Clinical trial results:
A Randomised, Double-Blind, Placebo-Controlled, Multi-centre, Phase III Study of Post-Operative Adjuvant Lapatinib or Placebo and Concurrent Chemoradiotherapy Followed by Maintenance Lapatinib or Placebo Monotherapy in High-Risk Subjects with Resected Squamous Cell Carcinoma of the Head and Neck (SCCHN)

Summary

EudraCT number	2006-001623-18
Trial protocol	FR IE GR AT SK GB DE CZ PT EE HU IT LV
Global end of trial date	15 November 2013

Results information

Result version number	v1 (current)
This version publication date	13 April 2016
First version publication date	03 June 2015

Trial information

Trial identification

Sponsor protocol code	EGF102988

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	GlaxoSmithKline
Sponsor organisation address	980 Great West Road, Brentford, Middlesex, United Kingdom,
Public contact	GSK Response Center, GlaxoSmithKline, 1 866-435-7343,
Scientific contact	GSK Response Center, GlaxoSmithKline, 1 866-435-7343,

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	14 March 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	15 November 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate and compare DFS from randomisation to the end of the study in high-risk subjects with resected stage III or IVa SCCHN treated with adjuvant placebo or lapatinib and chemoradiotherapy followed by maintenance placebo or lapatinib for 1 year.

Protection of trial subjects:

- Cardiac monitoring: an ECHO scan (or MUGA scan) was performed at screening, at the end of the CRT period and every 8 weeks during the maintenance phase. For subjects who had a decreased LEVF during the CRT and/or maintenance period, the ECHO or MUGA scans were performed in the follow-up period.
- Liver chemistry monitoring and follow-up criteria were implemented in order to follow up on any potential hepatobiliary disorders that may occur. Hepatic function was to be monitored every 4 weeks during treatment and stopping rules were defined for severe hepatic events.
- An IDMC (Independent Data Monitoring Committee) convened to review accumulating safety (every six months) and efficacy (DFS) (only at pre-planned interim, futility analysis) data and to provide an opportunity to terminate the study early in case of any concerns regarding safety and/or efficacy.
- Modification of the Timing of the primary analysis: with the plateauing of investigator observed DFS events, it was decided to conduct the primary analysis with fewer events than originally planned and to discontinue DFS assessments to reduce burden and exposure to invasive tests and scans for patients still in DFS follow-up. Upon approval of amendment 04, patients on DFS follow-up moved to survival follow-up. .
- Regarding compliance and study medication administration, subjects were allowed to take tablets as a suspension, in recognition of the particular difficulty some patients affected by SCCHN and its treatment could experience in swallowing tablets.
- Diarrhea Management guidelines/ recommendation were provided to Investigators to help managing any potential diarrhea AE
- Radiotherapy (RT) Quality Assurance program: in order to standardize RT practice an independent vendor qualified each site, provided RT guidelines, and reviewed the RT plan for every subject.

Background therapy: -
Evidence for comparator: -

Actual start date of recruitment	21 December 2006
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	Slovakia: 24
Country: Number of subjects enrolled	United Kingdom: 21
Country: Number of subjects enrolled	Austria: 15
Country: Number of subjects enrolled	Czech Republic: 29
Country: Number of subjects enrolled	Estonia: 1
Country: Number of subjects enrolled	France: 116

Country: Number of subjects enrolled	Germany: 51
Country: Number of subjects enrolled	Greece: 21
Country: Number of subjects enrolled	Hungary: 41
Country: Number of subjects enrolled	Italy: 17
Country: Number of subjects enrolled	Argentina: 9
Country: Number of subjects enrolled	Canada: 3
Country: Number of subjects enrolled	China: 80
Country: Number of subjects enrolled	Croatia: 18
Country: Number of subjects enrolled	Hong Kong: 8
Country: Number of subjects enrolled	India: 119
Country: Number of subjects enrolled	Philippines: 14
Country: Number of subjects enrolled	Russian Federation: 40
Country: Number of subjects enrolled	Spain: 36
Country: Number of subjects enrolled	Thailand: 22
Country: Number of subjects enrolled	United States: 3
Worldwide total number of subjects	688
EEA total number of subjects	390

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)	611
From 65 to 84 years	77
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Study completion was not defined by the protocol; however participants (par.) were to be followed up until death or 5 years after randomization of the last par. The study was terminated less than 5 years after randomization of the last par. and therefore the number of completing par. reported here is equal to the number of par. who died.

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, Monitor, Data analyst, Carer

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Participants received placebo per oral monotherapy once daily (QD) for 1 week, followed by radiotherapy of 2 Gray (Gy) per day for 5 days per week (for a total dose of 66 Gy for up to 7 weeks). Participants received concurrent cisplatin 100 milligrams per meters squared (mg/m^2) intravenously (IV) on Days 1, 22, and 43 of radiotherapy. One week prior to the start of chemoradiotherapy, then concurrently for 6 to approximately 7 weeks with chemoradiotherapy, participants received placebo per oral administration QD, followed by maintenance placebo per oral monotherapy QD for up to 1 year or until evidence of disease relapse, whichever was sooner.

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

Dosage and administration details:

6 tablets daily (1500 mg per day) one hour before or one hour after the morning meal

Arm title	Lapatinib 1500 mg

Arm description:

Participants received lapatinib 1500 mg per oral monotherapy QD for 1 week, followed by radiotherapy of 2 Gy per day for 5 days per week (for a total of 66 Gy for up to 7 weeks). Participants received concurrent cisplatin 100 mg/m^2 IV on Days 1, 22, and 43 of radiotherapy. One week prior to the start of chemoradiotherapy, then concurrently for 6 to approximately 7 weeks with chemoradiotherapy, participants received lapatinib 1500 mg per oral administration QD, followed by maintenance lapatinib 1500 mg per oral monotherapy QD for up to 1 year or until evidence of disease relapse, whichever was sooner.

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:

6 tablets daily (1500 mg per day) one hour before or one hour after the morning meal

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

Dosage and administration details:

Administered intravenously at a dose of 100mg/m2 on approximately days 1, 22 and 43 of radiotherapy (approximately study days 8, 29 and 50). Standard hydration therapy and anti-emetic prophylaxis (including dexamethasone) will be administered as per institutional standard of care.

Number of subjects in period 1	Placebo	Lapatinib 1500 mg
Started	342	346
Completed	115	111
Not completed	227	235
Consent withdrawn by subject	34	38
Sponsor Terminated Study	161	167
Physician decision	3	7
Cognitive Disturbance	1	-
Fatigue	1	-
Non-compliance by Participants	1	-
Lost to follow-up	26	20
Disease Progression	-	2
Protocol deviation	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Placebo

Reporting group description:

Participants received placebo per oral monotherapy once daily (QD) for 1 week, followed by radiotherapy of 2 Gray (Gy) per day for 5 days per week (for a total dose of 66 Gy for up to 7 weeks). Participants received concurrent cisplatin 100 milligrams per meters squared (mg/m^2) intravenously (IV) on Days 1, 22, and 43 of radiotherapy. One week prior to the start of chemoradiotherapy, then concurrently for 6 to approximately 7 weeks with chemoradiotherapy, participants received placebo per oral administration QD, followed by maintenance placebo per oral monotherapy QD for up to 1 year or until evidence of disease relapse, whichever was sooner.

Reporting group title	Lapatinib 1500 mg

Reporting group description:

Participants received lapatinib 1500 mg per oral monotherapy QD for 1 week, followed by radiotherapy of 2 Gy per day for 5 days per week (for a total of 66 Gy for up to 7 weeks). Participants received concurrent cisplatin 100 mg/m^2 IV on Days 1, 22, and 43 of radiotherapy. One week prior to the start of chemoradiotherapy, then concurrently for 6 to approximately 7 weeks with chemoradiotherapy, participants received lapatinib 1500 mg per oral administration QD, followed by maintenance lapatinib 1500 mg per oral monotherapy QD for up to 1 year or until evidence of disease relapse, whichever was sooner.

Reporting group values	Placebo	Lapatinib 1500 mg	Total
Number of subjects	342	346	688
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	53.7	53.8	
standard deviation	± 9.85	± 8.38	-
Gender categorical Units: Subjects			
Female	55	60	115
Male	287	286	573
Race Units: Subjects			
African American/African Heritage	1	0	1
Asian - Central/South Asian Heritage	61	53	114
Asian - East Asian Heritage	41	47	88
Asian - South East Asian Heritage	19	23	42
Asian - Mixed Race	0	1	1
White - Arabic/North African Heritage	1	3	4
White - White/Caucasian/European Heritage	219	219	438

End points

End points reporting groups

Reporting group title	Placebo

Reporting group description:

Participants received placebo per oral monotherapy once daily (QD) for 1 week, followed by radiotherapy of 2 Gray (Gy) per day for 5 days per week (for a total dose of 66 Gy for up to 7 weeks). Participants received concurrent cisplatin 100 milligrams per meters squared (mg/m^2) intravenously (IV) on Days 1, 22, and 43 of radiotherapy. One week prior to the start of chemoradiotherapy, then concurrently for 6 to approximately 7 weeks with chemoradiotherapy, participants received placebo per oral administration QD, followed by maintenance placebo per oral monotherapy QD for up to 1 year or until evidence of disease relapse, whichever was sooner.

Reporting group title	Lapatinib 1500 mg

Reporting group description:

Participants received lapatinib 1500 mg per oral monotherapy QD for 1 week, followed by radiotherapy of 2 Gy per day for 5 days per week (for a total of 66 Gy for up to 7 weeks). Participants received concurrent cisplatin 100 mg/m^2 IV on Days 1, 22, and 43 of radiotherapy. One week prior to the start of chemoradiotherapy, then concurrently for 6 to approximately 7 weeks with chemoradiotherapy, participants received lapatinib 1500 mg per oral administration QD, followed by maintenance lapatinib 1500 mg per oral monotherapy QD for up to 1 year or until evidence of disease relapse, whichever was sooner.

Subject analysis set title	Lapatinib 1500 mg
Subject analysis set type	Safety analysis

Subject analysis set description:

Participants received lapatinib 1500 mg per oral monotherapy QD for 1 week, followed by radiotherapy of 2 Gy per day for 5 days per week (for a total of 66 Gy for up to 7 weeks). Participants received concurrent cisplatin 100 mg/m^2 IV on Days 1, 22, and 43 of radiotherapy. One week prior to the start of chemoradiotherapy, then concurrently for 6 to approximately 7 weeks with chemoradiotherapy, participants received lapatinib 1500 mg per oral administration QD, followed by maintenance lapatinib 1500 mg per oral monotherapy QD for up to 1 year or until evidence of disease relapse, whichever was sooner.

Primary: Disease free survival (DFS)

End point title	Disease free survival (DFS)

End point description:

DFS is defined as the time from randomization until the earliest date of disease recurrence (evidence of local, regional, or distant disease progression, second primary tumor) or death due to any cause. Disease recurrence was based on the assessments from the blinded, independent reviewer (radiological and clinical). Par. who initiated alternative anti-cancer therapy prior to disease recurrence or death were treated as censored at the last assessment prior to the time of this initiation. For par. whose disease did not recur or who did not die, DFS was censored at the time of the last independently assessed radiological scan (where initiation of alternative anti-cancer therapy had not commenced). Par. who missed >=2 consecutive disease assessments were censored at the last assessment prior to the missed assessments. Par. considered to have malignant disease at Baseline were censored at the time of randomization. 99999 represents NA - insufficient number of events to calculate value.

End point type	Primary

End point timeframe:

From randomization until the earliest date of disease recurrence or death due to any cause (average of 101 study weeks)

End point values	Placebo	Lapatinib 1500 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	342[1]	346[2]		
Units: Months				
median (confidence interval 95%)	99999 (54.6 to 99999)	53.6 (45.8 to 99999)		

Notes:

[1] - Intent-to-Treat (ITT) Population: randomized par., irrespective of whether they received study med.

[2] - Intent-to-Treat (ITT) Population: randomized par., irrespective of whether they received study med.

Statistical analyses

Statistical analysis title	Analysis 1
Comparison groups	Placebo v Lapatinib 1500 mg
Number of subjects included in analysis	688
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2251 [3]
Method	Non-stratified log-rank test

Notes:

[3] - The one-sided p-value is unstratified as there are too few events per stratum to perform a stratified test.

Statistical analysis title	Analysis 2
Comparison groups	Placebo v Lapatinib 1500 mg
Number of subjects included in analysis	688
Analysis specification	Pre-specified
Analysis type	superiority[4]
P-value	= 0.4502 [5]
Method	Non-stratified log-rank test
Parameter estimate	Hazard ratio (HR)
Point estimate	1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.85
upper limit	1.43

Notes:

[4] - Hazard Ratios were estimated using a Pike estimator.

[5] - The one-sided p-value is unstratified as there are too few events per stratum to perform a stratified test.

Secondary: Overall survival (OS)

End point title	Overall survival (OS)

End point description:

OS is defined as the time from randomization until death due to any cause. For participants who did not die, the time to death was censored at the time of last visit/contact. 99999 represents NA - insufficient number of events to calculate value.

End point type	Secondary

End point timeframe:

From randomization until death due to any cause (average of 131 study weeks)

End point values	Placebo	Lapatinib 1500 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	342[6]	346[7]		
Units: Months				
median (confidence interval 95%)	99999 (99999 to 99999)	99999 (58.8 to 99999)		

Notes:

[6] - ITT Population

[7] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Disease specific survival (DSS)

End point title	Disease specific survival (DSS)

End point description:

DSS is defined as the time from randomization until death due to head and neck cancer. Participants whose death was not related to the disease under study were treated as competing risks at the time death occured. Participants who were alive were censored at the time of their last visit. 99999 represents NA - insufficient number of events to calculate value.

End point type	Secondary

End point timeframe:

From randomization until death due to head and neck cancer (average of 131 study weeks)

End point values	Placebo	Lapatinib 1500 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	342[8]	346[9]		
Units: Months				
median (confidence interval 95%)	99999 (99999 to 99999)	99999 (99999 to 99999)		

Notes:

[8] - ITT Population

[9] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Time to locoregional recurrence (TTLR)

End point title	Time to locoregional recurrence (TTLR)

End point description:

TTLR is defined as the time from randomization until the first occurrence that local and/or regional recurrence is documented or the date of censor. Local relapse is defined as recurrent cancer in the primary tumor bed not clearly attributable to a second primary neoplasm. Regional relapse is defined as recurrent cancer in the neck not clearly attributable to a second primary neoplasm. All other events prior to locoregional recurrence were treated as competing risks at the time they occured. All other

participants were treated as censored at the time of their last disease assessment. Participants with malignant disease at Baseline according to the independent review were censored at the time of randomization for the analysis of independently reviewed data. 99999 represents NA - insufficient number of events to calculate value.

End point type	Secondary

End point timeframe:

From randomization until thefirst occurrence that local and/or regional recurrence is documented or the date of censor (average of 101 study weeks)

End point values	Placebo	Lapatinib 1500 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	342[10]	346[11]		
Units: Months				
median (confidence interval 95%)	99999 (99999 to 99999)	99999 (99999 to 99999)		

Notes:

[10] - ITT Population

[11] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Time to distant relapse (TTDR)

End point title	Time to distant relapse (TTDR)

End point description:

TTDR is defined as the time from randomization until the first occurrence that distant relapse is documented. Distant relapse is defined as clear evidence of distant metastases (lung, bone, brain, etc.). Metastasis is defined as the spread of a cancer from one organ or part to another non-adjacent organ or part. All other events prior to a distant relapse were treated as competing risks at the time they occured. All other participants were treated as censored at the time of their last disease assessment. Participants with malignant disease at Baseline according to the independent review were censored at the time of randomization for the analysis of independently reviewed data. 99999 represents NA - insufficient number of events to calculate value.

End point type	Secondary

End point timeframe:

From randomization until the first documented occurrence that distant relapse is documented (average of 101 study weeks)

End point values	Placebo	Lapatinib 1500 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	342[12]	346[13]		
Units: Months				
median (confidence interval 95%)	99999 (99999 to 99999)	99999 (99999 to 99999)		

Notes:

[12] - ITT Population

[13] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with a second primary tumor

End point title	Number of participants with a second primary tumor

End point description:

Participants who developed a second primary tumor at the time of the first recurrence or within 28 days of the first recurrence were measured. The criteria for a second primary tumor are as follows: a distinct lesion separated from the primary tumor site by >2 centimeters of normal epithelium; or a new cancer with different histology; or any cancer, regardless of site, occurring >=3 years after initial treatment. Participants with baseline disease were included in the denominator when calculating the percentage.

End point type	Secondary

End point timeframe:

From randomization until development of second primary tumor or within 28 days of first recurrence (average of 101 study weeks)

End point values	Placebo	Lapatinib 1500 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	342[14]	346[15]		
Units: Participants	5	9		

Notes:

[14] - ITT Population

[15] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Extent of exposure

End point title	Extent of exposure[16]

End point description:

Extent of exposure is defined as the duration of treatment administered during the study. The mean duration of treatment is calculated as the number of days between the start of treatment and the end of treatment inclusive (i.e., treatment stop date minus treatment start date + 1). Participants were counted in a treatment phase (monotherapy, chemoradiotherapy, and maintenance) if they had received any dose in that phase. Participants randomized to placebo who received >=1 dose of lapatinib in error were included in the lapatinib arm. Safety Population (SP): all par. who were randomized and took >=1 dose of study medication. Only par. available at the specified time points were analyzed (represented by n=X, X in the category titles). Different par. may have been analyzed for different parameters, so the overall number of par. analyzed reflects everyone in the SP.

End point type	Secondary

End point timeframe:

From randomization until end of 1year maintenance treatment (average of 63 study weeks)

Notes:

[16] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The safety population was taken as all participants who received one dose of medication. If a participant was randomized to the placebo arm and received any lapatinib in error, they were counted in the lapatinib arm in terms of safety endpoints. Five subjects randomized to receive placebo were given lapatinib, and 3 randomized subjects did not receive any study medication (2 lapatinib, 1 placebo). The Lapatinib 1500 mg containing the Safety population was used for this outcome measure.

End point values	Placebo	Lapatinib 1500 mg		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	336[17]	349[18]		
Units: Weeks				
arithmetic mean (standard deviation)				
Monotherapy, n=332, 347	0.9 (± 0.32)	0.9 (± 0.27)		
Chemoradiotherapy, n=327, 344	6.6 (± 1.29)	6.5 (± 1.58)		
Maintenance, n=309, 321	41.5 (± 20)	41.1 (± 21.03)		

Notes:

[17] - Safety Population

[18] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with any adverse event (AE) or serious adverse event (SAE)

End point title	Number of participants with any adverse event (AE) or serious adverse event (SAE)[19]

End point description:

An AE is defined as any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. An SAE is defined as any untoward medical occurrence that, at any dose, results in death, is life threatening, requires hospitalization or prolongation of existing hospitalization, results in disability/incapacity, or is a congenital anomaly/birth defect. Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations. Refer to the General Adverse AE/SAE module for a complete list of non-serious AEs occurring at a frequency threshold of 5% and SAEs.

End point type	Secondary

End point timeframe:

From the first dose of lapatinib/placebo until 5 days after the last dose (average of 141 study weeks)

Notes:

[19] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The safety population was taken as all participants who received one dose of medication. If a participant was randomized to the placebo arm and received any lapatinib in error, they were counted in the lapatinib arm in terms of safety endpoints. Five subjects randomized to receive placebo were given lapatinib, and 3 randomized subjects did not receive any study medication (2 lapatinib, 1 placebo). The Lapatinib 1500 mg containing the Safety population was used for this outcome measure.

End point values	Placebo	Lapatinib 1500 mg		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	336[20]	349[21]		
Units: Participants				
Any AE	328	344		
Any SAE	133	169		

Notes:

[20] - Safety Population

[21] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with the indicated chemistry toxicities by maximum toxicity grade (G3 and G4) at the worst-case on-therapy visit

End point title	Number of participants with the indicated chemistry toxicities by maximum toxicity grade (G3 and G4) at the worst-case on-therapy visit[22]

End point description:

Data are summarized using the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 3 (NCI CTC version 3.0) toxicity grades. Data are reported as the number of par. who had a grade 3 (G3) or grade 4 (G4) toxicity for the indicated chemistry parameters, where G3 indicates a severe toxicity and G4 indicates a life-threatening toxicity. Clinical chemistry parameters included: albumin, alkaline phosphatase (AP), alanine amino transferase (ALT), aspartate amino transeferase (AST), total bilirubin (TB), calcium, carbon dioxide content/bicarbonate (CO2/HCO3), creatinine, glucose, potassium, and sodium. The worst-case on-therapy visit includes any scheduled or unscheduled post-Baseline visit. Only those par. available at the specified time points were analyzed (represented by n=X, X in the category titles). Different par. may have been analyzed for different parameters, so the overall number of par. analyzed reflects everyone in the Safety Population.

End point type	Secondary

End point timeframe:

From Baseline (within 8 weeks prior to randomization [Day 1]) until the end of the maintenance period/early withdrawal (up to Study Week 64)

Notes:

[22] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The safety population was taken as all participants who received one dose of medication. If a participant was randomized to the placebo arm and received any lapatinib in error, they were counted in the lapatinib arm in terms of safety endpoints. Five subjects randomized to receive placebo were given lapatinib, and 3 randomized subjects did not receive any study medication (2 lapatinib, 1 placebo). The Lapatinib 1500 mg containing the Safety population was used for this outcome measure.

End point values	Placebo	Lapatinib 1500 mg		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	336[23]	349[24]		
Units: Participants				
Albumin, Grade 3, n=330, 343	1	0		
Albumin, Grade 4, n=330, 343	0	0		
AP, Grade 3, n=333, 347	1	2		
AP, Grade 4, n=333, 347	0	0		
ALT, Grade 3, n=333, 348	9	3		
ALT, Grade 4, n=333, 348	1	0		
AST, Grade 3, n=333, 347	5	5		
AST, Grade 4, n=333, 347	1	0		
TB, Grade 3, n=333, 348	3	6		
TB, Grade 4, n=333, 348	0	0		
Hypercalcemia , Grade 3, n=333, 348	3	1		
Hypercalcemia , Grade 4, n=333, 348	1	1		
Hypocalcemia , Grade 3, n=333, 348	1	7		
Hypocalcemia , Grade 4, n=333, 348	1	3		
CO2/HCO3, Grade 3, n=187, 207	0	1		
CO2/HCO3, Grade 4, n=187, 207	0	0		
Creatinine, Grade 3, n=333, 348	3	9		
Creatinine, Grade 4, n=333, 348	2	0		
Hyperglycemia, Grade 3, n=332, 344	6	8		
Hypergylcemia, Grade 4, n=332, 344	1	0		

Hypoglycemia, Grade 3, n=332, 344	1	1		
Hypogylcemia, Grade 4, n=332, 344	2	2		
Hyperkalemia, Grade 3, n=333, 348	5	8		
Hyperkalemia, Grade 4, n=333, 348	2	2		
Hypokalemia, Grade 3, n=333, 348	17	35		
Hypokalemia, Grade 4, n=333, 348	1	7		
Hypernatremia, Grade 3, n=333, 348	0	0		
Hypernatremia, Grade 4, n=333, 348	1	1		
Hyponatremia, Grade 3, n=333, 348	59	85		
Hyponatremia, Grade 4, n=333, 348	11	0		

Notes:

[23] - Safety Population

[24] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with the indicated hematological toxicities by maximum toxicity grade (G3 and G4) at the worst-case on-therapy visit

End point title	Number of participants with the indicated hematological toxicities by maximum toxicity grade (G3 and G4) at the worst-case on-therapy visit[25]

End point description:

Data are summarized using the NCI CTC version 3.0 toxicity grades. Data are reported as the number of participants who had a grade 3 (G3) or grade 4 (G4) toxicity for the indicated hematological parameters, where G3 indicates a severe toxicity and G4 indicates a life-threatening toxicity. The worst-case on-therapy visit includes any scheduled or unscheduled post-Baseline visit. Hematology parameter included: hemoglobin, total neutrophils (TN), platelet count (PC), and White Blood Cell (WBC) count. Only those participants available at the specified time points were analyzed (represented by n=X, X in the category titles). Different participants may have been analyzed for different parameters, so the overall number of participants analyzed reflects everyone in the Safety Population.

End point type	Secondary

End point timeframe:

From Baseline (within 8 weeks prior torandomization [Day 1]) until the end of the maintenance period/early withdrawal (up to Study Week 64)

Notes:

[25] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The safety population was taken as all participants who received one dose of medication. If a participant was randomized to the placebo arm and received any lapatinib in error, they were counted in the lapatinib arm in terms of safety endpoints. Five subjects randomized to receive placebo were given lapatinib, and 3 randomized subjects did not receive any study medication (2 lapatinib, 1 placebo). The Lapatinib 1500 mg containing the Safety population was used for this outcome measure.

End point values	Placebo	Lapatinib 1500 mg		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	336[26]	349[27]		
Units: Participants				
Hemoglobin, Grade 3, n=333, 348	10	13		
Hemoglobin, Grade 4, n=333, 348	0	3		
Lymphocytes, Grade 3, n=333, 348	203	208		
Lymphocytes, Grade 4, n=333, 348	34	48		
TN, Grade 3, n=333, 348	57	47		
TN, Grade 4, n=333, 348	6	13		

PC, Grade 3, n=333, 348	0	3		
PC, Grade 4, n=333, 348	2	2		
WBC, Grade 3, n=333, 348	70	72		
WBC, Grade 4, n=333, 348	3	6		

Notes:

[26] - Safety Population

[27] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with on-therapy and follow-up late radiation morbidity events

End point title	Number of participants with on-therapy and follow-up late radiation morbidity events[28]

End point description:

Late radiation morbidity event data are summarized as the number of participants with late radiation morbidity events per system organ class (SOC). Late radiation effects are defined as those that first occur 90 days or more after the initiation of radiation therapy.

End point type	Secondary

End point timeframe:

From 180 days after completion of radiation until the last follow-up/withdrawal visit (average of 64 study weeks)

Notes:

[28] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The safety population was taken as all participants who received one dose of medication. If a participant was randomized to the placebo arm and received any lapatinib in error, they were counted in the lapatinib arm in terms of safety endpoints. Five subjects randomized to receive placebo were given lapatinib, and 3 randomized subjects did not receive any study medication (2 lapatinib, 1 placebo). The Lapatinib 1500 mg containing the Safety population was used for this outcome measure.

End point values	Placebo	Lapatinib 1500 mg		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	336[29]	349[30]		
Units: Participants				
Gastrointestinal disorders	25	23		
General disorders	8	13		
Skin and subcutaneous tissue disorders	8	13		
Musculoskeletal and connective tissue	13	6		
Respiratory, thoracic and mediastinal	10	7		
Injury, poisoning and procedural	13	3		
Nervous system disorders	6	8		
Endocrine disorders	4	3		
Infections and infestations	3	4		
Investigations	3	3		
Vascular disorders	4	2		
Blood and lymphatic system disorders	2	1		
Ear and labyrinth disorders	2	1		
Metabolism and nutrition disorders	0	1		
Neoplasm benign, malignant and unspecified	1	0		

Notes:

[29] - Safety Population

[30] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in blood pressure at the indicated time points

End point title	Change from Baseline in blood pressure at the indicated time points[31]

End point description:

Blood pressure measurement included systolic blood pressure (SBP) and diastolic blood pressure (DBP) at Week 1, Week 2, Week 3, Week 4, Week 5, Week 6, Week 7, End of CRT, MW 8, MW 16, MW 24, MW 32, MW 40, MW 48, MW 56, and at the time of withdrawal from IP. Change from Baseline was calculated as the post-Baseline value minus the Baseline value. Only those participants available at the specified time points were analyzed (represented by n=X, X in the category titles). Different participants may have been analyzed for different parameters, so the overall number of participants analyzed reflects everyone in the Safety Population.

End point type	Secondary

End point timeframe:

Week 1, Week 2, Week 3, Week 4, Week 5, Week 6, Week 7, End of chemoradiotherapy (CRT), Maintenance Week (MW) 8, MW 16, MW 24, MW 32, MW 40, MW 48, MW 56, Withdrawal from investigational product (IP; up to Study Week 64)

Notes:

[31] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The safety population was taken as all participants who received one dose of medication. If a participant was randomized to the placebo arm and received any lapatinib in error, they were counted in the lapatinib arm in terms of safety endpoints. Five subjects randomized to receive placebo were given lapatinib, and 3 randomized subjects did not receive any study medication (2 lapatinib, 1 placebo). The Lapatinib 1500 mg containing the Safety population was used for this outcome measure.

End point values	Placebo	Lapatinib 1500 mg		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	336[32]	349[33]		
Units: Millimeters of mercury (mmHg)				
arithmetic mean (standard deviation)				
SBP, Week 1, n=312, 339	-0.29 (± 14.153)	1.24 (± 14.273)		
SBP, Week 2, n=303, 327	-2.4 (± 13.815)	-1.56 (± 16.415)		
SBP, Week 3, n=310, 319	-2.64 (± 14.784)	-1.62 (± 15.046)		
SBP, Week 4, n=312, 319	-4.32 (± 15.414)	-2.63 (± 17.044)		
SBP, Week 5, n=302, 303	-4.05 (± 15.49)	-3.09 (± 16.472)		
SBP, Week 6, n=307, 307	-4.7 (± 15.571)	-4.07 (± 15.726)		
SBP, Week 7, n=282, 289	-4.06 (± 14.774)	-4.86 (± 17.046)		
SBP, End of CRT, n=304, 310	-4.79 (± 15.216)	-4.69 (± 16.692)		

SBP, MW 8, n=280, 279	-2.8 (± 14.137)	-3.58 (± 15.03)		
SBP, MW 16, n=257, 270	-2.86 (± 15.251)	-2.44 (± 15.718)		
SBP, MW 24, n=234, 252	-3.44 (± 15.918)	-2.48 (± 15.793)		
SBP, MW 32, n=212, 237	-1.71 (± 14.936)	-2.55 (± 15.47)		
SBP, MW 40, n=202, 222	-1.76 (± 14.979)	-1.84 (± 17.358)		
SBP, MW 48, n=199, 210	-1.57 (± 15.531)	-1.79 (± 15.7)		
SBP, MW 56, n=188, 204	-1.53 (± 13.942)	-1.64 (± 15.878)		
SBP, Withdrawal from IP, n=99, 84	-2.54 (± 15.746)	-1.38 (± 17.895)		
DBP, Week 1, n=312, 339	-0.07 (± 9.214)	0.63 (± 9.719)		
DBP, Week 2, n=303, 327	-0.81 (± 8.69)	-0.24 (± 9.933)		
DBP, Week 3, n=310, 319	-0.46 (± 9.245)	-0.68 (± 9.704)		
DBP, Week 4, n=312, 319	-2.54 (± 9.929)	-2.03 (± 9.797)		
DBP, Week 5, n=302, 303	-1.38 (± 10.1)	-1.6 (± 9.679)		
DBP, Week 6, n=307, 307	-1.85 (± 10.673)	-2.37 (± 9.514)		
DBP, Week 7, n=282, 289	-1.73 (± 11.095)	-2.93 (± 9.402)		
DBP, End of CRT, n=304, 310	-1.97 (± 10.224)	-2.11 (± 10.117)		
DBP, MW 8, n=280, 279	-0.8 (± 9.598)	-1.17 (± 9.877)		
DBP, MW 16, n=257, 270	-0.36 (± 9.98)	-0.98 (± 9.527)		
DBP, MW 24, n=234, 252	-1.26 (± 9.956)	-1.65 (± 9.842)		
DBP, MW 32, n=212, 237	-0.38 (± 9.677)	-1.34 (± 9.929)		
DBP, MW 40, n=202, 222	-0.69 (± 9.809)	-0.69 (± 11.54)		
DBP, MW 48, n=199, 210	0.34 (± 10.797)	-0.56 (± 10.057)		
DBP, MW 56, n=188, 204	0.2 (± 9.721)	-0.47 (± 10.475)		
DBP, Withdrawal from IP, n=99, 84	-0.27 (± 10.256)	-0.85 (± 11.806)		

Notes:

[32] - Safety Population

[33] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in heart rate at the indicated time points

End point title	Change from Baseline in heart rate at the indicated time

End point description:

Heart rate (HR) was measured at Week 1, Week 2, Week 3, Week 4, Week 5, Week 6, Week 7, End of

CRT, MW 8, MW 16, MW 24, MW 32, MW 40, MW 48, MW 56, and at the time of withdrawal from IP. Change from Baseline was calculated as the post-Baseline value minus the Baseline value. Only those participants available at the specified time points were analyzed (represented by n=X, X in the category titles). Different participants may have been analyzed for different parameters, so the overall number of participants analyzed reflects everyone in the Safety Population.

End point type	Secondary

End point timeframe:

Week 1, Week 2, Week 3, Week 4, Week 5, Week 6, Week 7, End of chemoradiotherapy (CRT), Maintenance Week (MW) 8, MW 16, MW 24, MW 32, MW 40, MW 48, MW 56, Withdrawal from IP (up to Study Week 64)

Notes:

[34] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The safety population was taken as all participants who received one dose of medication. If a participant was randomized to the placebo arm and received any lapatinib in error, they were counted in the lapatinib arm in terms of safety endpoints. Five subjects randomized to receive placebo were given lapatinib, and 3 randomized subjects did not receive any study medication (2 lapatinib, 1 placebo). The Lapatinib 1500 mg containing the Safety population was used for this outcome measure.

End point values	Placebo	Lapatinib 1500 mg		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	336[35]	349[36]		
Units: Beats per minute				
arithmetic mean (standard deviation)				
Week 1, n=312, 337	-0.18 (± 10.414)	-0.84 (± 10.71)		
Week 2, n=303, 326	-0.99 (± 10.91)	-1.17 (± 10.258)		
Week 3, n=306, 319	-0.45 (± 10.701)	-1.24 (± 9.766)		
Week 4, n=307, 318	-0.86 (± 11.116)	-0.39 (± 11.645)		
Week 5, n=298, 303	-0.68 (± 11.673)	-0.39 (± 11.588)		
Week 6, n=306, 306	-0.73 (± 11.933)	-0.43 (± 10.947)		
Week 7, n=279, 288	1.22 (± 11.491)	0.4 (± 11.184)		
End of CRT, n=300, 310	0.33 (± 12.362)	0.54 (± 11.683)		
MW 8, n=279, 277	-0.3 (± 10.684)	0.85 (± 10.632)		
MW 16, n=256, 268	-1.1 (± 11.238)	-0.96 (± 11.129)		
MW 24, n=235, 251	-0.98 (± 11.18)	-1.16 (± 9.793)		
MW 32, n=213, 238	-1.43 (± 11.934)	-1.24 (± 10.549)		
MW 40, n=203, 222	-2.72 (± 11.781)	-0.96 (± 10.556)		
MW 48, n=200, 210	-2.56 (± 12.158)	-0.93 (± 11.659)		
MW 56, n=189, 204	-3.08 (± 12.056)	-1.16 (± 11.331)		
Withdrawal from IP, n=99, 83	0.02 (± 12.719)	-0.69 (± 11.822)		

Notes:

[35] - Safety Population

[36] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in body temperature at the indicated time points

End point title	Change from Baseline in body temperature at the indicated time points[37]

End point description:

Body temperature was measured at Week 1, Week 2, Week 3, Week 4, Week 5, Week 6, Week 7, End of CRT, MW 8, MW 16, MW 24, MW 32, MW 40, MW 48, MW 56, and at the time of withdrawal from IP. Change from Baseline was calculated as the post-Baseline value minus the Baseline value. Only those participants available at the specified time points were analyzed (represented by n=X, X in the category titles). Different participants may have been analyzed for different parameters, so the overall number of participants analyzed reflects everyone in the Safety Population.

End point type	Secondary

End point timeframe:

Week 1, Week 2, Week 3, Week 4, Week 5, Week 6, Week 7, End of chemoradiotherapy (CRT), Maintenance Week (MW) 8, MW 16, MW 24, MW 32, MW 40, MW 48, MW 56, Withdrawal from IP (up to Study Week 64)

Notes:

[37] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The safety population was taken as all participants who received one dose of medication. If a participant was randomized to the placebo arm and received any lapatinib in error, they were counted in the lapatinib arm in terms of safety endpoints. Five subjects randomized to receive placebo were given lapatinib, and 3 randomized subjects did not receive any study medication (2 lapatinib, 1 placebo). The Lapatinib 1500 mg containing the Safety population was used for this outcome measure.

End point values	Placebo	Lapatinib 1500 mg		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	336[38]	349[39]		
Units: Degrees Centigrade				
arithmetic mean (standard deviation)				
Week 1, n=308, 331	-0.03 (± 0.42)	-0.01 (± 0.436)		
Week 2, n=303, 321	-0.01 (± 0.492)	0.01 (± 0.41)		
Week 3, n=308, 315	0.02 (± 0.504)	0.01 (± 0.431)		
Week 4, n=306, 317	0.02 (± 0.511)	0.04 (± 0.494)		
Week 5, n=300, 303	0 (± 0.514)	0.03 (± 0.416)		
Week 6, n=301, 302	0.06 (± 0.586)	0.02 (± 0.54)		
Week 7, n=277, 288	0.02 (± 0.526)	0.06 (± 0.507)		
End of CRT, n=297, 305	0.04 (± 0.545)	0.03 (± 0.469)		
MW 8, n=274, 273	0.02 (± 0.529)	0.01 (± 0.442)		
MW 16, n=253, 263	-0.02 (± 0.525)	-0.03 (± 0.4)		
MW 24, n=227, 244	-0.03 (± 0.516)	0.04 (± 0.425)		

MW 32, n=207, 235	-0.04 (± 0.559)	-0.02 (± 0.453)		
MW 40, n=199, 219	-0.04 (± 0.542)	0 (± 0.429)		
MW 48, n=195, 205	-0.02 (± 0.645)	-0.01 (± 0.464)		
MW 56, n=184, 200	-0.01 (± 0.563)	-0.02 (± 0.466)		
Withdrawal from IP, n=97, 78	0 (± 0.562)	0.03 (± 0.419)		

Notes:

[38] - Safety Population

[39] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in body weight at the indicated time points

End point title	Change from Baseline in body weight at the indicated time points[40]

End point description:

Body weight was measured at Week 1, Week 2, Week 3, Week 4, Week 5, Week 6, Week 7, End of CRT, MW 8, MW 16, MW 24, MW 32, MW 40, MW 48, MW 56, and at the time of withdrawal from IP. Change from Baseline was calculated as the post-Baseline value minus the Baseline value.Only those participants available at the specified time points were analyzed (represented by n=X, X in the category titles). Different participants may have been analyzed for different parameters, so the overall number of participants analyzed reflects everyone in the Safety Population.

End point type	Secondary

End point timeframe:

Week 1, Week 2, Week 3, Week 4, Week 5, Week 6, Week 7, End of chemoradiotherapy (CRT), Maintenance Week (MW) 8, MW 16, MW 24, MW 32, MW 40, MW 48, MW 56, Withdrawal from IP (up to Study Week 64)

Notes:

[40] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The safety population was taken as all participants who received one dose of medication. If a participant was randomized to the placebo arm and received any lapatinib in error, they were counted in the lapatinib arm in terms of safety endpoints. Five subjects randomized to receive placebo were given lapatinib, and 3 randomized subjects did not receive any study medication (2 lapatinib, 1 placebo). The Lapatinib 1500 mg containing the Safety population was used for this outcome measure.

End point values	Placebo	Lapatinib 1500 mg		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	336[41]	349[42]		
Units: Kilograms				
arithmetic mean (standard deviation)				
Week 1, n=317, 343	0.28 (± 2.301)	-0.04 (± 2.263)		
Week 2, n=314, 336	-0.39 (± 2.32)	-0.9 (± 2.747)		
Week 3, n=319, 328	-1.01 (± 2.638)	-1.46 (± 2.889)		
Week 4, n=316, 324	-1.74 (± 3.116)	-2.24 (± 3.352)		
Week 5, n=307, 309	-2.46 (± 3.424)	-3.3 (± 3.803)		
Week 6, n=314, 307	-3.22 (± 3.868)	-4.15 (± 3.912)		

Week 7, n=290, 297	-4.21 (± 4.072)	-4.94 (± 4.266)		
End of CRT, n=309, 311	-4.54 (± 4.566)	-5.36 (± 4.406)		
MW 8, n=287, 287	-4.56 (± 5.851)	-5.67 (± 5.326)		
MW 16, n=257, 275	-4.31 (± 6.521)	-5.64 (± 6.12)		
MW 24, n=236, 252	-4.26 (± 7.251)	-5.15 (± 6.723)		
MW 32, n=220, 241	-4.17 (± 7.685)	-4.73 (± 6.711)		
MW 40, n=208, 224	-3.63 (± 7.889)	-4.24 (± 7.348)		
MW 48, n=197, 212	-3.2 (± 7.951)	-3.44 (± 7.087)		
MW 56, n=191, 206	-2.95 (± 8.427)	-3.47 (± 7.44)		
Withdrawal from IP, n=106, 86	-4.21 (± 6.785)	-4.81 (± 7.649)		

Notes:

[41] - Safety Population

[42] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with abnormal 12-lead electrocardiogram (ECG) findings at the indicated time points

End point title	Number of participants with abnormal 12-lead electrocardiogram (ECG) findings at the indicated time points[43]

End point description:

A 12-lead ECG was recorded at Baseline, at the end of the CRT, at Maintenance Week 56, at withdrawal from IP, and at anytime post-baseline. Data are presented as clinically significant (CS) or not clinically significant (NCS) abnormal findings. The study investigator determined if an abnormal ECG finding was CS or NCS.Only those participants available at the specified time points were analyzed (represented by n=X, X in the category titles). Different participants may have been analyzed for different parameters, so the overall number of participants analyzed reflects everyone in the Safety Population.

End point type	Secondary

End point timeframe:

Baseline (BL; within 8 weeks prior to randomization [Day 1]), End of CRT, Maintenance Week 56, Withdrawal from IP, and at any time Post-Baseline (up to Study Week 64)

Notes:

[43] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The safety population was taken as all participants who received one dose of medication. If a participant was randomized to the placebo arm and received any lapatinib in error, they were counted in the lapatinib arm in terms of safety endpoints. Five subjects randomized to receive placebo were given lapatinib, and 3 randomized subjects did not receive any study medication (2 lapatinib, 1 placebo). The Lapatinib 1500 mg containing the Safety population was used for this outcome measure.

End point values	Placebo	Lapatinib 1500 mg		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	336[44]	349[45]		
Units: Participants				
BL, Abnormal NCS, n=334, 349	82	78		
BL, Abnormal CS, n=334, 349	1	0		
End of CRT, Abnormal NCS, n=287, 292	76	71		
End of CRT, Abnormal CS, n=287, 292	2	2		
Maintenance Week 56, Abnormal NCS, n=166, 174	32	32		
Maintenance Week 56, Abnormal CS, n=166, 174	2	0		
Withdrawal from IP, Abnormal NCS, n=70, 59	16	12		
Withdrawal from IP, Abnormal CS, n=70, 59	1	1		
Anytime post-baseline, Abnormal NCS, n=307, 312	94	88		
Anytime post-baseline, Abnormal CS, n=307, 312	4	3		

Notes:

[44] - Safety Population

[45] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with the indicated Eastern Cooperative Oncology Group (ECOG) performance status value

End point title	Number of participants with the indicated Eastern Cooperative Oncology Group (ECOG) performance status value[46]

End point description:

The Eastern Cooperative Oncology Group (ECOG) performance status scales and grades/criteria are used by doctors and researchers to assess how a participant's disease is progressing, to assess how the disease affects the daily living abilities of the participant, and to determine appropriate treatment and prognosis. Grade 0, fully active, able to carry on all pre-disease performance without restriction. Grade 1, restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work. Grade 2, ambulatory and capable of all selfcare, but unable to carry out any work activities; up and about more than 50% of waking hours. Grade 3, capable of only limited selfcare; confined to bed or chair more than 50% of waking hours. Grade 4, completely disabled; cannot carry on any selfcare; totally confined to bed or chair. Grade 5, dead.

End point type	Secondary

End point timeframe:

From Baseline (BL; within 8 weeks prior to randomization [Day 1]) until the end of the maintenance period/early withdrawal (up to Study Week 64)

Notes:

[46] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The safety population was taken as all participants who received one dose of medication. If a participant was randomized to the placebo arm and received any lapatinib in error, they were counted in the lapatinib arm in terms of safety endpoints. Five subjects randomized to receive placebo were given lapatinib, and 3 randomized subjects did not receive any study medication (2 lapatinib, 1 placebo). The Lapatinib 1500 mg containing the Safety population was used for this outcome measure.

End point values	Placebo	Lapatinib 1500 mg		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	336[47]	349[48]		
Units: Participants				
BL, ECOG 0, n=336, 349	173	179		
BL, ECOG 1, n=336, 349	161	157		
BL, ECOG 2, n=336, 349	2	13		
Week 1, ECOG 0, n=319, 342	160	174		
Week 1, ECOG 1, n=319, 342	156	159		
Week 1, ECOG 2, n=319, 342	3	9		
Week 1, ECOG 3, n=319, 342	0	0		
Week 1, ECOG 4-5, n=319, 342	0	0		
Week 2, ECOG 0, n=313, 333	142	149		
Week 2, ECOG 1, n=313, 333	166	168		
Week 2, ECOG 2, n=313, 333	5	16		
Week 2, ECOG 3, n=313, 333	0	0		
Week 2, ECOG 4-5, n=313, 333	0	0		
Week 3, ECOG 0, n=310, 329	138	131		
Week 3, ECOG 1, n=310, 329	169	183		
Week 3, ECOG 2, n=310, 329	3	15		
Week 3, ECOG 3, n=310, 329	0	0		
Week 3, ECOG 4-5, n=310, 329	0	0		
Week 4, ECOG 0, n=317, 327	115	111		
Week 4, ECOG 1, n=317, 327	191	194		
Week 4, ECOG 2, n=317, 327	11	21		
Week 4, ECOG 3, n=317, 327	0	1		
Week 4, ECOG 4-5, n=317, 327	0	0		
Week 5, ECOG 0, n=307, 312	100	95		
Week 5, ECOG 1, n=307, 312	191	183		
Week 5, ECOG 2, n=307, 312	16	30		
Week 5, ECOG 3, n=307, 312	0	4		
Week 5, ECOG 4-5, n=307, 312	0	0		
Week 6, ECOG 0, n=312, 309	97	88		
Week 6, ECOG 1, n=312, 309	187	186		
Week 6, ECOG 2, n=312, 309	26	32		
Week 6, ECOG 3, n=312, 309	2	3		
Week 6, ECOG 4-5, n=312, 309	0	0		
Week 7, ECOG 0, n=284, 295	83	88		
Week 7, ECOG 1, n=284, 295	175	176		
Week 7, ECOG 2, n=284, 295	23	30		
Week 7, ECOG 3, n=284, 295	3	1		
Week 7, ECOG 4-5, n=284, 295	0	0		
End of CRT, ECOG 0, n=307, 315	95	84		
End of CRT, ECOG 1, n=307, 315	184	186		
End of CRT, ECOG 2, n=307, 315	25	45		
End of CRT, ECOG 3, n=307, 315	3	0		
End of CRT, ECOG 4-5, n=307, 315	0	0		
Maintenance week 8, ECOG 0, n=286, 290	132	128		
Maintenance week 8, ECOG 1, n=286, 290	146	153		

Maintenance week 8, ECOG 2, n=286, 290	7	9		
Maintenance week 8, ECOG 3, n=286, 290	1	0		
Maintenance week 8, ECOG 4-5, n=286, 290	0	0		
Maintenance week 16, ECOG 0, n=260, 273	135	129		
Maintenance week 16, ECOG 1, n=260, 273	124	138		
Maintenance week 16, ECOG 2, n=260, 273	1	6		
Maintenance week 16, ECOG 3, n=260, 273	0	0		
Maintenance week 16, ECOG 4-5, n=260, 273	0	0		
Maintenance week 24, ECOG 0, n=235, 251	122	127		
Maintenance week 24, ECOG 1, n=235, 251	110	119		
Maintenance week 24, ECOG 2, n=235, 251	3	5		
Maintenance week 24, ECOG 3, n=235, 251	0	0		
Maintenance week 24, ECOG 4-5, n=235, 251	0	0		
Maintenance week 32, ECOG 0, n=218, 241	117	123		
Maintenance week 32, ECOG 1, n=218, 241	99	115		
Maintenance week 32, ECOG 2, n=218, 241	2	1		
Maintenance week 32, ECOG 3, n=218, 241	0	2		
Maintenance week 32, ECOG 4-5, n=218, 241	0	0		
Maintenance week 40, ECOG 0, n=208, 227	118	130		
Maintenance week 40, ECOG 1, n=208, 227	88	94		
Maintenance week 40, ECOG 2, n=208, 227	2	2		
Maintenance week 40, ECOG 3, n=208, 227	0	1		
Maintenance week 40, ECOG 4-5, n=208, 227	0	0		
Maintenance week 48, ECOG 0, n=205, 214	121	111		
Maintenance week 48, ECOG 1, n=205, 214	81	102		
Maintenance week 48, ECOG 2, n=205, 214	3	1		
Maintenance week 48, ECOG 3, n=205, 214	0	0		
Maintenance week 48, ECOG 4-5, n=205, 214	0	0		
Maintenance week 56, ECOG 0, n=194, 211	107	111		
Maintenance week 56, ECOG 1, n=194, 211	85	98		
Maintenance week 56, ECOG 2, n=194, 211	2	2		

Maintenance week 56, ECOG 3, n=194, 211	0	0		
Maintenance week 56, ECOG 4-5, n=194, 211	0	0		
Withdrawal from IP, ECOG 0, n=109, 92	44	38		
Withdrawal from IP, ECOG 1, n=109, 92	50	40		
Withdrawal from IP, ECOG 2, n=109, 92	12	11		
Withdrawal from IP, ECOG 3, n=109, 92	2	1		
Withdrawal from IP, ECOG 4-5, n=109, 92	1	2		
Last assessment on therapy, ECOG 0, n=334, 348	153	154		
Last assessment on therapy, ECOG 1, n=334, 348	158	165		
Last assessment on therapy, ECOG 2, n=334, 348	19	22		
Last assessment on therapy, ECOG 3, n=334, 348	3	5		
Last assessment on therapy, ECOG 4-5, n=334, 348	1	2		

Notes:

[47] - Safety Population

[48] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in quality of life status as assessed by the Functional Assessement of Cancer Therapy-Head and Neck (FACT-H&N) questionnaire

End point title	Change from Baseline in quality of life status as assessed by the Functional Assessement of Cancer Therapy-Head and Neck (FACT-H&N) questionnaire

End point description:

Change from Baseline (BL) in quality of life status was assessed using the FACT-H&N questionnaire, which is designed to measure multidimensional quality of life in participants with head and neck cancer. Change from Baseline was analyzed using parametric analysis of covariance (with the Baseline value as a covariate). The FACT-H&N questionnaire contains 39 items (27 general questions and 12 head and neck cancer-specific items) covering 4 dimensions and 1 subscale: physical well-being, social/family well-being, emotional well-being, functional well-being, and a head and neck cancer subscale. Possible subscale scores range from 0 to 36. Higher scores represent better quality of life. Data were adjusted for participant-reported quality of life scores at Baseline.

End point type	Secondary

End point timeframe:

From randomization until the last follow-up/withdrawal visit (up to 62 study weeks)

End point values	Placebo	Lapatinib 1500 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	171[49]	189[50]		
Units: scores on a scale				
least squares mean (standard error)				
Physical Well-being, n=171, 188	0.4 (± 0.33)	-0.1 (± 0.31)		
Social/Family Well-being, n=171, 189	-0.3 (± 0.36)	-1.7 (± 0.34)		

Emotional Well-being, n=169, 187	1 (± 0.27)	0 (± 0.26)		
Functional Well-being, n=168, 188	0.9 (± 0.39)	-0.4 (± 0.37)		
Head and Neck Cancer subscale, n=168, 189	-1.2 (± 0.43)	-1.7 (± 0.4)		

Notes:

[49] - Safety Population. Only those par. who had a BL and post-BL score at the time point were analyzed.
[50] - Safety Population. Only those par. who had a BL and post-BL score at the time point were analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in quality of life status as assessed by the EuroQol-5D (EQ-5D) scale

End point title	Change from Baseline in quality of life status as assessed by the EuroQol-5D (EQ-5D) scale

End point description:

Change from Baseline in quality of life status was assessed using the EQ-5D scale, a 5-item health status measure and a visual analog rating scale. Change from Baseline was analyzed using parametric analysis of covariance (with the Baseline value as a covariate). The EQ-5D is a generic measure of self-reported health outcomes that is applicable to a wide range of health conditions and treatments. The EQ-5D covers health status in 5 domains (3 questions each): mobility, self-care, usual activities, pain or discomfort, and anxiety or depression. Each item is scored as follows: 1, no problems; 2, some moderate problems; 3, extreme problems. The possible EQ-5D index utility values range from 0.594 to 1, and the thermometer score ranges from 0 to 100. Higher scores represent better quality of life. Data were adjusted for participant-reported quality of life scores at Baseline.

End point type	Secondary

End point timeframe:

From randomization until the last follow-up/withdrawal visit (up to 62 study weeks)

End point values	Placebo	Lapatinib 1500 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	173[51]	187[52]		
Units: scores on a scale				
least squares mean (standard error)				
Utility score, n=172, 186	0.1 (± 0.01)	0 (± 0.01)		
Thermometer score, n=173, 197	5.5 (± 1.29)	3.2 (± 1.25)		

Notes:

[51] - Safety Population. Only those par. who had a BL and post-BL score at the time point were analyzed.
[52] - Safety Population. Only those par. who had a BL and post-BL score at the time point were analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with the indicated biomarker expression status

End point title	Number of participants with the indicated biomarker expression status

End point description:

Biomarkers (which influence clinical response) assessed from tumor tissues included P16, Human

Papilloma virus (HPV), and Epidermal Growth Factor Receptor (EGFR)/Epidermal Growth Factor Receptor 1 (ErbB1). Biomarker expression is presented as positive, negative, or unknown. Participants in the ErbB1-positive category include those with results of positive or strongly positive.

End point type	Secondary

End point timeframe:

Baseline (BL; within 8 weeks prior to randomization [Day 1]) (up to Study Week 1)

End point values	Placebo	Lapatinib 1500 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	342[53]	346[54]		
Units: Participants				
P16, Positive	42	48		
P16, Negative	282	271		
P16, Unknown	18	27		
Overall HPV, Positive	21	23		
Overall HPV, Negative	284	276		
Overall HPV, Unknown	37	47		
ErbB1, Positive	330	338		
ErbB1, Negative	12	8		

Notes:

[53] - ITT Population

[54] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with the indicated worst-case on-therapy left ventricular ejection fraction (LVEF) change from Baseline

End point title	Number of participants with the indicated worst-case on-therapy left ventricular ejection fraction (LVEF) change from Baseline

End point description:

LVEF is the measurement of how much blood is being pumped out of the left ventricle of the heart with each contraction. LVEF was assessed using echocardiogram (ECHO: a test of the action of the heart using ultrasound waves to produce a visual display, for the diagnosis or monitoring of heart disease) and multigated acqusition scans (MUGA scan: a noninvasive diagnostic test used to evaluate the pumping function of the ventricles). Data from the ECHO and MUGA scans were combined, and the absolute change from Baseline (Abs) data are presented according to the following categories: No change or any increase, 0-<10% decrease, 10-19% decrease, >=20% decrease, >=10% decrease and >=the Lower Limit of Normal (LLN), >=10% decrease and below LLN, >=20% decrease and >=LLN, or >=20% decrease and below LLN. The relative percent change from Baseline (Rel) data are presented according to the following categories: >=20% decrease and >=LLN and >=20% decrease and below LLN.

End point type	Secondary

End point timeframe:

From the end of the CRT until the last follow-up visit (up to 141 study weeks)

End point values	Placebo	Lapatinib 1500 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	309[55]	311[56]		
Units: Participants				
Abs, No change/any increase	102	90		
Abs, >0 to <10% decrease	138	131		
Abs, 10 to 19% decrease	65	80		
Abs, >=20% decrease	4	10		
Abs, >=10% decrease and >=LLN	62	69		
Abs, >=10% decrease and below LLN	7	21		
Abs, >=20% decrease and >=LLN	3	5		
Abs, >=20% decrease and below LLN	1	5		
Rel, >=20% decrease and >=LLN	22	18		
Rel, >=20% decrease and below LLN	3	14		

Notes:

[55] - Safety Population. Only those participants available at the specified time points were analyzed.

[56] - Safety Population. Only those participants available at the specified time points were analyzed.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Serious adverse events (SAEs) and non-serious adverse events (AEs) were collected from the start of study medication until the follow up of treatment (average of 141 study weeks).

Adverse event reporting additional description:

SAEs and non-serious AEs were reported for members of the Safety Population, comprised of all participants who were randomized and took at least one dose of study medication. Participants randomized to placebo who received >=1 dose of lapatinib in error were included in the lapatinib arm.

Assessment type	Systematic

Dictionary used

Dictionary name	NCI-CTCAE
Dictionary version	3.0

Reporting groups

Reporting group title	Placebo

Reporting group description:

Participants received placebo per oral monotherapy once daily (QD) for 1 week, followed by radiotherapy of 2 Gray (Gy) per day for 5 days per week (for a total dose of 66 Gy for up to 7 weeks). Participants received concurrent cisplatin 100 milligrams per meters squared (mg/m^2) intravenously (IV) on Days 1, 22, and 43 of radiotherapy. One week prior to the start of chemoradiotherapy, then concurrently for 6 to approximately 7 weeks with chemoradiotherapy, participants received placebo per oral administration QD, followed by maintenance placebo per oral monotherapy QD for up to 1 year or until evidence of disease relapse, whichever was sooner.

Reporting group title	Lapatinib 1500 mg

Reporting group description:

Participants received lapatinib 1500 mg per oral monotherapy QD for 1 week, followed by radiotherapy of 2 Gy per day for 5 days per week (for a total of 66 Gy for up to 7 weeks). Participants received concurrent cisplatin 100 mg/m^2 IV on Days 1, 22, and 43 of radiotherapy. One week prior to the start of chemoradiotherapy, then concurrently for 6 to approximately 7 weeks with chemoradiotherapy, participants received lapatinib 1500 mg per oral administration QD, followed by maintenance lapatinib 1500 mg per oral monotherapy QD for up to 1 year or until evidence of disease relapse, whichever was sooner.

Serious adverse events	Placebo	Lapatinib 1500 mg	
Total subjects affected by serious adverse events			
subjects affected / exposed	133 / 336 (39.58%)	169 / 349 (48.42%)	
number of deaths (all causes)	115	111	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute myeloid leukaemia			
subjects affected / exposed	1 / 336 (0.30%)	0 / 349 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cancer			

subjects affected / exposed	0 / 336 (0.00%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchial carcinoma			
subjects affected / exposed	0 / 336 (0.00%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Lung neoplasm			
subjects affected / exposed	0 / 336 (0.00%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung neoplasm malignant			
subjects affected / exposed	0 / 336 (0.00%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Neoplasm recurrence			
subjects affected / exposed	1 / 336 (0.30%)	0 / 349 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal carcinoma			
subjects affected / exposed	1 / 336 (0.30%)	0 / 349 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Oesophageal neoplasm			
subjects affected / exposed	1 / 336 (0.30%)	0 / 349 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oral fibroma			
subjects affected / exposed	1 / 336 (0.30%)	0 / 349 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oral neoplasm			

subjects affected / exposed	0 / 336 (0.00%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatic carcinoma			
subjects affected / exposed	1 / 336 (0.30%)	0 / 349 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Prostate cancer			
subjects affected / exposed	1 / 336 (0.30%)	0 / 349 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Second primary malignancy			
subjects affected / exposed	0 / 336 (0.00%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma of the oral cavity			
subjects affected / exposed	0 / 336 (0.00%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Testis cancer			
subjects affected / exposed	0 / 336 (0.00%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Haematoma			
subjects affected / exposed	1 / 336 (0.30%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hypertension			
subjects affected / exposed	2 / 336 (0.60%)	0 / 349 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arterial rupture			

subjects affected / exposed	1 / 336 (0.30%)	0 / 349 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Arterial thrombosis			
subjects affected / exposed	1 / 336 (0.30%)	0 / 349 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	1 / 336 (0.30%)	0 / 349 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral artery occlusion			
subjects affected / exposed	1 / 336 (0.30%)	0 / 349 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage			
subjects affected / exposed	0 / 336 (0.00%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Superior vena cava syndrome			
subjects affected / exposed	1 / 336 (0.30%)	0 / 349 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Venous thrombosis			
subjects affected / exposed	0 / 336 (0.00%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous thrombosis limb			
subjects affected / exposed	1 / 336 (0.30%)	0 / 349 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			
Weight decreased			

subjects affected / exposed	1 / 336 (0.30%)	4 / 349 (1.15%)	
occurrences causally related to treatment / all	1 / 1	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Mucosal inflammation			
subjects affected / exposed	9 / 336 (2.68%)	17 / 349 (4.87%)	
occurrences causally related to treatment / all	3 / 9	9 / 18	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	5 / 336 (1.49%)	6 / 349 (1.72%)	
occurrences causally related to treatment / all	1 / 5	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	6 / 336 (1.79%)	4 / 349 (1.15%)	
occurrences causally related to treatment / all	2 / 7	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthenia			
subjects affected / exposed	3 / 336 (0.89%)	4 / 349 (1.15%)	
occurrences causally related to treatment / all	1 / 3	1 / 4	
deaths causally related to treatment / all	0 / 1	0 / 0	
Death			
subjects affected / exposed	1 / 336 (0.30%)	4 / 349 (1.15%)	
occurrences causally related to treatment / all	1 / 1	1 / 4	
deaths causally related to treatment / all	1 / 1	1 / 4	
Fatigue			
subjects affected / exposed	2 / 336 (0.60%)	2 / 349 (0.57%)	
occurrences causally related to treatment / all	0 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Impaired healing			
subjects affected / exposed	1 / 336 (0.30%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malaise			

subjects affected / exposed	2 / 336 (0.60%)	0 / 349 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Medical device complication			
subjects affected / exposed	1 / 336 (0.30%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheter site discharge			
subjects affected / exposed	1 / 336 (0.30%)	0 / 349 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheter site related reaction			
subjects affected / exposed	0 / 336 (0.00%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disease progression			
subjects affected / exposed	0 / 336 (0.00%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Face oedema			
subjects affected / exposed	0 / 336 (0.00%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucosal induration			
subjects affected / exposed	0 / 336 (0.00%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	0 / 336 (0.00%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Performance status decreased			

subjects affected / exposed	1 / 336 (0.30%)	0 / 349 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden death			
subjects affected / exposed	0 / 336 (0.00%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	2 / 336 (0.60%)	2 / 349 (0.57%)	
occurrences causally related to treatment / all	0 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Dyspnoea			
subjects affected / exposed	1 / 336 (0.30%)	3 / 349 (0.86%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngeal fistula			
subjects affected / exposed	2 / 336 (0.60%)	2 / 349 (0.57%)	
occurrences causally related to treatment / all	0 / 2	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	2 / 336 (0.60%)	2 / 349 (0.57%)	
occurrences causally related to treatment / all	0 / 2	1 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pulmonary embolism			
subjects affected / exposed	3 / 336 (0.89%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Laryngeal oedema			
subjects affected / exposed	3 / 336 (0.89%)	0 / 349 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			

subjects affected / exposed	0 / 336 (0.00%)	2 / 349 (0.57%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Haemoptysis			
subjects affected / exposed	1 / 336 (0.30%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngeal stenosis			
subjects affected / exposed	1 / 336 (0.30%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	1 / 336 (0.30%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory disorder			
subjects affected / exposed	1 / 336 (0.30%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory distress			
subjects affected / exposed	2 / 336 (0.60%)	0 / 349 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspiration			
subjects affected / exposed	0 / 336 (0.00%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 336 (0.00%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cough			

subjects affected / exposed	1 / 336 (0.30%)	0 / 349 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphonia			
subjects affected / exposed	0 / 336 (0.00%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngeal disorder			
subjects affected / exposed	1 / 336 (0.30%)	0 / 349 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung disorder			
subjects affected / exposed	0 / 336 (0.00%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngeal inflammation			
subjects affected / exposed	1 / 336 (0.30%)	0 / 349 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngeal stenosis			
subjects affected / exposed	0 / 336 (0.00%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 336 (0.30%)	0 / 349 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleurisy			
subjects affected / exposed	1 / 336 (0.30%)	0 / 349 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			

subjects affected / exposed	1 / 336 (0.30%)	0 / 349 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	1 / 336 (0.30%)	0 / 349 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 336 (0.30%)	2 / 349 (0.57%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Completed suicide			
subjects affected / exposed	1 / 336 (0.30%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Suicide attempt			
subjects affected / exposed	1 / 336 (0.30%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Confusional state			
subjects affected / exposed	1 / 336 (0.30%)	0 / 349 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Investigations			
Ejection fraction decreased			
subjects affected / exposed	3 / 336 (0.89%)	10 / 349 (2.87%)	
occurrences causally related to treatment / all	1 / 5	10 / 12	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood creatinine increased			
subjects affected / exposed	2 / 336 (0.60%)	5 / 349 (1.43%)	
occurrences causally related to treatment / all	2 / 2	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic enzyme increased			

subjects affected / exposed	2 / 336 (0.60%)	3 / 349 (0.86%)	
occurrences causally related to treatment / all	2 / 2	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Alanine aminotransferase increased			
subjects affected / exposed	3 / 336 (0.89%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	1 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood uric acid increased			
subjects affected / exposed	1 / 336 (0.30%)	2 / 349 (0.57%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	2 / 336 (0.60%)	0 / 349 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Glomerular filtration rate decreased			
subjects affected / exposed	1 / 336 (0.30%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Alanine aminotransferase abnormal			
subjects affected / exposed	0 / 336 (0.00%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood bilirubin abnormal			
subjects affected / exposed	0 / 336 (0.00%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Calcium ionised decreased			
subjects affected / exposed	0 / 336 (0.00%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrocardiogram change			

subjects affected / exposed	0 / 336 (0.00%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrocardiogram abnormal			
subjects affected / exposed	0 / 336 (0.00%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 336 (0.00%)	1 / 349 (0.29%)	
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			
Osteoradionecrosis			
subjects affected / exposed	6 / 336 (1.79%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 6	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tracheostomy malfunction			
subjects affected / exposed	1 / 336 (0.30%)	3 / 349 (0.86%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radiation mucositis			
subjects affected / exposed	1 / 336 (0.30%)	2 / 349 (0.57%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	1 / 336 (0.30%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Anastomotic stenosis			
subjects affected / exposed	1 / 336 (0.30%)	0 / 349 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ankle fracture			

subjects affected / exposed	1 / 336 (0.30%)	0 / 349 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Feeding tube complication			
subjects affected / exposed	1 / 336 (0.30%)	0 / 349 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	1 / 336 (0.30%)	0 / 349 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fibula fracture			
subjects affected / exposed	0 / 336 (0.00%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foreign body			
subjects affected / exposed	1 / 336 (0.30%)	0 / 349 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Implant tissue necrosis			
subjects affected / exposed	0 / 336 (0.00%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Limb injury			
subjects affected / exposed	0 / 336 (0.00%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haemorrhage			
subjects affected / exposed	1 / 336 (0.30%)	0 / 349 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radiation sickness syndrome			

subjects affected / exposed	1 / 336 (0.30%)	0 / 349 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tibia fracture			
subjects affected / exposed	0 / 336 (0.00%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Traumatic fracture			
subjects affected / exposed	1 / 336 (0.30%)	0 / 349 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper limb fracture			
subjects affected / exposed	0 / 336 (0.00%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound complication			
subjects affected / exposed	0 / 336 (0.00%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound dehiscence			
subjects affected / exposed	1 / 336 (0.30%)	0 / 349 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Lymphopenia			
subjects affected / exposed	17 / 336 (5.06%)	18 / 349 (5.16%)	
occurrences causally related to treatment / all	5 / 17	7 / 18	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aplasia			
subjects affected / exposed	0 / 336 (0.00%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			

Cardiac arrest			
subjects affected / exposed	2 / 336 (0.60%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Left ventricular dysfunction			
subjects affected / exposed	0 / 336 (0.00%)	2 / 349 (0.57%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	0 / 336 (0.00%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	1 / 336 (0.30%)	0 / 349 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure acute			
subjects affected / exposed	0 / 336 (0.00%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardio-respiratory arrest			
subjects affected / exposed	1 / 336 (0.30%)	0 / 349 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiopulmonary failure			
subjects affected / exposed	0 / 336 (0.00%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Diastolic dysfunction			
subjects affected / exposed	0 / 336 (0.00%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intracardiac mass			

subjects affected / exposed	0 / 336 (0.00%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Palpitations			
subjects affected / exposed	0 / 336 (0.00%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular hypokinesia			
subjects affected / exposed	1 / 336 (0.30%)	0 / 349 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Syncope			
subjects affected / exposed	2 / 336 (0.60%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral ischaemia			
subjects affected / exposed	0 / 336 (0.00%)	2 / 349 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ataxia			
subjects affected / exposed	0 / 336 (0.00%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain hypoxia			
subjects affected / exposed	1 / 336 (0.30%)	0 / 349 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain injury			
subjects affected / exposed	0 / 336 (0.00%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral infarction			

subjects affected / exposed	1 / 336 (0.30%)	0 / 349 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Convulsion			
subjects affected / exposed	1 / 336 (0.30%)	0 / 349 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	0 / 336 (0.00%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysgeusia			
subjects affected / exposed	0 / 336 (0.00%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyskinesia			
subjects affected / exposed	1 / 336 (0.30%)	0 / 349 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Grand mal convulsion			
subjects affected / exposed	0 / 336 (0.00%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paralysis			
subjects affected / exposed	0 / 336 (0.00%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subarachnoid haemorrhage			
subjects affected / exposed	1 / 336 (0.30%)	0 / 349 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Blood and lymphatic system disorders			
Neutropenia			

subjects affected / exposed	10 / 336 (2.98%)	10 / 349 (2.87%)	
occurrences causally related to treatment / all	7 / 10	6 / 10	
deaths causally related to treatment / all	1 / 1	0 / 0	
Anaemia			
subjects affected / exposed	3 / 336 (0.89%)	7 / 349 (2.01%)	
occurrences causally related to treatment / all	0 / 3	1 / 7	
deaths causally related to treatment / all	0 / 0	0 / 1	
Febrile neutropenia			
subjects affected / exposed	4 / 336 (1.19%)	5 / 349 (1.43%)	
occurrences causally related to treatment / all	3 / 5	4 / 5	
deaths causally related to treatment / all	0 / 1	0 / 0	
Leukopenia			
subjects affected / exposed	5 / 336 (1.49%)	4 / 349 (1.15%)	
occurrences causally related to treatment / all	3 / 5	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	3 / 336 (0.89%)	2 / 349 (0.57%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Bone marrow failure			
subjects affected / exposed	0 / 336 (0.00%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disseminated intravascular coagulation			
subjects affected / exposed	1 / 336 (0.30%)	0 / 349 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Haematotoxicity			
subjects affected / exposed	0 / 336 (0.00%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Hypoacusis			

subjects affected / exposed	1 / 336 (0.30%)	0 / 349 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neurosensory hypoacusis			
subjects affected / exposed	0 / 336 (0.00%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Conjunctival haemorrhage			
subjects affected / exposed	0 / 336 (0.00%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Periorbital oedema			
subjects affected / exposed	0 / 336 (0.00%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	8 / 336 (2.38%)	12 / 349 (3.44%)	
occurrences causally related to treatment / all	6 / 12	9 / 13	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	5 / 336 (1.49%)	11 / 349 (3.15%)	
occurrences causally related to treatment / all	1 / 6	6 / 12	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	3 / 336 (0.89%)	7 / 349 (2.01%)	
occurrences causally related to treatment / all	2 / 3	5 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	3 / 336 (0.89%)	6 / 349 (1.72%)	
occurrences causally related to treatment / all	2 / 3	2 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			

subjects affected / exposed	5 / 336 (1.49%)	4 / 349 (1.15%)	
occurrences causally related to treatment / all	2 / 5	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal stenosis			
subjects affected / exposed	1 / 336 (0.30%)	3 / 349 (0.86%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mouth haemorrhage			
subjects affected / exposed	1 / 336 (0.30%)	2 / 349 (0.57%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Oral pain			
subjects affected / exposed	1 / 336 (0.30%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal fistula			
subjects affected / exposed	0 / 336 (0.00%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	1 / 336 (0.30%)	0 / 349 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspepsia			
subjects affected / exposed	0 / 336 (0.00%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric perforation			
subjects affected / exposed	0 / 336 (0.00%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrooesophagitis			

subjects affected / exposed	0 / 336 (0.00%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematemesis			
subjects affected / exposed	0 / 336 (0.00%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Oesophageal fistula			
subjects affected / exposed	1 / 336 (0.30%)	0 / 349 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophagitis ulcerative			
subjects affected / exposed	0 / 336 (0.00%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	0 / 336 (0.00%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	1 / 336 (0.30%)	0 / 349 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumoperitoneum			
subjects affected / exposed	0 / 336 (0.00%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retroperitoneal haemorrhage			
subjects affected / exposed	1 / 336 (0.30%)	0 / 349 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis haemorrhagic			

subjects affected / exposed	0 / 336 (0.00%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hyperbilirubinaemia			
subjects affected / exposed	1 / 336 (0.30%)	2 / 349 (0.57%)	
occurrences causally related to treatment / all	1 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	2 / 336 (0.60%)	4 / 349 (1.15%)	
occurrences causally related to treatment / all	0 / 3	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin reaction			
subjects affected / exposed	3 / 336 (0.89%)	0 / 349 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ecchymosis			
subjects affected / exposed	1 / 336 (0.30%)	0 / 349 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pemphigus			
subjects affected / exposed	1 / 336 (0.30%)	0 / 349 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Swelling face			
subjects affected / exposed	0 / 336 (0.00%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	1 / 336 (0.30%)	3 / 349 (0.86%)	
occurrences causally related to treatment / all	1 / 1	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	

Renal failure acute			
subjects affected / exposed	3 / 336 (0.89%)	0 / 349 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal impairment			
subjects affected / exposed	1 / 336 (0.30%)	2 / 349 (0.57%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	1 / 336 (0.30%)	0 / 349 (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			
Neck pain			
subjects affected / exposed	1 / 336 (0.30%)	2 / 349 (0.57%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteonecrosis			
subjects affected / exposed	3 / 336 (0.89%)	0 / 349 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fistula			
subjects affected / exposed	1 / 336 (0.30%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Trismus			
subjects affected / exposed	1 / 336 (0.30%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	0 / 336 (0.00%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Joint range of motion decreased			
subjects affected / exposed	0 / 336 (0.00%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myalgia			
subjects affected / exposed	1 / 336 (0.30%)	0 / 349 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pain in jaw			
subjects affected / exposed	1 / 336 (0.30%)	0 / 349 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pathological fracture			
subjects affected / exposed	1 / 336 (0.30%)	0 / 349 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Temporomandibular joint syndrome			
subjects affected / exposed	1 / 336 (0.30%)	0 / 349 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	4 / 336 (1.19%)	6 / 349 (1.72%)	
occurrences causally related to treatment / all	1 / 4	0 / 7	
deaths causally related to treatment / all	0 / 1	0 / 2	
Sepsis			
subjects affected / exposed	2 / 336 (0.60%)	4 / 349 (1.15%)	
occurrences causally related to treatment / all	0 / 2	1 / 4	
deaths causally related to treatment / all	0 / 1	1 / 3	
Wound infection			
subjects affected / exposed	0 / 336 (0.00%)	3 / 349 (0.86%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Bronchopneumonia			

subjects affected / exposed	1 / 336 (0.30%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Erysipelas			
subjects affected / exposed	2 / 336 (0.60%)	0 / 349 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 336 (0.30%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Lung abscess			
subjects affected / exposed	0 / 336 (0.00%)	2 / 349 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	1 / 336 (0.30%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic sepsis			
subjects affected / exposed	1 / 336 (0.30%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oral infection			
subjects affected / exposed	0 / 336 (0.00%)	2 / 349 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess limb			
subjects affected / exposed	0 / 336 (0.00%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess neck			

subjects affected / exposed	1 / 336 (0.30%)	0 / 349 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			
subjects affected / exposed	0 / 336 (0.00%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blister infected			
subjects affected / exposed	1 / 336 (0.30%)	0 / 349 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheter site infection			
subjects affected / exposed	0 / 336 (0.00%)	1 / 349 (0.29%)	
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 / 336 (0.30%)	0 / 349 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile infection			
subjects affected / exposed	0 / 336 (0.00%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis E			
subjects affected / exposed	0 / 336 (0.00%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lobar pneumonia			
subjects affected / exposed	1 / 336 (0.30%)	0 / 349 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			

subjects affected / exposed	1 / 336 (0.30%)	0 / 349 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis			
subjects affected / exposed	1 / 336 (0.30%)	0 / 349 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Otitis media			
subjects affected / exposed	1 / 336 (0.30%)	0 / 349 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraoesophageal abscess			
subjects affected / exposed	0 / 336 (0.00%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parotid abscess			
subjects affected / exposed	1 / 336 (0.30%)	0 / 349 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Perichondritis			
subjects affected / exposed	1 / 336 (0.30%)	0 / 349 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary tuberculosis			
subjects affected / exposed	0 / 336 (0.00%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	0 / 336 (0.00%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			

subjects affected / exposed	0 / 336 (0.00%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis syndrome			
subjects affected / exposed	1 / 336 (0.30%)	0 / 349 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	1 / 336 (0.30%)	0 / 349 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Streptococcal sepsis			
subjects affected / exposed	1 / 336 (0.30%)	0 / 349 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Superinfection			
subjects affected / exposed	1 / 336 (0.30%)	0 / 349 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tooth abscess			
subjects affected / exposed	1 / 336 (0.30%)	0 / 349 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tooth infection			
subjects affected / exposed	1 / 336 (0.30%)	0 / 349 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tracheitis			
subjects affected / exposed	0 / 336 (0.00%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			

subjects affected / exposed	1 / 336 (0.30%)	0 / 349 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyponatraemia			
subjects affected / exposed	6 / 336 (1.79%)	12 / 349 (3.44%)	
occurrences causally related to treatment / all	1 / 6	1 / 12	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	5 / 336 (1.49%)	6 / 349 (1.72%)	
occurrences causally related to treatment / all	2 / 5	1 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperuricaemia			
subjects affected / exposed	4 / 336 (1.19%)	3 / 349 (0.86%)	
occurrences causally related to treatment / all	3 / 4	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	2 / 336 (0.60%)	5 / 349 (1.43%)	
occurrences causally related to treatment / all	0 / 2	2 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Decreased appetite			
subjects affected / exposed	3 / 336 (0.89%)	3 / 349 (0.86%)	
occurrences causally related to treatment / all	0 / 3	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malnutrition			
subjects affected / exposed	2 / 336 (0.60%)	4 / 349 (1.15%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrolyte imbalance			
subjects affected / exposed	2 / 336 (0.60%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia			

subjects affected / exposed	2 / 336 (0.60%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	0 / 336 (0.00%)	3 / 349 (0.86%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypocalcaemia			
subjects affected / exposed	0 / 336 (0.00%)	3 / 349 (0.86%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Feeding disorder			
subjects affected / exposed	0 / 336 (0.00%)	2 / 349 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypernatraemia			
subjects affected / exposed	0 / 336 (0.00%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypophagia			
subjects affected / exposed	0 / 336 (0.00%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolic disorder			
subjects affected / exposed	0 / 336 (0.00%)	1 / 349 (0.29%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	

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

Non-serious adverse events	Placebo	Lapatinib 1500 mg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	321 / 336 (95.54%)	337 / 349 (96.56%)	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	31 / 336 (9.23%)	30 / 349 (8.60%)	
occurrences (all)	42	38	
Aspartate aminotransferase increased			
subjects affected / exposed	28 / 336 (8.33%)	33 / 349 (9.46%)	
occurrences (all)	35	40	
Blood creatinine increased			
subjects affected / exposed	33 / 336 (9.82%)	44 / 349 (12.61%)	
occurrences (all)	43	50	
Creatinine renal clearance decreased			
subjects affected / exposed	17 / 336 (5.06%)	27 / 349 (7.74%)	
occurrences (all)	27	41	
Fatigue			
subjects affected / exposed	36 / 336 (10.71%)	41 / 349 (11.75%)	
occurrences (all)	44	51	
Haemoglobin decreased			
subjects affected / exposed	29 / 336 (8.63%)	33 / 349 (9.46%)	
occurrences (all)	37	49	
Lymphocyte count decreased			
subjects affected / exposed	18 / 336 (5.36%)	20 / 349 (5.73%)	
occurrences (all)	28	26	
Weight decreased			
subjects affected / exposed	64 / 336 (19.05%)	90 / 349 (25.79%)	
occurrences (all)	71	97	
White blood cell count decreased			
subjects affected / exposed	23 / 336 (6.85%)	30 / 349 (8.60%)	
occurrences (all)	51	57	
Injury, poisoning and procedural complications			
Radiation mucositis			
subjects affected / exposed	19 / 336 (5.65%)	13 / 349 (3.72%)	
occurrences (all)	19	13	
Radiation skin injury			

subjects affected / exposed	79 / 336 (23.51%)	55 / 349 (15.76%)	
occurrences (all)	92	59	
Nervous system disorders			
Dysgeusia			
subjects affected / exposed	45 / 336 (13.39%)	31 / 349 (8.88%)	
occurrences (all)	56	36	
Headache			
subjects affected / exposed	28 / 336 (8.33%)	20 / 349 (5.73%)	
occurrences (all)	33	22	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	61 / 336 (18.15%)	77 / 349 (22.06%)	
occurrences (all)	79	94	
Leukopenia			
subjects affected / exposed	99 / 336 (29.46%)	83 / 349 (23.78%)	
occurrences (all)	169	129	
Lymphopenia			
subjects affected / exposed	75 / 336 (22.32%)	87 / 349 (24.93%)	
occurrences (all)	104	99	
Neutropenia			
subjects affected / exposed	77 / 336 (22.92%)	70 / 349 (20.06%)	
occurrences (all)	118	98	
Thrombocytopenia			
subjects affected / exposed	25 / 336 (7.44%)	24 / 349 (6.88%)	
occurrences (all)	33	32	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	45 / 336 (13.39%)	59 / 349 (16.91%)	
occurrences (all)	62	67	
Mucosal inflammation			
subjects affected / exposed	208 / 336 (61.90%)	220 / 349 (63.04%)	
occurrences (all)	272	282	
Pyrexia			
subjects affected / exposed	60 / 336 (17.86%)	63 / 349 (18.05%)	
occurrences (all)	84	85	
Gastrointestinal disorders			

Constipation			
subjects affected / exposed	74 / 336 (22.02%)	60 / 349 (17.19%)	
occurrences (all)	99	69	
Diarrhoea			
subjects affected / exposed	41 / 336 (12.20%)	147 / 349 (42.12%)	
occurrences (all)	49	217	
Dry mouth			
subjects affected / exposed	131 / 336 (38.99%)	148 / 349 (42.41%)	
occurrences (all)	154	172	
Dyspepsia			
subjects affected / exposed	21 / 336 (6.25%)	30 / 349 (8.60%)	
occurrences (all)	24	34	
Dysphagia			
subjects affected / exposed	113 / 336 (33.63%)	125 / 349 (35.82%)	
occurrences (all)	137	158	
Nausea			
subjects affected / exposed	150 / 336 (44.64%)	181 / 349 (51.86%)	
occurrences (all)	237	275	
Odynophagia			
subjects affected / exposed	34 / 336 (10.12%)	41 / 349 (11.75%)	
occurrences (all)	45	47	
Oral pain			
subjects affected / exposed	35 / 336 (10.42%)	25 / 349 (7.16%)	
occurrences (all)	44	29	
Stomatitis			
subjects affected / exposed	50 / 336 (14.88%)	50 / 349 (14.33%)	
occurrences (all)	64	61	
Vomiting			
subjects affected / exposed	115 / 336 (34.23%)	154 / 349 (44.13%)	
occurrences (all)	164	262	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	37 / 336 (11.01%)	45 / 349 (12.89%)	
occurrences (all)	41	53	
Dysphonia			

subjects affected / exposed	21 / 336 (6.25%)	23 / 349 (6.59%)	
occurrences (all)	23	27	
Oropharyngeal pain			
subjects affected / exposed	67 / 336 (19.94%)	45 / 349 (12.89%)	
occurrences (all)	76	51	
Productive cough			
subjects affected / exposed	36 / 336 (10.71%)	25 / 349 (7.16%)	
occurrences (all)	36	26	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	9 / 336 (2.68%)	23 / 349 (6.59%)	
occurrences (all)	10	26	
Rash			
subjects affected / exposed	101 / 336 (30.06%)	167 / 349 (47.85%)	
occurrences (all)	133	249	
Skin reaction			
subjects affected / exposed	37 / 336 (11.01%)	41 / 349 (11.75%)	
occurrences (all)	37	42	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	20 / 336 (5.95%)	17 / 349 (4.87%)	
occurrences (all)	23	22	
Musculoskeletal and connective tissue disorders			
Musculoskeletal pain			
subjects affected / exposed	23 / 336 (6.85%)	15 / 349 (4.30%)	
occurrences (all)	23	15	
Neck pain			
subjects affected / exposed	28 / 336 (8.33%)	20 / 349 (5.73%)	
occurrences (all)	31	22	
Infections and infestations			
Oral candidiasis			
subjects affected / exposed	22 / 336 (6.55%)	17 / 349 (4.87%)	
occurrences (all)	23	17	
Metabolism and nutrition disorders			
Decreased appetite			

subjects affected / exposed	69 / 336 (20.54%)	62 / 349 (17.77%)	
occurrences (all)	86	78	
Hypokalaemia			
subjects affected / exposed	28 / 336 (8.33%)	42 / 349 (12.03%)	
occurrences (all)	33	57	
Hyponatraemia			
subjects affected / exposed	25 / 336 (7.44%)	33 / 349 (9.46%)	
occurrences (all)	28	42	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 September 2006	Amendment No. 1: To provide further clarification on: (1) Radiological assessments: frequency and type updated to reflect current clinical practice; (2) Addition of fiberoptic endoscopy procedure in the assessments updated to reflect current clinical practice; (3) Inclusion criteria modification to include subjects that express all levels of ErbB1 based on current scientific evidence and application of testing methods; (4) Stratification criteria updates to nodal status, geographical region and ErbB1 expression (tumour site unchanged).
07 July 2008	Amendment No. 02: Global amendment to: Amend inclusion criteria to exclude subjects with a second primary tumour that has been resected at the same time as the original tumour. Exclusion criteria added to exclude patients with active hepatic disease. Add additional SAE definition, reporting criteria and follow-up assessments for hepatic toxicity. Add additional liver function assessments every 4 weeks Allow the use of carboplatin for subjects who cannot tolerate cisplatin (after consultation with the medical monitor). Clarify radiotherapy quality assurance process. Clarify CT/MRI scan requirements. Remove requirement for brain scan unless clinically indicated. Clarify screening windows and requirements for bone scan and panendoscopy procedures. Clarify the dose modifications required in the event of toxicities. Clarify the dose of concurrent dexamethasone allowed. Clarify the definition of the evaluable population. Clarify that all subjects will continue in the maintenance phase even if they may not qualify within the evaluable population. Remove the Serum EGFR assessments. Allow screening procedures to commence immediately following surgery. Allow a total screening window of 8 weeks between surgery and randomization, and, subsequently, a total 9 weeks window before starting lapatinib/placebo. Updates to statistical section; including a planned interim for futility following 50% of events, updated recruitment rates and clarification of the DFS endpoint. Amend frequency of survival calls to approximately every 6 months. Clarify the follow-up of patients until disease progression. Clarify the follow-up of patients when they withdraw from IP. Confirmation that patients will be followed-up for a maximum of 5 years after last patient has been randomised. General corrections and clarifications to protocol text, including the abbreviations, study schema, and time and events table.
29 July 2008	Amendment No. 2 - Inclusion of the updated version of the Radiotherapy Protocol in Appendix 7.

20 July 2010	Amendment No. 03: Global Amendment to: Update the Statistical section to: 1) Clarify the target patient accrual as 680; 2) Re-adjust the anticipated improvement in the DFS interval; 3) Increase the target number of DFS ITT events to 298; 4) Update the target number of events for non-binding interim analysis for futility. Remove the Radiotherapy Protocol from Appendix 7 and referenced now in the Study Procedures Manual. Updated prohibited medications list. General corrections and clarifications to protocol text, including the abbreviations, and time and events table.
30 July 2010	Amendment No. 03: Global Amendment to: Revised text within Appendix 7 – Amendment #3 'Main reason for change'.
23 May 2013	Amendment No.: 04 Modified the timing for the primary analysis of the study (Rationale described in Section 1.2.4). Moved patients currently in DFS follow-up into OS follow-up, hence removing the requirement for radiological scans and endoscopies. Described the planned overall survival analyses (Section 8.3.5). Stop study follow-up in the event of a non-significant primary analysis of DFS.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported