 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.nov for complete trial results.

Summary

EudraCT number	2008-000673-38
Trial protocol	DE FR ES BE IT SE DK HU GB GR
Global end of trial date	22 March 2018

Results information

Result version number	v1 (current)
This version publication date	07 April 2019
First version publication date	07 April 2019

Trial information

Trial identification

Sponsor protocol code	EGF111438

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00820222
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, novartis.email@novartis.com
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, novartis.email@novartis.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	22 March 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	22 March 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to evaluate the effect of lapatinib plus capecitabine on incidence of central nervous system (CNS) metastases as site of first relapse as compared with trastuzumab plus capecitabine.

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	14 April 2009
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	Belgium: 4
Country: Number of subjects enrolled	Denmark: 3
Country: Number of subjects enrolled	France: 30
Country: Number of subjects enrolled	Germany: 32
Country: Number of subjects enrolled	Greece: 7
Country: Number of subjects enrolled	Hungary: 20
Country: Number of subjects enrolled	Italy: 47
Country: Number of subjects enrolled	Poland: 86
Country: Number of subjects enrolled	Russian Federation: 197
Country: Number of subjects enrolled	Spain: 31
Country: Number of subjects enrolled	Sweden: 8
Country: Number of subjects enrolled	Thailand: 8
Country: Number of subjects enrolled	United Kingdom: 64
Country: Number of subjects enrolled	United States: 3
Worldwide total number of subjects	540
EEA total number of subjects	332

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)	447
From 65 to 84 years	93
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was terminated based on the IDMC recommendation in 2012 and collection of efficacy data was discontinued.

Pre-assignment

Screening details:

An amended protocol allowed subjects to enroll in a Long Term Follow Up if they had evidence of clinical benefit but no local access to standard of care treatments. Subjects received study treatment until until disease progression, unacceptable toxicity, or participant withdrawal.

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 plus Capecitabine

Arm description:

Participants received a daily dose of 5 tablets of lapatinib (1250 milligrams [mg]) at approximately the same time every day, either 1 hour (or more) before breakfast or 1 hour (or more) after breakfast. 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. Participants received study medication until disease progression, unacceptable toxicity, or participant withdrawal.

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

Dosage and administration details:

Lapatinib 1250 mg 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:

Capecitabine 2000mg/m2/day, days 1-14, every 21 days

Arm title	Trastuzumab plus Capecitabine

Arm description:

Participants received an intravenous (IV) infusion of trastuzumab 8 mg/kilogram (kg) on Day 1, followed by a 6 mg/kg infusion every 3 weeks. Participants also received capecitabine 2500 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. Participants received study medication until disease progression, unacceptable toxicity, or participant withdrawal.

Arm type	Active comparator

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

Dosage and administration details:

Trastuzumab loading dose of 8mg/kg followed by 6mg/kg q3weekly infusions.

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

Dosage and administration details:

Capecitabine 2500mg/m2/day, days 1-14, every 21 days

Number of subjects in period 1	Lapatinib plus Capecitabine	Trastuzumab plus Capecitabine
Started	271	269
Completed	95	79
Not completed	176	190
Consent withdrawn by subject	19	21
Physician decision	93	88
Sponsor Terminated Study	43	65
Lost to follow-up	10	9
Unkown	11	7

Baseline characteristics

Reporting groups

Reporting group title	Lapatinib plus Capecitabine

Reporting group description:

Participants received a daily dose of 5 tablets of lapatinib (1250 milligrams [mg]) at approximately the same time every day, either 1 hour (or more) before breakfast or 1 hour (or more) after breakfast. 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. Participants received study medication until disease progression, unacceptable toxicity, or participant withdrawal.

Reporting group title	Trastuzumab plus Capecitabine

Reporting group description:

Participants received an intravenous (IV) infusion of trastuzumab 8 mg/kilogram (kg) on Day 1, followed by a 6 mg/kg infusion every 3 weeks. Participants also received capecitabine 2500 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. Participants received study medication until disease progression, unacceptable toxicity, or participant withdrawal.

Reporting group values	Lapatinib plus Capecitabine	Trastuzumab plus Capecitabine	Total
Number of subjects	271	269	540
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)	237	210	447
From 65-84 years	34	59	93
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	53.4	55.8	
standard deviation	± 10.23	± 10.26	-
Sex: Female, Male Units: Subjects			
Female	271	269	540
Male	0	0	0
Race/Ethnicity, Customized Units: Subjects			
White - White/Caucasian/European	266	260	526
White - Arabic/North African Heritage	0	1	1
African American/African Heritage	1	1	2
Asian - Central/South Asian Heritage	1	1	2
Asian - East Asian Heritage	1	2	3
Asian - South East Asian Heritage	2	3	5

Native Hawaiian or other Pacific Islander	0	1	1

End points

End points reporting groups

Reporting group title	Lapatinib plus Capecitabine

Reporting group description:

Participants received a daily dose of 5 tablets of lapatinib (1250 milligrams [mg]) at approximately the same time every day, either 1 hour (or more) before breakfast or 1 hour (or more) after breakfast. 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. Participants received study medication until disease progression, unacceptable toxicity, or participant withdrawal.

Reporting group title	Trastuzumab plus Capecitabine

Reporting group description:

Participants received an intravenous (IV) infusion of trastuzumab 8 mg/kilogram (kg) on Day 1, followed by a 6 mg/kg infusion every 3 weeks. Participants also received capecitabine 2500 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. Participants received study medication until disease progression, unacceptable toxicity, or participant withdrawal.

Primary: Number of participants with Central Nervous System (CNS) metastases (as assessed by independent review) as the site of first relapse

End point title	Number of participants with Central Nervous System (CNS) metastases (as assessed by independent review) as the site of first relapse

End point description:

CNS relapse is defined as the appearance of >=1 enhancing lesion measuring >=6 millimeters (mm) on T1Weighted (T1W) Magnetic Resonance Imaging (MRI) without CNS symptoms that were considered to be unequivocal based on all relevant radiological features (e.g., associated T2W signal abnormality); the appearance of any enhancing lesion on T1W MRI with CNS symptoms; unequivocal finding of leptomeningeal disease (defined as the dissemination of cancer throughout the spinal fluid), with or without symptoms; and unequivocal finding of multifocal intraparenchymal lesions with or without symptoms. In the event of the appearance of a <6 mm lesions(s) without CNS lesions, or equivocal findings potentially suggesting leptomeningeal disease, these findings were followed with a subsequent scan within 6 weeks. If unequivocal progression was determined with the subsequent scan and/or CNS symptoms occurred, then CNS relapse crieria were met.

End point type	Primary

End point timeframe:

From randomization until disease progression, death, or discontinuation from the study (average of 10 months). Cut-off 11-Jun-2012

End point values	Lapatinib plus Capecitabine	Trastuzumab plus Capecitabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	251	250		
Units: participants	8	12		

Statistical analyses

Statistical analysis title	Comparison of CNS metastases
Comparison groups	Lapatinib plus Capecitabine v Trastuzumab plus Capecitabine
Number of subjects included in analysis	501
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.36
Method	Odds Ratio
Parameter estimate	Odds ratio (OR)
Point estimate	0.65
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.26
upper limit	1.63

Secondary: Progression free survival (PFS), as assessed by the investigator	
End point title	Progression free survival (PFS), as assessed by the investigator
End point description:	
PFS is defined as the interval between the date of randomization and the earliest date of progressive disease (PD), or death due to any cause. PD is defined as at least a 20% increase in the sum of the longest diameter (LD) of target lesions, compared with the smallest sum LD recorded since the treatment started, or the appearance of 1 or more new lesions based on investigator assessment of both CNS and non-CNS for response.	
End point type	Secondary
End point timeframe:	
From randomization until disease progression, death, or discontinuation from the study (average of 10 months). Cut-off 11-Jun-2012	

End point values	Lapatinib plus Capecitabine	Trastuzumab plus Capecitabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	271	269		
Units: months				
median (confidence interval 95%)	6.60 (5.72 to 8.11)	8.05 (6.14 to 8.90)		

Statistical analyses

Statistical analysis title	Hazard Ratio for Progression Free Survival
Comparison groups	Lapatinib plus Capecitabine v Trastuzumab plus Capecitabine

Number of subjects included in analysis	540
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.021
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.04
upper limit	1.64

Notes:

[1] - A HR > 1 indicates a higher risk for lapatinib+capecitabine compared with trastuzumab+capecitabine.

Secondary: Time to first CNS progression, defined as the time from randomization until the date of documented CNS progression as the first site of relapse

End point title	Time to first CNS progression, defined as the time from randomization until the date of documented CNS progression as the first site of relapse

End point description:

CNS relapse is defined as the appearance of >=1 enhancing lesion measuring >=6 mm on T1W MRI without CNS symptoms that were considered to be unequivocal based on all relevant radiological features (e.g., associated T2W signal abnormality); the appearance of any enhancing lesion on T1W MRI with CNS symptoms; unequivocal finding of leptomeningeal disease (defined as the dissemination of cancer throughout the spinal fluid), with or without symptoms; and unequivocal finding of multifocal intraparenchymal lesions with or without symptoms. In the event of the appearance of a <6 mm lesions(s) without CNS lesions, or equivocal findings potentially suggesting leptomeningeal disease, these findings were followed with a subsequent scan within 6 weeks. If unequivocal progression was determined with the subsequent scan and/or CNS symptoms occurred, then CNS relapse crieria were met.

End point type	Secondary

End point timeframe:

From randomization until the date of documented CNS progression (average of 10 months). Cut-off 11-Jun-2012

End point values	Lapatinib plus Capecitabine	Trastuzumab plus Capecitabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	12		
Units: months				
arithmetic mean (standard deviation)	8.2 (± 6.78)	6.7 (± 6.94)		

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 the time from randomization until death due to any cause or to the date of censor. In the absence of confirmation of death, survival time was to be censored at the time of the last investigator contact.

End point type	Secondary

End point timeframe:

From randomization until death due to any cause (average of 10 months). Cut-off 11-Jun-2012

End point values	Lapatinib plus Capecitabine	Trastuzumab plus Capecitabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	271	269		
Units: months				
median (confidence interval 95%)	22.7 (19.5 to 999)	27.3 (23.7 to 999)		

Statistical analyses

Statistical analysis title	Hazard Ratio for Overall Survival
Comparison groups	Lapatinib plus Capecitabine v Trastuzumab plus Capecitabine
Number of subjects included in analysis	540
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	= 0.095
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.34
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.95
upper limit	1.9

Notes:

[2] - A HR > 1 indicates a higher risk for lapatinib+capecitabine compared with trastuzumab+capecitabine.

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

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

End point description:

OR is defined as the number of participants with either a confirmed complete response (CR; disappearance of all target lesions) or partial response (PR: at least a 30% decrease in the sum of the LD of the target lesions, compared with the baseline sum LD). CR and PR were assessed per Response Evaluation Criteria in Solid Tumors (RECIST). To be assigned a status of PR or CR, a confirmatory disease assessment was to be performed 28 days (4 weeks) or greater after the criteria for response were first met. In addition, a bone scan must have been obtained to rule out the presence of new bone lesions or progression of existing bone lesions, even if the participant had no bone lesions present at Baseline. If a bone scan was performed at the time of initial response or near the time of response, the bone scan did not need to be repeated.

End point type	Secondary

End point timeframe:

From randomization until disease progression, death, or discontinuation from the study (average of 10 months). Cut-off 11-Jun-2012

End point values	Lapatinib plus Capecitabine	Trastuzumab plus Capecitabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	271	269		
Units: participants				
CR	8	12		
PR	65	73		
Overall Response (CR + PR)	73	85		

Statistical analyses

Statistical analysis title	Odds Ratio for Overall Response
Comparison groups	Lapatinib plus Capecitabine v Trastuzumab plus Capecitabine
Number of subjects included in analysis	540
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2731
Method	Fisher exact
Parameter estimate	Odds ratio (OR)
Point estimate	0.7984
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5407
upper limit	1.1771

Secondary: Number of participants with clinical benefit (CB)

End point title	Number of participants with clinical benefit (CB)

End point description:

CB is defined as the number of participants with evidence of confirmed CR (disappearance of all target lesions) or PR (at least a 30% decrease in the sum of the LD of the target lesions, compared with the baseline sum LD) at any time or stable disease (SD, neither sufficient shrinkage to qualify for a PR nor sufficient increase to qualify for PD [defined as at least a 20% increase in the sum of the LD of target lesions, compared with the smallest sum LD recorded since the treatment started, or the appearance of 1 or more new lesions] based on investigator assessment), for at least 24 weeks.

End point type	Secondary

End point timeframe:

From randomization until disease progression, death, or discontinuation from the study (average of 10 months). Cut-off 11-Jun-2012

End point values	Lapatinib plus Capecitabine	Trastuzumab plus Capecitabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	271	269		
Units: participants				
CR	8	12		
PR	65	73		
SD >= 24 weeks	39	33		
Clinical Benefit (CR + PR + SD >= 24 weeks)	112	118		

Statistical analyses

Statistical analysis title	Odds Ratio for Clinical Benefit
Comparison groups	Lapatinib plus Capecitabine v Trastuzumab plus Capecitabine
Number of subjects included in analysis	540
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6106
Method	Fisher exact
Parameter estimate	Odds ratio (OR)
Point estimate	0.9016
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.6315
upper limit	1.2866

Secondary: Duration of response

End point title	Duration of response

End point description:

Duration of response is defined as the time from the first documented evidence of CR (disappearance of all target lesions) or PR (at least a 30% decrease in the sum of the LD of the target lesions, compared with the baseline sum LD) until the first documented sign of PD (at least a 20% increase in the sum of the LD of target lesions, compared with the smallest sum LD recorded since the treatment started, or the appearance of 1 or more new lesions) or death due to breast cancer. In the absence of confirmation of death, survival time was to be censored at the time of the last investigator contact.

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 10 months). Cut-off 11-Jun-2012

End point values	Lapatinib plus Capecitabine	Trastuzumab plus Capecitabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	73	85		
Units: months				
median (confidence interval 95%)	6.2 (5.3 to 10.6)	8.4 (6.0 to 21.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with CNS progression at any time

End point title	Number of participants with CNS progression at any time

End point description:

CNS progression was documented by a brain scan and was indicated by the investigator on the follow-up electronic Case Report Form. CNS relapse is defined as the appearance of >=1 enhancing lesion measuring >=6 mm on T1W MRI without CNS symptoms that were considered to be unequivocal based on all relevant radiological features (e.g., associated T2W signal abnormality); the appearance of any enhancing lesion on T1W MRI with CNS symptoms; unequivocal finding of leptomeningeal disease, with or without symptoms; and unequivocal finding of multifocal intraparenchymal lesions with or without symptoms. In the event of the appearance of a <6 mm lesions(s) without CNS lesions, or equivocal findings potentially suggesting leptomeningeal disease, these findings were followed with a subsequent scan within 6 weeks. If unequivocal progression was determined with the subsequent scan and/or CNS symptoms occurred, then CNS relapse crieria were met.

End point type	Secondary

End point timeframe:

From the time of randomization until death due to any cause (average of 10 months). Cut-off 11-Jun-2012

End point values	Lapatinib plus Capecitabine	Trastuzumab plus Capecitabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	251	250		
Units: participants	17	15		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with qualitative and quantitative toxicities

End point title	Number of participants with qualitative and quantitative toxicities

End point description:

Qualitative and quantitative toxicities were measured as AEs. See the outcome measure entitled "Number of participants with the indicated Grade 3 or Grade 4 Adverse Events (AEs) occurring in >=2 participants in either treatment arm" and the AE module of this results summary for a list of AEs

occurring in the study. An AE is defined as any untoward medical occurrence in a participant administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment.

End point type	Secondary

End point timeframe:

From the first dose of study medication until 30 days after the last dose of study treatment (average of 10 months)

End point values	Lapatinib plus Capecitabine	Trastuzumab plus Capecitabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[3]	0[4]		
Units: participants				

Notes:

[3] - Reported in the AE module of this results summary.

[4] - Reported in the AE module of this results summary.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants expressing glucocorticoid receptor, phosphatase and tensin homolog (PTEN), phosphatidylinositide 3-kinase (PI3K)/AKT, protein 53 (P53), insulin-like growth factor-1 (IGF-1), and genes involved in cell cycle regulation

End point title	Number of participants expressing glucocorticoid receptor, phosphatase and tensin homolog (PTEN), phosphatidylinositide 3-kinase (PI3K)/AKT, protein 53 (P53), insulin-like growth factor-1 (IGF-1), and genes involved in cell cycle regulation

End point description:

Because the study terminated early, pharmacogenetic and biomarker analyses were not performed.

End point type	Secondary

End point timeframe:

Baseline

End point values	Lapatinib plus Capecitabine	Trastuzumab plus Capecitabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[5]	0[6]		
Units: participants				

Notes:

[5] - Because the study terminated early, pharmacogenetic and biomarker analyses were not performed.

[6] - Because the study terminated early, pharmacogenetic and biomarker analyses were not performed.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with the indicated Grade 3 or Grade 4 Adverse Events (AEs) occurring in >=2% of participants in either treatment arm

End point title	Number of participants with the indicated Grade 3 or Grade 4 Adverse Events (AEs) occurring in >=2% of participants in either treatment arm

End point description:

An AE is defined as any untoward medical occurrence in a participant administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. The Investigator assessed whether the AE was related to study drug. AEs were graded using the Common Toxicity Criteria from the Cancer Therapy Evaluation Program, Division of Cancer Therapy, National Cancer Institute. 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 the first dose of study medication until 30 days after the last dose of study treatment (average of 10 months).

End point values	Lapatinib plus Capecitabine	Trastuzumab plus Capecitabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	270	267		
Units: participants				
Palmar-plantar erythrodysaesthesia syndrome	29	45		
Diarrhoea	19	22		
Aspartate aminotransferase increased	11	4		
Neutropenia	9	18		
Asthenia	9	6		
Fatigue	7	4		
Alanine aminotransferase increased	4	6		
Hypokalaemia	3	11		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From randomization until up to and including 30 days after the last dose of study treatment (up to 7 years post randomization)

Adverse event reporting additional description:

Consistent with EudraCT disclosure specifications, Novartis has reported under the Serious adverse events field "number of deaths resulting from adverse events" all those deaths, resulting from serious adverse events that are deemed to be causally related to treatment by the investigator.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.1

Reporting groups

Reporting group title	Lapatinib + Capecitabine

Reporting group description:

Lapatinib + Capecitabine

Reporting group title	Trastuzumab + Capecitabine

Reporting group description:

Trastuzumab + Capecitabine

Serious adverse events	Lapatinib + Capecitabine	Trastuzumab + Capecitabine	
Total subjects affected by serious adverse events			
subjects affected / exposed	41 / 270 (15.19%)	51 / 267 (19.10%)	
number of deaths (all causes)	12	3	
number of deaths resulting from adverse events	0	1	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour haemorrhage			
subjects affected / exposed	0 / 270 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 270 (0.37%)	2 / 267 (0.75%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic venous thrombosis			

subjects affected / exposed	1 / 270 (0.37%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombophlebitis			
subjects affected / exposed	1 / 270 (0.37%)	2 / 267 (0.75%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombosis			
subjects affected / exposed	0 / 270 (0.00%)	2 / 267 (0.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vena cava thrombosis			
subjects affected / exposed	0 / 270 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 270 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	1 / 270 (0.37%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	0 / 270 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucosal inflammation			
subjects affected / exposed	0 / 270 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			

subjects affected / exposed	0 / 270 (0.00%)	2 / 267 (0.75%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	0 / 270 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	3 / 270 (1.11%)	3 / 267 (1.12%)	
occurrences causally related to treatment / all	4 / 6	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Cervical dysplasia			
subjects affected / exposed	1 / 270 (0.37%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Aspiration			
subjects affected / exposed	0 / 270 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 270 (0.37%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	0 / 270 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			

subjects affected / exposed	2 / 270 (0.74%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleurisy			
subjects affected / exposed	1 / 270 (0.37%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleuritic pain			
subjects affected / exposed	0 / 270 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Productive cough			
subjects affected / exposed	1 / 270 (0.37%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	3 / 270 (1.11%)	6 / 267 (2.25%)	
occurrences causally related to treatment / all	1 / 3	3 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	1 / 270 (0.37%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	2 / 270 (0.74%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood bilirubin increased			
subjects affected / exposed	1 / 270 (0.37%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ejection fraction decreased			

subjects affected / exposed	0 / 270 (0.00%)	3 / 267 (1.12%)	
occurrences causally related to treatment / all	0 / 0	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelet count decreased			
subjects affected / exposed	0 / 270 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Overdose			
subjects affected / exposed	0 / 270 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Left ventricular dysfunction			
subjects affected / exposed	0 / 270 (0.00%)	2 / 267 (0.75%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebral haematoma			
subjects affected / exposed	1 / 270 (0.37%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	1 / 270 (0.37%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Haemorrhagic stroke			
subjects affected / exposed	1 / 270 (0.37%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Headache			
subjects affected / exposed	1 / 270 (0.37%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Hemiplegia			
subjects affected / exposed	0 / 270 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	1 / 270 (0.37%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neurological decompensation			
subjects affected / exposed	1 / 270 (0.37%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	0 / 270 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 270 (0.37%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			
subjects affected / exposed	0 / 270 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	2 / 270 (0.74%)	6 / 267 (2.25%)	
occurrences causally related to treatment / all	2 / 2	5 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	0 / 270 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			

subjects affected / exposed	1 / 270 (0.37%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 270 (0.37%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	1 / 270 (0.37%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	0 / 270 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	2 / 270 (0.74%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	4 / 270 (1.48%)	10 / 267 (3.75%)	
occurrences causally related to treatment / all	5 / 6	10 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspepsia			
subjects affected / exposed	1 / 270 (0.37%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal inflammation			
subjects affected / exposed	0 / 270 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrooesophageal reflux disease			

subjects affected / exposed	1 / 270 (0.37%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	1 / 270 (0.37%)	2 / 267 (0.75%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	2 / 270 (0.74%)	2 / 267 (0.75%)	
occurrences causally related to treatment / all	2 / 3	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Biliary colic			
subjects affected / exposed	0 / 270 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	1 / 270 (0.37%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash			
subjects affected / exposed	1 / 270 (0.37%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stevens-Johnson syndrome			
subjects affected / exposed	0 / 270 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	1 / 270 (0.37%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Hydronephrosis			
subjects affected / exposed	1 / 270 (0.37%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 270 (0.37%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	1 / 270 (0.37%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	1 / 6	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone pain			
subjects affected / exposed	0 / 270 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular weakness			
subjects affected / exposed	1 / 270 (0.37%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal chest pain			
subjects affected / exposed	0 / 270 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myalgia			
subjects affected / exposed	0 / 270 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	0 / 270 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 270 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	1 / 270 (0.37%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile infection			
subjects affected / exposed	0 / 270 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	1 / 270 (0.37%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	1 / 270 (0.37%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 270 (0.37%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis bacterial			
subjects affected / exposed	1 / 270 (0.37%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	1 / 270 (0.37%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Localised infection			

subjects affected / exposed	1 / 270 (0.37%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngitis			
subjects affected / exposed	1 / 270 (0.37%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	2 / 270 (0.74%)	2 / 267 (0.75%)	
occurrences causally related to treatment / all	0 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pyelonephritis acute			
subjects affected / exposed	1 / 270 (0.37%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 270 (0.37%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	0 / 270 (0.00%)	2 / 267 (0.75%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Upper respiratory tract infection			
subjects affected / exposed	1 / 270 (0.37%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 270 (0.37%)	2 / 267 (0.75%)	
occurrences causally related to treatment / all	0 / 4	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			

subjects affected / exposed	1 / 270 (0.37%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral pharyngitis			
subjects affected / exposed	1 / 270 (0.37%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			
subjects affected / exposed	0 / 270 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 270 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	0 / 270 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia			
subjects affected / exposed	1 / 270 (0.37%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	0 / 270 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperuricaemia			
subjects affected / exposed	2 / 270 (0.74%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			

subjects affected / exposed	0 / 270 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	0 / 270 (0.00%)	3 / 267 (1.12%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypomagnesaemia			
subjects affected / exposed	0 / 270 (0.00%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	1 / 270 (0.37%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Lapatinib + Capecitabine	Trastuzumab + Capecitabine	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	241 / 270 (89.26%)	236 / 267 (88.39%)	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	34 / 270 (12.59%)	35 / 267 (13.11%)	
occurrences (all)	45	43	
Aspartate aminotransferase increased			
subjects affected / exposed	33 / 270 (12.22%)	30 / 267 (11.24%)	
occurrences (all)	42	39	
Blood alkaline phosphatase increased			
subjects affected / exposed	17 / 270 (6.30%)	11 / 267 (4.12%)	
occurrences (all)	18	15	
Blood bilirubin increased			
subjects affected / exposed	19 / 270 (7.04%)	9 / 267 (3.37%)	
occurrences (all)	48	15	

Nervous system disorders			
Headache			
subjects affected / exposed	15 / 270 (5.56%)	17 / 267 (6.37%)	
occurrences (all)	26	17	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	22 / 270 (8.15%)	27 / 267 (10.11%)	
occurrences (all)	31	38	
Leukopenia			
subjects affected / exposed	11 / 270 (4.07%)	21 / 267 (7.87%)	
occurrences (all)	19	43	
Neutropenia			
subjects affected / exposed	38 / 270 (14.07%)	44 / 267 (16.48%)	
occurrences (all)	77	91	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	46 / 270 (17.04%)	45 / 267 (16.85%)	
occurrences (all)	80	63	
Fatigue			
subjects affected / exposed	26 / 270 (9.63%)	33 / 267 (12.36%)	
occurrences (all)	47	41	
Mucosal inflammation			
subjects affected / exposed	21 / 270 (7.78%)	27 / 267 (10.11%)	
occurrences (all)	31	42	
Pyrexia			
subjects affected / exposed	19 / 270 (7.04%)	25 / 267 (9.36%)	
occurrences (all)	28	34	
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	21 / 270 (7.78%)	16 / 267 (5.99%)	
occurrences (all)	27	20	
Diarrhoea			
subjects affected / exposed	125 / 270 (46.30%)	107 / 267 (40.07%)	
occurrences (all)	300	209	
Dyspepsia			

subjects affected / exposed	21 / 270 (7.78%)	19 / 267 (7.12%)	
occurrences (all)	24	20	
Nausea			
subjects affected / exposed	82 / 270 (30.37%)	50 / 267 (18.73%)	
occurrences (all)	116	79	
Stomatitis			
subjects affected / exposed	16 / 270 (5.93%)	23 / 267 (8.61%)	
occurrences (all)	22	27	
Vomiting			
subjects affected / exposed	35 / 270 (12.96%)	27 / 267 (10.11%)	
occurrences (all)	60	35	
Hepatobiliary disorders			
Hyperbilirubinaemia			
subjects affected / exposed	35 / 270 (12.96%)	26 / 267 (9.74%)	
occurrences (all)	67	50	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	22 / 270 (8.15%)	16 / 267 (5.99%)	
occurrences (all)	25	16	
Dyspnoea			
subjects affected / exposed	11 / 270 (4.07%)	18 / 267 (6.74%)	
occurrences (all)	12	18	
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	15 / 270 (5.56%)	7 / 267 (2.62%)	
occurrences (all)	18	7	
Nail disorder			
subjects affected / exposed	21 / 270 (7.78%)	13 / 267 (4.87%)	
occurrences (all)	21	14	
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	142 / 270 (52.59%)	160 / 267 (59.93%)	
occurrences (all)	238	222	
Rash			
subjects affected / exposed	66 / 270 (24.44%)	21 / 267 (7.87%)	
occurrences (all)	90	26	
Musculoskeletal and connective tissue			

disorders Back pain subjects affected / exposed occurrences (all) Pain in extremity subjects affected / exposed occurrences (all)	 16 / 270 (5.93%) 22 14 / 270 (5.19%) 15	 13 / 267 (4.87%) 14 9 / 267 (3.37%) 15	
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	 28 / 270 (10.37%) 33	 21 / 267 (7.87%) 21	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 March 2009	Country specific amendment was done for Sweden to modify exclusion criteria and allow subjects participating in Study LAP112867 who had short exposure to lapatinib to be eligible for this study.
08 September 2010	Changed description of the primary endpoint of the study and mandated independent review of baseline brain MRI scan for eligibility purpose and changes in analysis plan. Other amendments were made on inclusion/exclusion criteria and some study procedures and biomarker research.
30 November 2011	Minimum of one primary analysis utilizing an IDMC review to assess safety, PFS events and futility analysis on primary endpoint.
10 September 2012	The study was terminated based on the IDMC recommendation. However, this amendment allowed subjects to receive either lapatinib in combination with capecitabine or trastuzumab in combination with capecitabine where there was no local access to standard of care treatments.
24 March 2016	Deleted or replaced references to GSK or its staff with that of Novartis/Novartis and its authorized agents. Made administrative changes to align with Novartis processes and procedures.

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.nov for complete trial results.

Notes: