



Clinical trial results:

A Phase III Study for ErbB2 Positive Advanced or Metastatic Gastric, Esophageal, or Gastroesophageal Junction Adenocarcinoma treated with Capecitabine plus Oxaliplatin with or without Lapatinib

Summary

EudraCT number	2007-005725-29
Trial protocol	EE IT NL HU
Global end of trial date	03 October 2024

Results information

Result version number	v1 (current)
This version publication date	23 October 2025
First version publication date	23 October 2025

Trial information

Trial identification

Sponsor protocol code	EGF110656
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00680901
WHO universal trial number (UTN)	-
Other trial identifiers	CLAP016C2301: Novartis

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	Lichtstrasse 35, Basel, Switzerland, 4056
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	03 October 2024
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	03 October 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This was an international multi-center trial that enrolled patients with locally advanced, unresectable, or metastatic gastric, esophageal, or gastro-esophageal junction cancer whose tumors had amplification of the ErbB2 (HER2) gene. The trial investigated whether lapatinib, when added to the chemotherapy regimen, capecitabine plus oxaliplatin (CapeOx), extended the time to progression and overall survival. Tumor ErbB2 (HER2) status had to be known before trial entry. CapeOx was administered to all patients, and patients were randomly assigned to receive either lapatinib or placebo.

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	04 June 2008
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	Argentina: 16
Country: Number of subjects enrolled	Brazil: 29
Country: Number of subjects enrolled	Canada: 6
Country: Number of subjects enrolled	Chile: 17
Country: Number of subjects enrolled	China: 120
Country: Number of subjects enrolled	Estonia: 10
Country: Number of subjects enrolled	Hong Kong: 4
Country: Number of subjects enrolled	Hungary: 8
Country: Number of subjects enrolled	India: 18
Country: Number of subjects enrolled	Israel: 3
Country: Number of subjects enrolled	Italy: 38
Country: Number of subjects enrolled	Korea, Republic of: 92
Country: Number of subjects enrolled	Mexico: 4
Country: Number of subjects enrolled	Netherlands: 15
Country: Number of subjects enrolled	Peru: 5
Country: Number of subjects enrolled	Poland: 34
Country: Number of subjects enrolled	Russian Federation: 62

Country: Number of subjects enrolled	Taiwan: 4
Country: Number of subjects enrolled	Türkiye: 1
Country: Number of subjects enrolled	Ukraine: 48
Country: Number of subjects enrolled	United States: 11
Worldwide total number of subjects	545
EEA total number of subjects	105

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)	368
From 65 to 84 years	176
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

This study was conducted at 186 centers in 21 countries in North America (Canada and US), Asia (China, Hong Kong, Korea and Taiwan), and Rest of World (ROW) (Argentina, Brazil, Chile, Estonia, Hungary, India, Israel, Italy, Mexico, Netherlands, Peru, Poland, Russian Federation, Turkey, and Ukraine).

Pre-assignment

Screening details:

Participants were randomized into one of two treatment arms: CapeOx plus lapatinib (the experimental arm) or CapeOx plus placebo (the control arm) using a 1:1 randomization.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	CapeOx plus Lapatinib

Arm description:

Participants received a combination therapy consisting of: 1) Oxaliplatin (Ox): 130 mg/m² intravenously on Day 1 of each 21-day cycle, for up to 8 cycles. 2) Capecitabine (Cape): 1700 mg/m² per day, taken orally in two divided doses from the evening of Day 1 to the morning of Day 15 (28 doses per cycle), followed by a minimum 6.5-day rest period. The dose could be increased to 2000 mg/m²/day after the first cycle at the investigator's discretion. 3) Lapatinib: 1250 mg orally once daily, starting on Day 1 and continued daily throughout the cycle, including the rest period. After discontinuing oxaliplatin, capecitabine and lapatinib were continued until disease progression, unacceptable toxicity, or withdrawal of consent.

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

Dosage and administration details:

5 pills at 250mg each once daily

Investigational medicinal product name	Oxaliplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion, Solution for infusion, Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

130mg/m² on day 1

Investigational medicinal product name	Capecitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:
1700mg/m²/day in two daily doses

Arm title	CapeOx plus Placebo
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Arm description:

Participants received a combination therapy consisting of: 1) Oxaliplatin (Ox): 130 mg/m² intravenously on Day 1 of each 21-day cycle, for up to 8 cycles. 2) Capecitabine (Cape): 1700 mg/m² per day, taken orally in two divided doses from the evening of Day 1 to the morning of Day 15 (28 doses per cycle), followed by a minimum 6.5-day rest period. The dose could be increased to 2000 mg/m²/day after the first cycle at the investigator's discretion. 3) Lapatinib matching placebo: Taken orally once daily starting on Day 1 and continued throughout each cycle, including the rest period. After discontinuing oxaliplatin, capecitabine and the lapatinib placebo were continued until disease progression, unacceptable toxicity, or withdrawal of consent.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Pillules
Routes of administration	Oral use

Dosage and administration details:

5 pills each once daily

Investigational medicinal product name	Oxaliplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion, Solution for infusion, Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

130mg/m² on day 1

Investigational medicinal product name	Capecitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

1700mg/m²/day in two daily doses

Number of subjects in period 1	CapeOx plus Lapatinib	CapeOx plus Placebo
Started	272	273
Primary Efficacy (PE) population	249	238
Safety population	270	267
Ongoing: On Study Treatment	1 ^[1]	0 ^[2]
Ongoing: In Follow Up	1 ^[3]	0 ^[4]
Completed	243	233
Not completed	29	40
Physician decision	-	2

Adverse event, non-fatal	1	1
Ongoing: On Study Treatment	1	-
Other protocol defined stopping criteria	17	17
Ongoing: In Follow Up	1	-
Lost to follow-up	3	5
Sponsor decision	1	-
Subject reached protocol defined stopping criteria	1	-
Subject decided to withdraw from the study	4	15

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Due to local regulations in China, data from Chinese subjects dated from 01-Jul-2016 onward was excluded. As noted in the primary CSR, the subject had been withdrawn from the study on 05 Apr 2011 due to being lost to follow-up, and overall survival was unknown. However, a data transition issue from the previous database (TRIO) led to the subject being incorrectly reported as "ongoing" for study arm "CapeOx plus Lapatinib"

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Due to local regulations in China (HGRAC), data collection at all sites in China was immediately stopped as of 01-Jul-2016. No data from Chinese subjects was transferred or processed thereafter. Consequently, one subject was marked as "ongoing" in the database for study arm "CapeOx plus Lapatinib"

[3] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Due to local regulations in China (HGRAC), data collection at all sites in China was immediately stopped as of 01-Jul-2016. No data from Chinese subjects was transferred or processed thereafter. Consequently, one subject was marked as "ongoing" in the database for study arm "CapeOx plus Lapatinib"

[4] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Due to local regulations in China, data from Chinese subjects dated from 01-Jul-2016 onward was excluded. As noted in the primary CSR, the subject had been withdrawn from the study on 05 Apr 2011 due to being lost to follow-up, and overall survival was unknown. However, a data transition issue from the previous database (TRIO) led to the subject being incorrectly reported as "ongoing" for study arm "CapeOx plus Lapatinib"

Baseline characteristics

Reporting groups

Reporting group title	CapeOx plus Lapatinib
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Reporting group description:

Participants received a combination therapy consisting of: 1) Oxaliplatin (Ox): 130 mg/m² intravenously on Day 1 of each 21-day cycle, for up to 8 cycles. 2) Capecitabine (Cape): 1700 mg/m² per day, taken orally in two divided doses from the evening of Day 1 to the morning of Day 15 (28 doses per cycle), followed by a minimum 6.5-day rest period. The dose could be increased to 2000 mg/m²/day after the first cycle at the investigator's discretion. 3) Lapatinib: 1250 mg orally once daily, starting on Day 1 and continued daily throughout the cycle, including the rest period. After discontinuing oxaliplatin, capecitabine and lapatinib were continued until disease progression, unacceptable toxicity, or withdrawal of consent.

Reporting group title	CapeOx plus Placebo
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Reporting group description:

Participants received a combination therapy consisting of: 1) Oxaliplatin (Ox): 130 mg/m² intravenously on Day 1 of each 21-day cycle, for up to 8 cycles. 2) Capecitabine (Cape): 1700 mg/m² per day, taken orally in two divided doses from the evening of Day 1 to the morning of Day 15 (28 doses per cycle), followed by a minimum 6.5-day rest period. The dose could be increased to 2000 mg/m²/day after the first cycle at the investigator's discretion. 3) Lapatinib matching placebo: Taken orally once daily starting on Day 1 and continued throughout each cycle, including the rest period. After discontinuing oxaliplatin, capecitabine and the lapatinib placebo were continued until disease progression, unacceptable toxicity, or withdrawal of consent.

Reporting group values	CapeOx plus Lapatinib	CapeOx plus Placebo	Total
Number of subjects	272	273	545
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)	183	185	368
From 65-84 years	88	88	176
85 years and over	1	0	1
Gender categorical			
Units: Subjects			
Female	66	73	139
Male	206	200	406
GenderNIH			
Units: Subjects			
Female	66	73	139
Male	206	200	406
Race/Ethnicity, Customized			
Units: Subjects			
African American/African Heritage (Hrtg)	2	3	5
American Indian or Alaska Native	3	3	6
Central/South Asian Hrtg	11	3	14

Japanese/East Asian Hrtg/South East Asian Hrtg	112	114	226
White	144	150	294

AgeContinuous			
Units: Years			
arithmetic mean	59.4	58.5	
standard deviation	± 11.20	± 11.23	-

End points

End points reporting groups

Reporting group title	CapeOx plus Lapatinib
Reporting group description:	
Participants received a combination therapy consisting of: 1) Oxaliplatin (Ox): 130 mg/m ² intravenously on Day 1 of each 21-day cycle, for up to 8 cycles. 2) Capecitabine (Cape): 1700 mg/m ² per day, taken orally in two divided doses from the evening of Day 1 to the morning of Day 15 (28 doses per cycle), followed by a minimum 6.5-day rest period. The dose could be increased to 2000 mg/m ² /day after the first cycle at the investigator's discretion. 3) Lapatinib: 1250 mg orally once daily, starting on Day 1 and continued daily throughout the cycle, including the rest period. After discontinuing oxaliplatin, capecitabine and lapatinib were continued until disease progression, unacceptable toxicity, or withdrawal of consent.	
Reporting group title	CapeOx plus Placebo
Reporting group description:	
Participants received a combination therapy consisting of: 1) Oxaliplatin (Ox): 130 mg/m ² intravenously on Day 1 of each 21-day cycle, for up to 8 cycles. 2) Capecitabine (Cape): 1700 mg/m ² per day, taken orally in two divided doses from the evening of Day 1 to the morning of Day 15 (28 doses per cycle), followed by a minimum 6.5-day rest period. The dose could be increased to 2000 mg/m ² /day after the first cycle at the investigator's discretion. 3) Lapatinib matching placebo: Taken orally once daily starting on Day 1 and continued throughout each cycle, including the rest period. After discontinuing oxaliplatin, capecitabine and the lapatinib placebo were continued until disease progression, unacceptable toxicity, or withdrawal of consent.	

Primary: Overall Survival in all randomized participants at the time of Primary Analysis

End point title	Overall Survival in all randomized participants at the time of Primary Analysis
End point description:	
Overall Survival was defined as the time from randomization to death from any cause. Participants who had not died were censored at their follow-up visit, either because follow-up had ended or was still ongoing.	
End point type	Primary
End point timeframe:	
From date of randomization till death due to any cause, assessed up the cut-off date for Primary Analysis (24-Sep-2012) (average of 4 years)	

End point values	CapeOx plus Lapatinib	CapeOx plus Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	272	273		
Units: Months				
median (confidence interval 95%)	11.9 (10.4 to 13.8)	10.4 (9.1 to 11.3)		

Statistical analyses

Statistical analysis title	Primary Analysis: OS (ITT population)
Comparison groups	CapeOx plus Lapatinib v CapeOx plus Placebo

Number of subjects included in analysis	545
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.3244 ^[1]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.91
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.74
upper limit	1.1

Notes:

[1] - Stratified log-rank test was conducted stratifying for prior adjuvant/neo-adjuvant treatment use and region.

Primary: Overall Survival at the time of Primary Analysis

End point title	Overall Survival at the time of Primary Analysis
End point description:	Overall Survival was defined as the time from randomization to death from any cause. Participants who had not died were censored at their follow-up visit, either because follow-up had ended or was still ongoing.
End point type	Primary
End point timeframe:	From date of randomization till death due to any cause, assessed up the cut-off date for Primary Analysis (24-Sep-2012) (average of 4 years)

End point values	CapeOx plus Lapatinib	CapeOx plus Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	249	238		
Units: Months				
median (confidence interval 95%)	12.2 (10.6 to 14.2)	10.5 (9.0 to 11.3)		

Statistical analyses

Statistical analysis title	Primary Analysis: OS (PE population)
Comparison groups	CapeOx plus Lapatinib v CapeOx plus Placebo
Number of subjects included in analysis	487
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.3492 ^[2]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.91

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.73
upper limit	1.12

Notes:

[2] - Stratified log-rank test was conducted stratifying for prior adjuvant/neo-adjuvant treatment use and region.

Secondary: Overall Survival at the time of Final Analysis

End point title	Overall Survival at the time of Final Analysis
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End point description:

Overall Survival was defined as the time from randomization to death from any cause. Participants who had not died were censored at their follow-up visit, either because follow-up had ended or was still ongoing.

End point type	Secondary
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End point timeframe:

From date of randomization till death due to any cause, assessed up the cut-off date for Final Analysis (03-Oct-2024) (average of 16 years)

End point values	CapeOx plus Lapatinib	CapeOx plus Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	249	238		
Units: Months				
median (confidence interval 95%)	12.0 (10.4 to 13.8)	10.4 (9.0 to 11.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival (PFS)

End point title	Progression Free Survival (PFS)
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End point description:

Progression-Free Survival (PFS) was defined as the time from randomization to the earliest occurrence of disease progression or death from any cause. Per RECIST v1.0, progression was defined as at least a 20% increase in the sum of diameters of target lesions from the smallest recorded sum or the appearance of one or more new lesions. Participants with symptomatic progression, even without radiological confirmation, were also counted. Those who had neither progressed nor died were censored at their follow-up visit, either because follow-up had ended or was ongoing. Participants who received non-study anti-cancer therapies before progression were also censored.

End point type	Secondary
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End point timeframe:

From date of randomization till the earliest date of disease progression or death due to any cause, assessed up the cut-off date for Final Analysis (03-Oct-2024) (average of 16 years)

End point values	CapeOx plus Lapatinib	CapeOx plus Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	249	238		
Units: Months				
median (confidence interval 95%)	6.2 (5.6 to 7.0)	5.4 (4.4 to 5.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with a confirmed Complete Response (CR) or a Partial Response (PR)

End point title	Percentage of Participants with a confirmed Complete Response (CR) or a Partial Response (PR)
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End point description:

A participant was considered a responder if they had achieved either a complete response (CR), defined as the disappearance of all target and non-target lesions, or a partial response (PR), defined as at least a 30% reduction in the sum of the longest diameters of target lesions from baseline, as assessed by the investigator and confirmed by radiographic imaging within four weeks of the initial observation.

End point type	Secondary
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End point timeframe:

From date of randomization till the date of the first documented response of CR or PR, assessed up the cut-off date for Final Analysis (03-Oct-2024) (average of 16 years)

End point values	CapeOx plus Lapatinib	CapeOx plus Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	249	238		
Units: Participants	131	94		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Clinical Benefit (CB)

End point title	Percentage of Participants with Clinical Benefit (CB)
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End point description:

Clinical Benefit (CB) was defined as evidence of a complete response (CR), partial response (PR), or stable disease (SD). CR referred to the disappearance of all target and non-target lesions, PR to at least a 30% reduction in the sum of the longest diameters of target lesions from baseline, and SD to neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progression, based on the smallest sum of diameters recorded since treatment initiation. All assessments were made by the investigator.

End point type	Secondary
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End point timeframe:

From date of randomization till date of disease progression (PD) or death due to any cause, assessed up the cut-off date for Final Analysis (03-Oct-2024) (average of 16 years)

End point values	CapeOx plus Lapatinib	CapeOx plus Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	249	238		
Units: Participants	199	188		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR)

End point title	Duration of Response (DOR)
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End point description:

Duration of Response (DOR) was defined as the time from the first documented evidence of a complete response (CR) or partial response (PR) until the first recorded sign of disease progression or death from any cause. According to RECIST, progression was defined as at least a 20% increase in the sum of diameters of target lesions from the smallest recorded sum or the appearance of one or more new lesions. Participants who had neither progressed nor died were censored at their follow-up visit, either because follow-up had ended or was ongoing. Those who received non-study anti-cancer therapies before progression were also censored.

End point type	Secondary
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End point timeframe:

From the time of the first documented evidence of a confirmed CR or PR until the earliest date of disease progression or death due to any cause, assessed up the cut-off date for Final Analysis (03-Oct-2024) (average of 16 years)

End point values	CapeOx plus Lapatinib	CapeOx plus Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	131	94		
Units: Months				
median (confidence interval 95%)	7.3 (6.4 to 8.5)	5.6 (4.6 to 6.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to response (TTR)

End point title	Time to response (TTR)
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End point description:

Time to Response (TTR) was defined as the duration from randomization to the first documented evidence of either a complete response (CR) (the disappearance of all target and non-target lesions) or a partial response (PR) (at least a 30% reduction in the sum of the longest diameters of target lesions from baseline) as assessed by the investigator.

End point type	Secondary
End point timeframe:	
From date of randomization till the first documented evidence of confirmed CR or PR, assessed up the cut-off date for Final Analysis (03-Oct-2024) (average of 16 years)	

End point values	CapeOx plus Lapatinib	CapeOx plus Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	131	94		
Units: Months				
median (confidence interval 95%)	1.4 (1.4 to 1.5)	1.4 (1.4 to 1.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with any on-therapy Adverse Event (AE) and Serious Adverse Event (SAE)

End point title	Percentage of participants with any on-therapy Adverse Event (AE) and Serious Adverse Event (SAE)
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End point description:

An Adverse Event (AE) was defined as any untoward medical occurrence in a participant that was temporally associated with the use of a medicinal product, regardless of its causal relationship. This included any unfavorable or unintended sign (such as abnormal lab findings), symptom, or disease, whether new or worsened. A Serious Adverse Event (SAE) was defined as any such occurrence that, at any dose, resulted in death, was life-threatening, required hospitalization or its prolongation, caused disability or incapacity, led to a congenital anomaly or birth defect, or was a potential case of drug-induced liver injury.

End point type	Secondary
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End point timeframe:

From the first dose of study medication until 30 days after the last dose, assessed up the cut-off date for Final Analysis (03-Oct-2024) (average of 16 years)

End point values	CapeOx plus Lapatinib	CapeOx plus Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	270	267		
Units: Participants				
On-Therapy AEs (All, regardless of seriousness)	255	237		
On-Therapy SAEs	73	54		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with on-therapy Adverse Event (AE) by Maximum Grade

End point title	Percentage of participants with on-therapy Adverse Event (AE) by Maximum Grade
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End point description:

An Adverse Event (AE) was defined as any untoward medical occurrence in a participant that was temporally associated with the use of a medicinal product, regardless of its relationship to the product. This included any unfavorable or unintended sign (such as abnormal lab results), symptom, or disease, whether new or worsened. The severity of AEs was graded according to NCI CTCAE version 3.0: Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), Grade 4 (life-threatening), and Grade 5 (death related to toxicity).

End point type	Secondary
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End point timeframe:

From the first dose of study medication until 30 days after the last dose, assessed up the cut-off date for Final Analysis (03-Oct-2024) (average of 16 years)

End point values	CapeOx plus Lapatinib	CapeOx plus Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	255	237		
Units: Participants				
Grade 1	43	56		
Grade 2	85	78		
Grade 3	94	69		
Grade 4	17	25		
Grade 5	16	9		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with on-therapy Serious Adverse Event (SAE) by Maximum Grade

End point title	Percentage of participants with on-therapy Serious Adverse Event (SAE) by Maximum Grade
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End point description:

A Serious Adverse Event (SAE) was defined as any such occurrence that resulted in death, was life-threatening, required hospitalization or its prolongation, caused disability or incapacity, led to a congenital anomaly or birth defect, or was a potential case of drug-induced liver injury. The severity of SAEs was graded according to NCI CTCAE version 3.0: Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), Grade 4 (life-threatening), and Grade 5 (death related to toxicity).

End point type	Secondary
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End point timeframe:

From the first dose of study medication until 30 days after the last dose, assessed up the cut-off date for Final Analysis (03-Oct-2024) (average of 16 years)

End point values	CapeOx plus Lapatinib	CapeOx plus Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	73	54		
Units: Participants				
Grade 1	3	3		
Grade 2	6	4		
Grade 3	37	21		
Grade 4	13	18		
Grade 5	14	8		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from Baseline in the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life (QOL) Questionnaire Core 30 (QLQ-C30) Domain Scores

End point title	Mean change from Baseline in the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life (QOL) Questionnaire Core 30 (QLQ-C30) Domain Scores
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End point description:

The EORTC QLQ-C30 is a comprehensive questionnaire developed for assessing the quality of life of cancer patients across different aspects including function scales namely physical, role, cognitive, emotional and social; symptom scales such as fatigue, pain, nausea and vomiting; and a global scale pronouncing overall health status. Its scoring method involves a 4-point Likert scale (ranging from 1 'Not at all' to 4 'Very Much'). Domain scores are calculated by averaging the items within the respective domain and then linearly transforming the score to fit within a 0-100 scale to finalize the scores. In terms of interpretation, a high scale score represents a higher response level. Thus a high score for a functional scale represents a high / healthy level of functioning, a high score for the global health status / QoL represents a high QoL, but a high score for a symptom scale / item represents a high level of symptomatology / problems.

End point type	Secondary
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End point timeframe:

From Baseline up to disease progression (PD), assessed up the cut-off date for Final Analysis (03-Oct-2024) (average of 16 years)

End point values	CapeOx plus Lapatinib	CapeOx plus Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61	61		
Units: Scores on a scale				
arithmetic mean (standard deviation)				
Global health status/QoL	-6.6 (± 24.63)	-5.1 (± 23.97)		
Physical functioning	-9.4 (± 25.61)	-9.6 (± 22.33)		
Role functioning	-8.9 (± 34.64)	-11.7 (± 31.67)		

Emotional functioning	-3.8 (± 27.37)	-7.1 (± 23.61)		
Cognitive functioning	-7.4 (± 21.41)	-10.4 (± 21.98)		
Social functioning	-4.9 (± 32.54)	-0.5 (± 26.52)		
Fatigue	5.5 (± 26.42)	5.6 (± 25.30)		
Nausea and vomiting	3.3 (± 27.69)	4.4 (± 20.62)		
Pain	4.9 (± 30.48)	7.7 (± 30.06)		
Dyspnoea	6.7 (± 26.61)	7.8 (± 27.70)		
Insomnia	0.0 (± 33.33)	3.3 (± 35.09)		
Appetite loss	-0.5 (± 39.20)	5.5 (± 37.11)		
Constipation	-0.6 (± 32.18)	-3.8 (± 34.48)		
Diarrhoea	4.4 (± 29.49)	1.1 (± 23.95)		
Financial difficulties	0.0 (± 29.81)	0.6 (± 24.16)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from Baseline in the EORTC Quality of Life (QOL) Questionnaire of Stomach 22 (QLQ-STO22) Scales/Items Score Scale

End point title	Mean change from Baseline in the EORTC Quality of Life (QOL) Questionnaire of Stomach 22 (QLQ-STO22) Scales/Items Score Scale
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End point description:

The QLQ-STO22 consists of 22 items divided into five subscales: dysphagia, pain, reflux, eating restrictions and anxiety, as well as single items addressing dry mouth, body image, taste, and hair loss. Each item is answered on a 4-point scale, ranging from 1 (not at all) to 4 (very much). Raw scores for each subscale or single item are calculated by averaging the scores of the individual items that make up the scale. These scores are then linearly transformed to range from 0 to 100. In terms of interpretation, a higher score indicates a worse quality of life concerning the specific symptoms assessed.

End point type	Secondary
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End point timeframe:

From Baseline up to disease progression (PD), assessed up the cut-off date for Final Analysis (03-Oct-2024) (average of 16 years)

End point values	CapeOx plus Lapatinib	CapeOx plus Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	60	54		
Units: Scores on a scale				
arithmetic mean (standard deviation)				
Dysphagia scale	3.4 (± 22.99)	-3.1 (± 16.92)		
Pain scale	-1.5 (± 22.20)	-0.6 (± 18.71)		
Reflux scale	-1.4 (± 21.86)	-4.1 (± 18.48)		
Eating restrictions scale	1.2 (± 27.83)	-3.2 (± 22.11)		
Anxiety scale	-2.9 (± 27.42)	-7.5 (± 24.38)		
Dry mouth scale	2.8 (± 31.13)	1.9 (± 32.00)		
Taste scale	4.5 (± 37.37)	9.2 (± 32.03)		
Body image scale	-3.3 (± 37.68)	-1.9 (± 30.66)		

Hair loss scale	-16.7 (± 23.57)	0.0 (± 33.33)		
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Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from Baseline in Utility Score (Health Utility Index) in the EuroQoL-5 Dimensions (EQ-5D) Questionnaire

End point title	Mean change from Baseline in Utility Score (Health Utility Index) in the EuroQoL-5 Dimensions (EQ-5D) Questionnaire
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End point description:

The EQ-5D is a standardized instrument developed by the EuroQoL Group to measure health-related quality of life. It includes a descriptive system covering five dimensions and a Visual Analogue Scale (VAS), often referred to as the Thermometer Score.

The Utility Score (Health Utility Index) is derived from the five dimensions of the EQ-5D descriptive system (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). Each dimension has levels indicating severity (e.g., 1 = no problems, 2 = some problems, 3 = extreme problems). These combinations form a health state, which is then converted into a single index value using a country-specific value set. In the UK-based value set, the possible EQ-5D index utility values range from -0.594 to 1.0, where: 1.0 = perfect health, 0 = death and < 0 = health states considered worse than death.

End point type	Secondary
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End point timeframe:

From Baseline up to disease progression (PD), assessed up the cut-off date for Final Analysis (03-Oct-2024) (average of 16 years)

End point values	CapeOx plus Lapatinib	CapeOx plus Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	59	57		
Units: Scores on a scale				
arithmetic mean (standard deviation)	-0.17 (± 0.347)	-0.07 (± 0.328)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from Baseline in Thermometer Score (EQ VAS) in the EuroQoL-5 Dimensions (EQ-5D) Questionnaire

End point title	Mean change from Baseline in Thermometer Score (EQ VAS) in the EuroQoL-5 Dimensions (EQ-5D) Questionnaire
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End point description:

The EQ-5D is a standardized instrument developed by the EuroQoL Group to measure health-related quality of life. It includes a descriptive system covering five dimensions and a Visual Analogue Scale (VAS), often referred to as the Thermometer Score.

The Thermometer Score is a self-rated health score using a vertical visual analogue scale , where

respondents rate their overall health on a scale from 0 (worst imaginable health) to 100 (best imaginable health).

End point type	Secondary
End point timeframe:	
From Baseline up to disease progression (PD), assessed up the cut-off date for Final Analysis (03-Oct-2024) (average of 16 years)	

End point values	CapeOx plus Lapatinib	CapeOx plus Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61	60		
Units: Scores on a scale				
arithmetic mean (standard deviation)	-4.61 (± 23.054)	-7.90 (± 17.349)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with worst-case on-therapy Chemistry Toxicities

End point title	Percentage of participants with worst-case on-therapy Chemistry Toxicities
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End point description:

The severity of chemistry parameters was graded according to NCI CTCAE version 3.0: Grade 0 (No adverse event or within normal limits), Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe) and Grade 4 (life-threatening).

Chemistry data included: Alanine aminotransferase (ALT), Albumin, Alkaline phosphatases (ALP), Aspartate aminotransferase (AST), Calcium (hypercalcemia), Calcium (hypocalcemia), Creatine Kinase (CK), Creatine, Glucose (hyperglycemia), Glucose (hypoglycemia), Magnesium (hypermagnesemia), Magnesium (hypomagnesemia), Potassium (hyperkalemia), Potassium (hypokalemia), Sodium (hyponatremia), Sodium (hyponatremia) and Total Bilirubin.

End point type	Secondary
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End point timeframe:

From the first dose of study medication until 30 days after the last dose, assessed up the cut-off date for Final Analysis (03-Oct-2024) (average of 16 years)

End point values	CapeOx plus Lapatinib	CapeOx plus Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	260	262		
Units: Participants				
Alanine aminotransferase (ALT) Grade 0	163	153		
Albumin Grade 0	123	140		
Alkaline phosphatases (ALP) Grade 0	120	114		
Aspartate aminotransferase (AST) Grade 0	108	93		

Calcium (hypercalcemia) Grade 0	237	242		
Calcium (hypocalcemia) Grade 0	129	134		
Creatine Kinase (CK) Grade 0	1	3		
Creatinine Grade 0	230	228		
Glucose (hyperglycemia) Grade 0	107	119		
Glucose (hypoglycemia) Grade 0	223	237		
Magnesium (hypermagnesemia) Grade 0	229	234		
Magnesium (hypomagnesemia) Grade 0	189	199		
Potassium (hyperkalemia) Grade 0	228	234		
Potassium (hypokalemia) Grade 0	160	195		
Sodium (hypernatremia) Grade 0	234	234		
Sodium (hyponatremia) Grade 0	186	199		
Total Bilirubin Grade 0	153	178		
Alanine aminotransferase (ALT) Grade 1	87	94		
Albumin Grade 1	72	66		
Alkaline phosphatases (ALP) Grade 1	113	109		
Aspartate aminotransferase (AST) Grade 1	133	142		
Calcium (hypercalcemia) Grade 1	17	19		
Calcium (hypocalcemia) Grade 1	74	81		
Creatine Kinase (CK) Grade 1	0	0		
Creatinine Grade 1	21	33		
Glucose (hyperglycemia) Grade 1	115	103		
Glucose (hypoglycemia) Grade 1	32	20		
Magnesium (hypermagnesemia) Grade 1	20	17		
Magnesium (hypomagnesemia) Grade 1	59	52		
Potassium (hyperkalemia) Grade 1	20	14		
Potassium (hypokalemia) Grade 1	75	54		
Sodium (hypernatremia) Grade 1	18	20		
Sodium (hyponatremia) Grade 1	52	42		
Total Bilirubin Grade 1	55	42		
Alanine aminotransferase (ALT) Grade 2	8	11		
Albumin Grade 2	59	48		
Alkaline phosphatases (ALP) Grade 2	22	25		
Aspartate aminotransferase (AST) Grade 2	16	21		
Calcium (hypercalcemia) Grade 2	2	1		
Calcium (hypocalcemia) Grade 2	50	43		
Creatine Kinase (CK) Grade 2	0	0		
Creatinine Grade 2	7	0		
Glucose (hyperglycemia) Grade 2	30	32		
Glucose (hypoglycemia) Grade 2	3	2		
Magnesium (hypermagnesemia) Grade 2	0	0		
Magnesium (hypomagnesemia) Grade 2	5	5		
Potassium (hyperkalemia) Grade 2	8	11		
Potassium (hypokalemia) Grade 2	0	0		
Sodium (hypernatremia) Grade 2	2	5		
Sodium (hyponatremia) Grade 2	0	0		
Total Bilirubin Grade 2	43	33		
Alanine aminotransferase (ALT) Grade 3	2	4		

Albumin Grade 3	3	4		
Alkaline phosphatases (ALP) Grade 3	5	12		
Aspartate aminotransferase (AST) Grade 3	3	6		
Calcium (hypercalcemia) Grade 3	0	0		
Calcium (hypocalcemia) Grade 3	3	4		
Creatine Kinase (CK) Grade 3	0	0		
Creatinine Grade 3	2	1		
Glucose (hyperglycemia) Grade 3	6	8		
Glucose (hypoglycemia) Grade 3	1	1		
Magnesium (hypermagnesemia) Grade 3	5	5		
Magnesium (hypomagnesemia) Grade 3	1	0		
Potassium (hyperkalemia) Grade 3	2	2		
Potassium (hypokalemia) Grade 3	21	11		
Sodium (hypernatremia) Grade 3	3	2		
Sodium (hyponatremia) Grade 3	19	16		
Total Bilirubin Grade 3	7	3		
Alanine aminotransferase (ALT) Grade 4	0	0		
Albumin Grade 4	0	0		
Alkaline phosphatases (ALP) Grade 4	0	0		
Aspartate aminotransferase (AST) Grade 4	0	0		
Calcium (hypercalcemia) Grade 4	0	0		
Calcium (hypocalcemia) Grade 4	0	0		
Creatine Kinase (CK) Grade 4	0	0		
Creatinine Grade 4	0	0		
Glucose (hyperglycemia) Grade 4	1	0		
Glucose (hypoglycemia) Grade 4	0	2		
Magnesium (hypermagnesemia) Grade 4	0	0		
Magnesium (hypomagnesemia) Grade 4	0	0		
Potassium (hyperkalemia) Grade 4	1	0		
Potassium (hypokalemia) Grade 4	3	1		
Sodium (hypernatremia) Grade 4	2	0		
Sodium (hyponatremia) Grade 4	2	4		
Total Bilirubin Grade 4	2	5		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with worst-case on-therapy Hematologic Toxicities

End point title	Percentage of participants with worst-case on-therapy Hematologic Toxicities
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End point description:

The severity of hematologic parameters was graded according to NCI CTCAE version 3.0: Grade 0 (No adverse event or within normal limits), Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe) and Grade 4 (life-threatening).

Hematology data included: Hemoglobin, Platelet count, Total Neutrophils (Total ANC - Total Absolute Neutrophil Count) and White Blood Cell count.

End point type	Secondary
End point timeframe:	
From the first dose of study medication until 30 days after the last dose, assessed up the cut-off date for Final Analysis (03-Oct-2024) (average of 16 years)	

End point values	CapeOx plus Lapatinib	CapeOx plus Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	261	263		
Units: Participants				
Hemoglobin Grade 0	18	22		
Platelet count Grade 0	97	116		
Total ANC (Absolute Neutrophil Count) Grade 0	112	127		
White Blood Cell count Grade 0	126	136		
Hemoglobin Grade 1	104	121		
Platelet count Grade 1	95	86		
Total ANC (Absolute Neutrophil Count) Grade 1	42	45		
White Blood Cell count Grade 1	71	74		
Hemoglobin Grade 2	104	93		
Platelet count Grade 2	43	27		
Total ANC (Absolute Neutrophil Count) Grade 2	58	48		
White Blood Cell count Grade 2	50	47		
Hemoglobin Grade 3	35	27		
Platelet count Grade 3	21	30		
Total ANC (Absolute Neutrophil Count) Grade 3	22	27		
White Blood Cell count Grade 3	12	4		
Hemoglobin Grade 4	0	0		
Platelet count Grade 4	5	2		
Total ANC (Absolute Neutrophil Count) Grade 4	6	2		
White Blood Cell count Grade 4	2	1		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events (AEs) were documented from the first administration of the study medication through the end of the Long-Term Follow-up (LTFU) period, covering a duration of up to approximately 16 years.

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
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	27.1
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Reporting groups

Reporting group title	CapeOx + Lapatinib 1250 mg
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Reporting group description:

CapeOx + Lapatinib 1250 mg

Reporting group title	CapeOx + Placebo
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Reporting group description:

CapeOx + Placebo

Serious adverse events	CapeOx + Lapatinib 1250 mg	CapeOx + Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	73 / 270 (27.04%)	54 / 267 (20.22%)	
number of deaths (all causes)	42	40	
number of deaths resulting from adverse events	4	1	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour haemorrhage			
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	
Vascular disorders			
Haemorrhage			
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	
Deep vein thrombosis			

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	
Circulatory collapse			
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	
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	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	2 / 270 (0.74%)	4 / 267 (1.50%)	
occurrences causally related to treatment / all	2 / 2	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Condition aggravated			
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	
Death			
subjects affected / exposed	2 / 270 (0.74%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Drowning			
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 / 1	
Fatigue			
subjects affected / exposed	3 / 270 (1.11%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple organ dysfunction syndrome			

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	1 / 1	0 / 0	
Oedema peripheral			
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	
Sudden death			
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	
Pyrexia			
subjects affected / exposed	4 / 270 (1.48%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Drug hypersensitivity			
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	
Contrast media reaction			
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	
Respiratory, thoracic and mediastinal disorders			
Pharyngeal haemorrhage			
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	
Bronchospasm			
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	

Pulmonary infarction			
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%)	2 / 267 (0.75%)	
occurrences causally related to treatment / all	1 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
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	
Psychiatric disorders			
Confusional state			
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	
Product issues			
Device occlusion			
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	
Investigations			
Alanine aminotransferase increased			
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	
Haemoglobin decreased			
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	
Blood bilirubin increased			

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	
Liver function test abnormal			
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	
Platelet count decreased			
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	
Weight 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	
Ejection fraction decreased			
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	
Injury, poisoning and procedural complications			
Face injury			
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	
Femur fracture			
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	
Spinal cord injury thoracic			
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			

Pericardial effusion			
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	
Left ventricular dysfunction			
subjects affected / exposed	2 / 270 (0.74%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardio-respiratory arrest			
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	
Cardiac tamponade			
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	
Acute myocardial infarction			
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	
Acute coronary syndrome			
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	
Atrial fibrillation			
subjects affected / exposed	2 / 270 (0.74%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Aphasia			
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	
Epilepsy			

subjects affected / exposed	1 / 270 (0.37%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Dizziness			
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	
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	
Haemorrhage intracranial			
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	
Nervous system disorder			
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	
Paraesthesia			
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	
Seizure			
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	
Speech disorder			
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	
Syncope			

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	7 / 270 (2.59%)	4 / 267 (1.50%)	
occurrences causally related to treatment / all	4 / 9	4 / 5	
deaths causally related to treatment / all	0 / 0	0 / 1	
Thrombocytopenia			
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	
Neutropenia			
subjects affected / exposed	3 / 270 (1.11%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 270 (0.74%)	3 / 267 (1.12%)	
occurrences causally related to treatment / all	0 / 2	2 / 3	
deaths causally related to treatment / all	0 / 1	0 / 0	
Haematemesis			
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 / 1	
Gingival bleeding			
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 obstruction			
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	
Gastrointestinal haemorrhage			

subjects affected / exposed	3 / 270 (1.11%)	2 / 267 (0.75%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric haemorrhage			
subjects affected / exposed	1 / 270 (0.37%)	2 / 267 (0.75%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric dilatation			
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	
Enterocutaneous fistula			
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	
Dysphagia			
subjects affected / exposed	2 / 270 (0.74%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	16 / 270 (5.93%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	20 / 20	1 / 1	
deaths causally related to treatment / all	2 / 2	0 / 0	
Ascites			
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	
Abdominal pain upper			
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	
Ileus spastic			

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	
Nausea			
subjects affected / exposed	6 / 270 (2.22%)	2 / 267 (0.75%)	
occurrences causally related to treatment / all	5 / 6	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mesenteric vein 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	
Melaena			
subjects affected / exposed	1 / 270 (0.37%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine perforation			
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 / 1	
Intestinal obstruction			
subjects affected / exposed	2 / 270 (0.74%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obstruction gastric			
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	
Upper gastrointestinal haemorrhage			
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	
Vomiting			

subjects affected / exposed	7 / 270 (2.59%)	6 / 267 (2.25%)	
occurrences causally related to treatment / all	4 / 7	6 / 6	
deaths causally related to treatment / all	0 / 1	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	2 / 270 (0.74%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Jaundice cholestatic			
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	
Jaundice			
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	
Renal and urinary disorders			
Renal failure			
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	
Oliguria			
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	
Acute kidney injury			
subjects affected / exposed	1 / 270 (0.37%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
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	

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	
Infections and infestations			
Abdominal 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 / 1	0 / 0	
Bacteraemia			
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	
Cellulitis			
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 / 1	
Gastroenteritis			
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 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	
Herpes zoster			
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	
Large intestine infection			
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	1 / 1	
Lung abscess			

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	
Peritonitis			
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	
Pneumonia			
subjects affected / exposed	6 / 270 (2.22%)	3 / 267 (1.12%)	
occurrences causally related to treatment / all	1 / 6	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pneumonia aspiration			
subjects affected / exposed	2 / 270 (0.74%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Sepsis			
subjects affected / exposed	1 / 270 (0.37%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	1 / 1	0 / 1	
Upper respiratory tract 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	4 / 270 (1.48%)	3 / 267 (1.12%)	
occurrences causally related to treatment / all	3 / 4	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	6 / 270 (2.22%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	4 / 6	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			

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	
Hyperkalaemia			
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	
Hypokalaemia			
subjects affected / exposed	2 / 270 (0.74%)	1 / 267 (0.37%)	
occurrences causally related to treatment / all	2 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	2 / 270 (0.74%)	0 / 267 (0.00%)	
occurrences causally related to treatment / all	2 / 2	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	CapeOx + Lapatinib 1250 mg	CapeOx + Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	243 / 270 (90.00%)	214 / 267 (80.15%)	
Investigations			
Weight decreased			
subjects affected / exposed	43 / 270 (15.93%)	33 / 267 (12.36%)	
occurrences (all)	44	33	
Nervous system disorders			
Dizziness			
subjects affected / exposed	14 / 270 (5.19%)	14 / 267 (5.24%)	
occurrences (all)	17	19	
Peripheral sensory neuropathy			
subjects affected / exposed	34 / 270 (12.59%)	29 / 267 (10.86%)	
occurrences (all)	69	64	
Neuropathy peripheral			
subjects affected / exposed	53 / 270 (19.63%)	58 / 267 (21.72%)	
occurrences (all)	70	81	

Headache subjects affected / exposed occurrences (all)	7 / 270 (2.59%) 8	14 / 267 (5.24%) 18	
General disorders and administration site conditions Pyrexia subjects affected / exposed occurrences (all)	30 / 270 (11.11%) 46	26 / 267 (9.74%) 38	
Oedema peripheral subjects affected / exposed occurrences (all)	14 / 270 (5.19%) 16	18 / 267 (6.74%) 20	
Fatigue subjects affected / exposed occurrences (all)	64 / 270 (23.70%) 89	60 / 267 (22.47%) 100	
Asthenia subjects affected / exposed occurrences (all)	46 / 270 (17.04%) 55	36 / 267 (13.48%) 43	
Gastrointestinal disorders Abdominal distension subjects affected / exposed occurrences (all)	16 / 270 (5.93%) 23	9 / 267 (3.37%) 9	
Abdominal pain subjects affected / exposed occurrences (all)	27 / 270 (10.00%) 34	32 / 267 (11.99%) 45	
Abdominal pain upper subjects affected / exposed occurrences (all)	20 / 270 (7.41%) 22	27 / 267 (10.11%) 31	
Constipation subjects affected / exposed occurrences (all)	30 / 270 (11.11%) 33	54 / 267 (20.22%) 72	
Diarrhoea subjects affected / exposed occurrences (all)	146 / 270 (54.07%) 325	77 / 267 (28.84%) 157	
Dyspepsia subjects affected / exposed occurrences (all)	14 / 270 (5.19%) 17	20 / 267 (7.49%) 24	
Nausea			

subjects affected / exposed	128 / 270 (47.41%)	113 / 267 (42.32%)	
occurrences (all)	270	266	
Stomatitis			
subjects affected / exposed	19 / 270 (7.04%)	10 / 267 (3.75%)	
occurrences (all)	21	12	
Vomiting			
subjects affected / exposed	116 / 270 (42.96%)	93 / 267 (34.83%)	
occurrences (all)	207	204	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	12 / 270 (4.44%)	19 / 267 (7.12%)	
occurrences (all)	15	22	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	18 / 270 (6.67%)	5 / 267 (1.87%)	
occurrences (all)	22	7	
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	57 / 270 (21.11%)	40 / 267 (14.98%)	
occurrences (all)	71	47	
Rash			
subjects affected / exposed	46 / 270 (17.04%)	16 / 267 (5.99%)	
occurrences (all)	51	17	
Skin hyperpigmentation			
subjects affected / exposed	16 / 270 (5.93%)	7 / 267 (2.62%)	
occurrences (all)	16	7	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	9 / 270 (3.33%)	16 / 267 (5.99%)	
occurrences (all)	10	17	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	107 / 270 (39.63%)	85 / 267 (31.84%)	
occurrences (all)	163	151	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 May 2008	Amendment 1: Update of the safety monitoring for hepatotoxicity; clarification of screening assessments; administrative changes.
13 August 2008	Amendment 2: Administrative update and pharmacokinetic sample was appended to the supplemental liver chemistry follow-up criteria sample panel to obtain serum levels of the study treatment (lapatinib).
10 September 2009	Amendment 3: Revision to statistical plan; administrative updates; clarification of operational elements and text
28 October 2010	Amendment 4: Clarification to prior use of oxaliplatin; updated prohibited medications table; elimination of collection of serum and RNA blood samples; administrative updates and clarifications to enhance consistency and quality of document, removal from the protocol of supportive care guidance (Appendix 5), to be placed in Study Procedures Manual
22 August 2011	Amendment 5: Statistical revisions: the definition of the primary efficacy population was revised to include all subjects centrally confirmed by FISH, whether or not the subject had taken study medication. The addition of per protocol population to support the sensitivity analysis of selective efficacy data in subjects who comply most closely with the intended protocol population and updated clarifications in prohibited medications table. Administration changes and clarification of operational procedures to enhance protocol uniformity
28 September 2011	Amendment 5: republished due to discrepancy in headers. No changes to the body of the protocol
13 December 2011	Amendment 6: Local amendment for sites in China to allow continuation of recruitment given the Chinese regulatory authority's requirement for a minimum number of local subjects to participate in the study. Of note, no additional subjects were enrolled
06 March 2014	Amendment 7: This amendment is being implemented to discontinue collection of many studies specific assessments while allowing subjects currently on study treatment to have continued access to this treatment until the occurrence of unacceptable toxicity or disease progression (as determined by the Investigator) or withdrawal for any reasons. The aim is to continue to protect the safety of the subject, whilst removing the requirement for assessments intended to collect further efficacy data, unless clinically indicate; Amendment of study assessments: clinical assessments of safety and efficacy will be performed as directed by the Investigator judgment; Amendment to stop data collection for all subjects currently on follow -up; To ensure the safety of the subjects, Investigators will be asked to collect and report to the Sponsor all serious adverse events (SAEs) and pregnancies, and date and reasons for study treatment discontinuation (including adverse events (AEs) leading to discontinuation of study treatment and all other reasons for discontinuation of study treatment
27 April 2015	Amendment 8: Clarification to lapatinib drug supply, liver event data collection and interval of long-term follow-up period
22 March 2016	Amendment 9: Delete or replace references to GSK or its staff with that of Novartis/Novartis and its authorized agents. Make administrative changes to align with Novartis processes and procedures

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported