



Clinical trial results:

A Randomized, Double-Blind, Placebo-Controlled, Multicentre, Phase II Study of Oral Lapatinib in combination with Concurrent Radiotherapy and Cisplatin versus Radiotherapy and Cisplatin alone, in Subjects with Stage III and IVA,B Squamous Cell Carcinoma of the Head and Neck (SCCHN)

Summary

EudraCT number	2005-003767-23
Trial protocol	GB HU ES NL
Global end of trial date	21 January 2014

Results information

Result version number	v1 (current)
This version publication date	27 April 2016
First version publication date	03 June 2015

Trial information

Trial identification

Sponsor protocol code	EGF105884
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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	22 August 2014
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	21 January 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate and explore the activity of lapatinib or placebo in the two treatment groups with respect to the complete response rate (per RECIST) at six months (24 weeks) from chemoradiation completion in subjects with locally advanced SCCHN.

Protection of trial subjects:

Independent Data Monitoring Committee to review safety data (6-monthly).

Monitoring and management of potential treatment-specific adverse events (liver toxicity, cardiac dysfunction, pneumonitis).

Study drug interruptions reported to medical monitor if related to an adverse event, to provide 'real time' awareness of any unexpected issues.

Protocol amendment after analysis of primary endpoint data to minimize study-specific procedures. Thorough screening and inclusion/exclusion criteria to ensure an appropriate patient population is enrolled.

A radiotherapy (RT) quality assurance program was included: 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	16 November 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	Netherlands: 2
Country: Number of subjects enrolled	Spain: 6
Country: Number of subjects enrolled	United Kingdom: 13
Country: Number of subjects enrolled	Hungary: 6
Country: Number of subjects enrolled	Canada: 1
Country: Number of subjects enrolled	France: 20
Country: Number of subjects enrolled	India: 12
Country: Number of subjects enrolled	Peru: 4
Country: Number of subjects enrolled	United States: 3
Worldwide total number of subjects	67
EEA total number of subjects	47

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)	62
From 65 to 84 years	5
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Study completion was not well defined by the protocol. However, participants were to be followed up until death, unless withdrawn from the study. Therefore the number of participants completing the study is equal to the number of participants who died whilst on-study.

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, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Chemoradiotherapy + Placebo, followed by Placebo

Arm description:

Participants received radiotherapy once daily (OD), with a dose/fraction <2.5 Gray (Gy) to a total dose of 70 Gy (using two-dimensional [2D] or 3D techniques) or 65 Gy (using Intensity Modulated Radiation Therapy [IMRT]) to the gross site of disease. Concurrent chemotherapy of cisplatin 100 milligrams per meters squared (mg/m²) was administered intravenously (IV) on Days 1, 22, and 43 of the course of radiotherapy (Study Days 8, 29, and 50). Matching placebo administration commenced 1 week (or less than or equal to 3 days) prior to the concurrent administration with chemoradiation for a duration of up to 6 to 7 weeks. After the completion of chemoradiotherapy, placebo monotherapy was administered until disease progression or withdrawal.

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:

Six tablets once daily as monotherapy for one week, then concurrently with chemoradiation for 6 to 7 weeks, then as monotherapy until disease progression or withdrawal from the study. Tablets were to be taken whole at least one hour before or one hour after the morning meal. Tablets could be crushed and taken as a suspension in water by subjects who were unable to swallow tablets.

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

Dosage and administration details:

Cisplatin was administered intravenously at a dose of 100 mg/m² on days 1, 22 and 43 of radiotherapy.

Arm title	Chemoradiotherapy + Lapatinib, followed by Lapatinib
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Arm description:

Participants received radiotherapy once daily (OD), with a dose/fraction <2.5 Gy to a total dose of 70 Gy (using 2D or 3D techniques) or 65 Gy (using IMRT) to the gross site of disease. Concurrent chemotherapy of cisplatin 100 mg/m² was administered IV on Days 1, 22, and 43 of the course of radiotherapy (Study Days 8, 29, and 50). Lapatinib 1500 mg OD administration commenced 1 week (or less than or equal to 3 days) prior to the concurrent administration with chemoradiation for a duration of up to 6 to 7 weeks. After the completion of chemoradiotherapy, lapatinib 1500 mg OD monotherapy was

administered until disease progression or withdrawal.

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

Dosage and administration details:

1500 mg once daily as monotherapy for one week, then concurrently with chemoradiation for 6 to 7 weeks, then as monotherapy until disease progression or withdrawal from the study. Lapatinib was provided as 250 mg tablets, to be taken whole at least one hour before or one hour after the morning meal. Tablets could be crushed and taken as a suspension in water by subjects who were unable to swallow tablets.

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

Dosage and administration details:

Cisplatin was administered intravenously at a dose of 100 mg/m² on days 1, 22 and 43 of radiotherapy.

Number of subjects in period 1	Chemoradiotherapy + Placebo, followed by Placebo	Chemoradiotherapy + Lapatinib, followed by Lapatinib
Started	33	34
Completed	16	16
Not completed	17	18
Consent withdrawn by subject	3	2
Physician decision	-	1
Sponsor Unblinded	1	-
Required by Protocol Amendment #4	12	10
Lost to follow-up	-	4
Serious Adverse Event	1	1

Baseline characteristics

Reporting groups

Reporting group title	Chemoradiotherapy + Placebo, followed by Placebo
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Reporting group description:

Participants received radiotherapy once daily (OD), with a dose/fraction <2.5 Gray (Gy) to a total dose of 70 Gy (using two-dimensional [2D] or 3D techniques) or 65 Gy (using Intensity Modulated Radiation Therapy [IMRT]) to the gross site of disease. Concurrent chemotherapy of cisplatin 100 milligrams per meters squared (mg/m²) was administered intravenously (IV) on Days 1, 22, and 43 of the course of radiotherapy (Study Days 8, 29, and 50). Matching placebo administration commenced 1 week (or less than or equal to 3 days) prior to the concurrent administration with chemoradiation for a duration of up to 6 to 7 weeks. After the completion of chemoradiotherapy, placebo monotherapy was administered until disease progression or withdrawal.

Reporting group title	Chemoradiotherapy + Lapatinib, followed by Lapatinib
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Reporting group description:

Participants received radiotherapy once daily (OD), with a dose/fraction <2.5 Gy to a total dose of 70 Gy (using 2D or 3D techniques) or 65 Gy (using IMRT) to the gross site of disease. Concurrent chemotherapy of cisplatin 100 mg/m² was administered IV on Days 1, 22, and 43 of the course of radiotherapy (Study Days 8, 29, and 50). Lapatinib 1500 mg OD administration commenced 1 week (or less than or equal to 3 days) prior to the concurrent administration with chemoradiation for a duration of up to 6 to 7 weeks. After the completion of chemoradiotherapy, lapatinib 1500 mg OD monotherapy was administered until disease progression or withdrawal.

Reporting group values	Chemoradiotherapy + Placebo, followed by Placebo	Chemoradiotherapy + Lapatinib, followed by Lapatinib	Total
Number of subjects	33	34	67
Age categorical Units: Subjects			

Age continuous Units: years arithmetic mean standard deviation	56.5 ± 6.61	55.8 ± 5.73	-
Gender categorical Units: Subjects			
Female	2	5	7
Male	31	29	60
Race Units: Subjects			
African American/African Heritage	0	1	1
American Indian or Alaska Native	2	2	4
Asian - Central/South Asian Heritage	3	6	9
Asian - South East Asian Heritage	2	1	3
White - White/Caucasian/European Heritage	26	24	50

End points

End points reporting groups

Reporting group title	Chemoradiotherapy + Placebo, followed by Placebo
Reporting group description: Participants received radiotherapy once daily (OD), with a dose/fraction <2.5 Gray (Gy) to a total dose of 70 Gy (using two-dimensional [2D] or 3D techniques) or 65 Gy (using Intensity Modulated Radiation Therapy [IMRT]) to the gross site of disease. Concurrent chemotherapy of cisplatin 100 milligrams per meters squared (mg/m ²) was administered intravenously (IV) on Days 1, 22, and 43 of the course of radiotherapy (Study Days 8, 29, and 50). Matching placebo administration commenced 1 week (or less than or equal to 3 days) prior to the concurrent administration with chemoradiation for a duration of up to 6 to 7 weeks. After the completion of chemoradiotherapy, placebo monotherapy was administered until disease progression or withdrawal.	
Reporting group title	Chemoradiotherapy + Lapatinib, followed by Lapatinib
Reporting group description: Participants received radiotherapy once daily (OD), with a dose/fraction <2.5 Gy to a total dose of 70 Gy (using 2D or 3D techniques) or 65 Gy (using IMRT) to the gross site of disease. Concurrent chemotherapy of cisplatin 100 mg/m ² was administered IV on Days 1, 22, and 43 of the course of radiotherapy (Study Days 8, 29, and 50). Lapatinib 1500 mg OD administration commenced 1 week (or less than or equal to 3 days) prior to the concurrent administration with chemoradiation for a duration of up to 6 to 7 weeks. After the completion of chemoradiotherapy, lapatinib 1500 mg OD monotherapy was administered until disease progression or withdrawal.	

Primary: Number of participants (par.) with Complete Response (CR), as assessed by independent radiological review

End point title	Number of participants (par.) with Complete Response (CR), as assessed by independent radiological review
End point description: Participants with CR are defined as those who achieved a complete tumor response at 6 months after the completion of the chemoradiation treatment (CRT), as assessed by independent radiological review. Tumor response was assessed using modified Response Evaluation Criteria in Solid Tumors (RECIST) criteria. Per RECIST, CR is defined as the disappearance of all target and non-target lesions. Data are based on Week 24 scans from participants receiving study treatment at that time and on those in follow-up. Intent-to-Treat (ITT) Population: all participants who were randomized to study treatment, regardless of whether they actually received study medication.	
End point type	Primary
End point timeframe: From the date of randomization until 6 months post chemoradiation treatment, assessed for a median time of 13 months	

End point values	Chemoradiotherapy + Placebo, followed by Placebo	Chemoradiotherapy + Lapatinib, followed by Lapatinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33 ^[1]	34 ^[2]		
Units: Participants	12	18		

Notes:

[1] - ITT Population

[2] - ITT Population

Statistical analyses

Statistical analysis title	Analysis 1
Comparison groups	Chemoradiotherapy + Placebo, followed by Placebo v Chemoradiotherapy + Lapatinib, followed by Lapatinib
Number of subjects included in analysis	67
Analysis specification	Pre-specified
Analysis type	superiority ^[3]
P-value	= 0.3658 ^[4]
Method	Fisher exact
Parameter estimate	Difference in percentage of par. with CR
Point estimate	10.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.4
upper limit	37.3

Notes:

[3] - Complete response was defined as the percentage of participants achieving a CR as determined by an independent radiological review.

[4] - From exact test that common odds ratio equals 1

Secondary: Number of participants with CR, as assessed by the investigator

End point title	Number of participants with CR, as assessed by the investigator
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End point description:

Participants with CR are defined as those who achieved a complete tumor response at 6 months after the completion of the CRT, as determined by the investigator. Tumor response was assessed using modified RECIST criteria. Per RECIST, CR is defined as the disappearance of all target and non-target lesions. Data are based on Week 24 scans from participants receiving study treatment at that time and on those in follow-up.

End point type	Secondary
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End point timeframe:

From the date of randomization until 6 months post chemoradiation treatment, assessed after a median time of 13 months of follow-up

End point values	Chemoradiotherapy + Placebo, followed by Placebo	Chemoradiotherapy + Lapatinib, followed by Lapatinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33 ^[5]	34 ^[6]		
Units: Participants	7	17		

Notes:

[5] - ITT Population

[6] - ITT Population

Statistical analyses

Statistical analysis title	Analysis 1
Comparison groups	Chemoradiotherapy + Placebo, followed by Placebo v Chemoradiotherapy + Lapatinib, followed by Lapatinib

Number of subjects included in analysis	67
Analysis specification	Pre-specified
Analysis type	superiority ^[7]
P-value	= 0.013 ^[8]
Method	Fisher exact
Parameter estimate	Difference in percentage of par. with CR
Point estimate	28.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	5.7
upper limit	53.6

Notes:

[7] - Complete response was defined as the percentage of participants achieving a CR as determined by the investigator.

[8] - From exact test that common odds ratio equals 1

Secondary: Progression-Free Survival (PFS), as assessed by the investigator

End point title	Progression-Free Survival (PFS), as assessed by the investigator
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End point description:

PFS=the time from randomization until the earliest date of disease progression or death due to any cause, if sooner. Per RECIST, progressive disease=a \geq 20% increase in the sum of the longest diameter of target lesions (TLs), or the appearance of \geq 1 new L, symptomatic progression and/or unequivocal progression of existing non-TLs. For participants who did not progress or die at the time of reporting (data cut-off 1-Aug-2014), PFS data were censored at the time of the last investigator assessed radiological scan preceding the initiation of any alternative anti-cancer therapy. There were too few events to allow for the calculation of the upper limit of the confidence interval; therefore, 99999 was entered which represents NA.

End point type	Secondary
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End point timeframe:

From the date of randomization until the date of disease progression or death due to any cause, assessed after a median of 22 months of follow-up

End point values	Chemoradiotherapy + Placebo, followed by Placebo	Chemoradiotherapy + Lapatinib, followed by Lapatinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33 ^[9]	34 ^[10]		
Units: Months				
median (confidence interval 95%)	12.1 (7.3 to 99999)	20.4 (10.8 to 99999)		

Notes:

[9] - ITT Population

[10] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)
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End point description:

OS is defined as the time from randomization until death due to any cause. Time to death (data cut-off 1-Aug-2014) was censored at the time of last contact for participants who did not die. There were too few events to allow for the calculation of the upper limit of the confidence interval; therefore, 99999 was entered which indicates NA.

End point type	Secondary
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End point timeframe:

From the date of randomization until the date of death due to any cause, assessed after a median of 30.9 months

End point values	Chemoradiotherapy + Placebo, followed by Placebo	Chemoradiotherapy + Lapatinib, followed by Lapatinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33 ^[11]	34 ^[12]		
Units: Months				
median (confidence interval 95%)	23 (14.2 to 99999)	48.4 (18.8 to 99999)		

Notes:

[11] - ITT Population

[12] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants who died due to progressive disease

End point title	Number of participants who died due to progressive disease
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End point description:

The number of participants who died due to progressive disease (a $\geq 20\%$ increase in the sum of the longest diameter of target lesions, or the appearance of ≥ 1 new lesion, symptomatic progression and/or unequivocal progression of existing non-target lesions), or died due to head and neck cancer without evidence of disease progression, after randomization in the study is presented, using a data cut of 1 August 2014.

End point type	Secondary
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End point timeframe:

From the date of randomization until the date of death due to disease under study, assessed after a median of 30.9 months

End point values	Chemoradiotherapy + Placebo, followed by Placebo	Chemoradiotherapy + Lapatinib, followed by Lapatinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33 ^[13]	34 ^[14]		
Units: Participants	11	8		

Notes:

[13] - ITT Population

[14] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Disease-specific Survival

End point title	Disease-specific Survival
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End point description:

Disease-specific survival is defined as the time from randomization until death due to head and neck cancer. The cumulative incidence remained lower than 25% in the lapatinib arm, so neither the median nor the inter-quartile range were observed; therefore, 99999 was entered which represents NA. The cumulative incidence in the placebo arm remained lower than 50%, so the median and upper quartile were not observed; therefore, 99999 was entered which represents NA.

End point type	Secondary
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End point timeframe:

From the date of randomization until the date of death due to disease, assessed after a median of 13 months of follow-up

End point values	Chemoradiotherapy + Placebo, followed by Placebo	Chemoradiotherapy + Lapatinib, followed by Lapatinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33 ^[15]	34 ^[16]		
Units: Months				
arithmetic mean (inter-quartile range (Q1-Q3))	99999 (15.6 to 99999)	99999 (99999 to 99999)		

Notes:

[15] - ITT Population. For par. who did not die, time to death was censored at the time of last contact.

[16] - ITT Population. For par. who did not die, time to death was censored at the time of last contact.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with loco-regional recurrence of initial disease

End point title	Number of participants with loco-regional recurrence of initial disease
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End point description:

Participants with loco-regional recurrence were those who had progression of disease in the T and N sites. Per the Tumor, Node, and Metastases (TNM) staging of tumors: T describes the size of the tumor and whether it has invaded nearby tissue, and N describes regional lymph nodes that are involved. If a participant had progression in the T or N sites, then the participant was counted as having had an event of interest.

End point type	Secondary
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End point timeframe:

From the date of randomization until progression in the T or N site or death due to any cause, assessed

End point values	Chemoradiotherapy + Placebo, followed by Placebo	Chemoradiotherapy + Lapatinib, followed by Lapatinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33 ^[17]	34 ^[18]		
Units: Participants	7	4		

Notes:

[17] - ITT Population

[18] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Loco-regional control

End point title	Loco-regional control
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End point description:

Loco-regional control is defined as the time from the date of randomization until progression in the T or N site. Participants who died or had secondary primary malignancies in the head and neck region outside of the T and N site or distant metastasis were not counted as an event and were instead treated as competing risks. Per the TNM staging of tumors: T describes the size of the tumor and whether it has invaded nearby tissue, and N describes regional lymph nodes that are involved. Due to the minimal events reported (data cut-off 30-Sep-2010), valid analysis could not be performed for loco-regional control rate.

End point type	Secondary
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End point timeframe:

From the date of randomization until progression in the T or N site or death due to any cause, assessed after a median of 30.9 months

End point values	Chemoradiotherapy + Placebo, followed by Placebo	Chemoradiotherapy + Lapatinib, followed by Lapatinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0 ^[19]	0 ^[20]		
Units: Months				
arithmetic mean (standard deviation)	()	()		

Notes:

[19] - ITT Population

[20] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with distant recurrence of initial disease

End point title	Number of participants with distant recurrence of initial disease
End point description:	
Participants were analyzed for the occurrence of distant metastasis (spread of a disease from one organ or part to another non-adjacent organ or part) after randomization in the study until data cut-off date 1-Aug-2014. Participants who died or had recurrence of disease in the T or N sites or secondary primary malignancies in the head and neck region outside of the original T and N site were not counted as an event and were instead treated as competing risks.	
End point type	Secondary
End point timeframe:	
From the date of randomization until the first occurrence of distant metastasis, assessed after a median of 30.9 months	

End point values	Chemoradiotherapy + Placebo, followed by Placebo	Chemoradiotherapy + Lapatinib, followed by Lapatinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33 ^[21]	34 ^[22]		
Units: Participants	5	8		

Notes:

[21] - ITT Population

[22] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Distant Relapse

End point title	Distant Relapse
End point description:	
Distant relapse is defined as the time from the date of randomization until the first occurrence of distant metastasis (spread of a disease from one organ or part to another non-adjacent organ or part). Participants who died or had recurrence of disease in the T or N sites or secondary primary malignancies in the head and neck region outside of the original T and N site were not counted as an event and were instead treated as competing risks. If a participant had a distant metastasis and then died, then the participant was counted as having had an event of interest. The cumulative incidence in the lapatinib arm did not reach 50% (most participants had not relapsed), so the median and the upper limit of the interquartile range were not observed; therefore, 99999 was entered which represents NA. The cumulative incidence remained below 25% in the placebo arm, so neither the median nor the interquartile range were observed; therefore, 99999 was entered which represents NA.	
End point type	Secondary
End point timeframe:	
From the date of randomization until the first occurrence of distant metastasis, assessed after a median of 30.9 months	

End point values	Chemoradiotherapy + Placebo, followed by Placebo	Chemoradiotherapy + Lapatinib, followed by Lapatinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33 ^[23]	34 ^[24]		
Units: Months				
median (inter-quartile range (Q1-Q3))	99999 (99999 to 99999)	99999 (56.8 to 99999)		

Notes:

[23] - ITT Population

[24] - ITT Population

Statistical analyses

No statistical analyses for this end point

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

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

Participants with OR were those who achieved either a CR or partial response (PR) from the assessment of overall tumor response at 6 months (24 weeks) following completion of CRT (data cut-off 30-Sep-2010). Per RECIST, CR is defined as the disappearance of all target and non-target lesions; PR is defined as at least a 30% decrease in the sum of the long diameter (LD) of target lesions, taking as a reference, the baseline sum LD. Data are based on Week 24 scans from participants receiving study treatment at that time point.

End point type	Secondary
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End point timeframe:

From the date of randomization until 6 months post chemoradiation treatment, assessed for a median of 13 months

End point values	Chemoradiotherapy + Placebo, followed by Placebo	Chemoradiotherapy + Lapatinib, followed by Lapatinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33 ^[25]	34 ^[26]		
Units: Participants	15	21		

Notes:

[25] - ITT Population

[26] - ITT Population

Statistical analyses

Statistical analysis title	Analysis 1
Comparison groups	Chemoradiotherapy + Placebo, followed by Placebo v Chemoradiotherapy + Lapatinib, followed by Lapatinib

Number of subjects included in analysis	67
Analysis specification	Pre-specified
Analysis type	superiority ^[27]
P-value	= 0.1969 ^[28]
Method	Fisher exact
Parameter estimate	Difference in overall response rate
Point estimate	16.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.6
upper limit	42.1

Notes:

[27] - Overall response was defined as the percentage of participants achieving a PR or CR as determined by the investigator.

[28] - From exact test that common odds ratio equals 1

Secondary: Number of participants positive and negative for the expression of biomarkers in tumor tissue: human epidermal growth factor receptor (HER)-1, HER2, HER3, HER4, P16, and transforming growth factor (TGF-alpha)

End point title	Number of participants positive and negative for the expression of biomarkers in tumor tissue: human epidermal growth factor receptor (HER)-1, HER2, HER3, HER4, P16, and transforming growth factor (TGF-alpha)
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End point description:

Paraffin-embedded tissue block (or sections) from archived tumor tissue sample, if available (from time of original diagnosis) or fresh tumor tissue, was sent for testing to determine intra-tumoral biomarker expression by immunohistochemistry (IHC) or fluorescent in situ hybridization (FISH) assay. Stained tumor slides or tissue micro arrays (TMAs) were scored by a pathologist from 0 (no expression) to 3+ (high expression). An expression level of $\geq 2+$ was considered positive.

End point type	Secondary
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End point timeframe:

Up to 28 days prior to the date of the first dose of lapatinib/placebo start

End point values	Chemoradiotherapy + Placebo, followed by Placebo	Chemoradiotherapy + Lapatinib, followed by Lapatinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30 ^[29]	27 ^[30]		
Units: Participants				
HER1, Positive, n=27, 24	27	19		
HER1, Negative, n=27, 24	0	5		
HER2, Positive, n=26, 25	3	0		
HER2, Negative, n=26, 25	23	24		
HER2, Missing, n=26, 25	0	1		
HER3, Positive, n=27, 22	8	5		
HER3, Negative, n=27, 22	18	16		
HER3, Missing, n=27, 22	1	1		
HER4, Positive, n=26, 25	0	0		
HER4, Negative, n=26, 25	26	24		
HER4, Missing, n=26, 25	0	1		

P16 Positive, n=23, 23	3	4		
P16, Negative, n=23, 23	20	19		
TGF-alpha, Positive, n=24, 25	7	4		
TGF-alpha, Negative, n=24, 25	17	20		
TGF-alpha, Missing, n=24, 25	0	1		

Notes:

[29] - ITT Population. Only those participants who had sufficient tumor sample for testing were analyzed.

[30] - ITT Population. Only those participants who had sufficient tumor sample for testing were analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Proteome Analysis

End point title	Plasma Proteome Analysis
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End point description:

Proteomic analyses of blood plasma samples were to be conducted to identify any changes in the proteome profile that could be related to the treatment response. Examination of pre-dosing (screening) plasma protein profiles could uncover novel blood-borne protein candidate biomarkers/profiles, which could be used to predict drug response. Plasma proteome data have not been analyzed (tested); thus, data are not available to disclose. Based on the negative outcome of Study EGF102988 (NCT00424255), no suitable analyses have been proposed for this small sample size.

End point type	Secondary
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End point timeframe:

From up to 28 days prior to the first dose of lapatinib/placebo start to 8 weeks after the first dose

End point values	Chemoradiotherapy + Placebo, followed by Placebo	Chemoradiotherapy + Lapatinib, followed by Lapatinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0 ^[31]	0 ^[32]		
Units: Participants				

Notes:

[31] - ITT Population

[32] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Analysis of deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) from tumor samples

End point title	Analysis of deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) from tumor samples
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End point description:

No analysis was performed for tumor sample RNA/DNA. DNA/RNA from tumors has not been analyzed (tested); therefore, data are not available. No suitable analyses of DNA/RNA have been proposed for this small sample size of tumor samples.

End point type	Secondary
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End point timeframe:

Screening

End point values	Chemoradiotherapy + Placebo, followed by Placebo	Chemoradiotherapy + Lapatinib, followed by Lapatinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0 ^[33]	0 ^[34]		
Units: Participants				

Notes:

[33] - ITT Population

[34] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants negative and positive for Human Papilloma Virus (HPV) infection, as determined from tumor samples

End point title	Number of participants negative and positive for Human Papilloma Virus (HPV) infection, as determined from tumor samples
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End point description:

Analysis was performed for HPV infection analysis from the tumor biopsy samples obtained during the Screening period. p16 was used as a marker for HPV; thus, "negative" participants did not have the p16 marker.

End point type	Secondary
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End point timeframe:

Up to 28 days prior to the first dose of lapatinib/placebo

End point values	Chemoradiotherapy + Placebo, followed by Placebo	Chemoradiotherapy + Lapatinib, followed by Lapatinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33 ^[35]	34 ^[36]		
Units: Participants				
Negative	20	19		
Positive	3	4		
Unknown	10	11		

Notes:

[35] - ITT Population

[36] - ITT Population

Statistical analyses

Secondary: Number of participants positive and negative for biomarker HER1/ErbB1 categorized in the indicated independent review panel-assessed tumor responses by expression of biomarkers from tumor tissue: sensitivity analysis - 0 versus (1, 2, 3)

End point title	Number of participants positive and negative for biomarker HER1/ErbB1 categorized in the indicated independent review panel-assessed tumor responses by expression of biomarkers from tumor tissue: sensitivity analysis - 0 versus (1, 2, 3)
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End point description:

Tumor tissue (fresh or archived) was sent to a central laboratory for biomarker HER1/ErbB1 and tumor genetics analysis up to 1 week after randomization. Per RECIST: CR, disappearance of all lesions; PR, a $\geq 30\%$ decrease in the sum of the longest dimensions (LD) of the target lesions (TLs) taking as a reference the baseline sum LD; Progressive disease (PD), a $\geq 20\%$ increase in the sum of the LD of TLs, or the appearance of ≥ 1 new lesion; Stable Disease (SD), neither PR nor PD, persistence of ≥ 1 non-TL. 0=negative; 1, 2, 3=positive (increasing level of biomarker expression).

End point type	Secondary
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End point timeframe:

From the date of randomization until 6 months post chemoradiation treatment, assessed for up to 24 weeks

End point values	Chemoradiotherapy + Placebo, followed by Placebo	Chemoradiotherapy + Lapatinib, followed by Lapatinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27 ^[37]	24 ^[38]		
Units: Participants				
Negative, CR	0	0		
Negative, PR	0	0		
Negative, SD	0	0		
Negative, PD (Week 24)	0	0		
Negative, PD or Death (prior to Week 24)	0	0		
Negative, Not Evaluable	0	0		
Negative, Unknown	0	0		
Positive, CR	9	14		
Positive, PR	4	3		
Positive, SD	0	0		
Positive, PD (Week 24)	4	1		
Positive, PD or Death (prior to Week 24)	5	4		
Positive, Not Evaluable	1	0		
Positive, Unknown	4	2		

Notes:

[37] - ITT Population. Participants assessed for HER1/ ErbB1 expression were analyzed.

[38] - ITT Population. Participants assessed for HER1/ ErbB1 expression were analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants positive and negative for biomarker HER1/ErbB1

categorized in the indicated independent review panel-assessed tumor responses by expression of biomarkers from tumor tissues: sensitivity analysis - 0, 1, 2 versus 3

End point title	Number of participants positive and negative for biomarker HER1/ErbB1 categorized in the indicated independent review panel-assessed tumor responses by expression of biomarkers from tumor tissues: sensitivity analysis - 0, 1, 2 versus 3
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End point description:

Tumor tissue (fresh or archived) was sent to a central laboratory for biomarker HER1/ErbB1 and tumor genetics analysis up to 1 week after randomization. Per RECIST: CR, disappearance of all lesions; PR, a $\geq 30\%$ decrease in the sum of the longest dimensions (LD) of the target lesions (TLs) taking as a reference the baseline sum LD; Progressive disease (PD), a $\geq 20\%$ increase in the sum of the LD of TLs, or the appearance of ≥ 1 new lesion; Stable Disease (SD), neither PR nor PD, persistence of ≥ 1 non-TL. 0=negative; 1, 2, 3=positive (increasing level of biomarker expression).

End point type	Secondary
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End point timeframe:

From the date of randomization until 6 months post chemoradiation treatment, assessed for up to 24 weeks

End point values	Chemoradiotherapy + Placebo, followed by Placebo	Chemoradiotherapy + Lapatinib, followed by Lapatinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33 ^[39]	34 ^[40]		
Units: Participants				
Negative, CR	5	9		
Negative, PR	2	2		
Negative, SD	0	0		
Negative, PD (Week 24)	1	0		
Negative, PD or Death (prior to Week 24)	2	4		
Negative, Not Evaluable	0	0		
Negative, Unknown	1	1		
Positive, CR	4	5		
Positive, PR	2	1		
Positive, SD	0	0		
Positive, PD (Week 24)	3	1		
Positive, PD or Death (prior to Week 24)	3	0		
Positive, Not Evaluable	1	0		
Positive, Unknown	3	1		

Notes:

[39] - ITT Population. Participants assessed for HER1/ ErbB1 expression were analyzed.

[40] - ITT Population. Participants assessed for HER1/ ErbB1 expression were analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants classified as responders, as per volumetric tumor response

End point title	Number of participants classified as responders, as per volumetric tumor response
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End point description:

A formal analysis of this outcome measure was never performed; thus data are not available and cannot be reported.

End point type	Secondary
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End point timeframe:

From the date of randomization until 6 months post chemoradiation treatment, assessed for a median of 13 months

End point values	Chemoradiotherapy + Placebo, followed by Placebo	Chemoradiotherapy + Lapatinib, followed by Lapatinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0 ^[41]	0 ^[42]		
Units: Participants				

Notes:

[41] - ITT Population

[42] - ITT Population

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Data are presented as of the cut-off date of 1-August-2014.

Adverse event reporting additional description:

Data are presented for the Safety Population (SP)=participants (par.) who were randomized and took ≥ 1 dose of study medication (SM). One par. randomized to placebo received lapatinib in error and was assigned to the lapatinib arm in the SP. One par. randomized to placebo withdrew from the study prior to receiving SM and was not included in the SP.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	16.1
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Reporting groups

Reporting group title	Chemoradiotherapy + Placebo, followed by Placebo
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Reporting group description:

Participants received radiotherapy once daily (OD), with a dose/fraction < 2.5 Gray (Gy) to a total dose of 70 Gy (using two-dimensional [2D] or 3D techniques) or 65 Gy (using Intensity Modulated Radiation Therapy [IMRT]) to the gross site of disease. Concurrent chemotherapy of cisplatin 100 milligrams per meters squared (mg/m^2) was administered intravenously (IV) on Days 1, 22, and 43 of the course of radiotherapy (Study Days 8, 29, and 50). Matching placebo administration commenced 1 week (or less than or equal to 3 days) prior to the concurrent administration with chemoradiation for a duration of up to 6 to 7 weeks. After the completion of chemoradiotherapy, placebo monotherapy was administered until disease progression or withdrawal.

Reporting group title	Chemoradiotherapy + Lapatinib, followed by Lapatinib
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Reporting group description:

Participants received radiotherapy once daily (OD), with a dose/fraction < 2.5 Gy to a total dose of 70 Gy (using 2D or 3D techniques) or 65 Gy (using IMRT) to the gross site of disease. Concurrent chemotherapy of cisplatin 100 mg/m^2 was administered IV on Days 1, 22, and 43 of the course of radiotherapy (Study Days 8, 29, and 50). Lapatinib 1500 mg OD administration commenced 1 week (or less than or equal to 3 days) prior to the concurrent administration with chemoradiation for a duration of up to 6 to 7 weeks. After the completion of chemoradiotherapy, lapatinib 1500 mg OD monotherapy was administered until disease progression or withdrawal.

Serious adverse events	Chemoradiotherapy + Placebo, followed by Placebo	Chemoradiotherapy + Lapatinib, followed by Lapatinib	
Total subjects affected by serious adverse events			
subjects affected / exposed	18 / 31 (58.06%)	22 / 35 (62.86%)	
number of deaths (all causes)	16	16	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour haemorrhage			
subjects affected / exposed	2 / 31 (6.45%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Metastatic neoplasm			

subjects affected / exposed	0 / 31 (0.00%)	1 / 35 (2.86%)	
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 tongue			
subjects affected / exposed	0 / 31 (0.00%)	1 / 35 (2.86%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Haemorrhage			
subjects affected / exposed	1 / 31 (3.23%)	1 / 35 (2.86%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arterial occlusive disease			
subjects affected / exposed	0 / 31 (0.00%)	1 / 35 (2.86%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
General disorders and administration site conditions			
Mucosal inflammation			
subjects affected / exposed	1 / 31 (3.23%)	3 / 35 (8.57%)	
occurrences causally related to treatment / all	1 / 1	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthenia			
subjects affected / exposed	1 / 31 (3.23%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	0 / 31 (0.00%)	1 / 35 (2.86%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Fatigue			
subjects affected / exposed	0 / 31 (0.00%)	1 / 35 (2.86%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Localised oedema			
subjects affected / exposed	0 / 31 (0.00%)	1 / 35 (2.86%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Soft tissue inflammation			
subjects affected / exposed	0 / 31 (0.00%)	1 / 35 (2.86%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	2 / 31 (6.45%)	1 / 35 (2.86%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	1 / 31 (3.23%)	1 / 35 (2.86%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Aspiration			
subjects affected / exposed	1 / 31 (3.23%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Lung disorder			
subjects affected / exposed	1 / 31 (3.23%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Obstructive airways disorder			
subjects affected / exposed	1 / 31 (3.23%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngeal ulceration			
subjects affected / exposed	1 / 31 (3.23%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Respiratory distress			
subjects affected / exposed	0 / 31 (0.00%)	1 / 35 (2.86%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory failure			
subjects affected / exposed	1 / 31 (3.23%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Stridor			
subjects affected / exposed	1 / 31 (3.23%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Investigations			
Weight decreased			
subjects affected / exposed	2 / 31 (6.45%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Creatinine renal clearance decreased			
subjects affected / exposed	0 / 31 (0.00%)	1 / 35 (2.86%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ejection fraction decreased			
subjects affected / exposed	1 / 31 (3.23%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Gastrostomy failure			
subjects affected / exposed	1 / 31 (3.23%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Left ventricular dysfunction			

subjects affected / exposed	1 / 31 (3.23%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	0 / 31 (0.00%)	1 / 35 (2.86%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial effusion			
subjects affected / exposed	0 / 31 (0.00%)	1 / 35 (2.86%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	1 / 31 (3.23%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Dizziness			
subjects affected / exposed	0 / 31 (0.00%)	1 / 35 (2.86%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemiparesis			
subjects affected / exposed	0 / 31 (0.00%)	1 / 35 (2.86%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoaesthesia			
subjects affected / exposed	0 / 31 (0.00%)	1 / 35 (2.86%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Quadriparesis			
subjects affected / exposed	0 / 31 (0.00%)	1 / 35 (2.86%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Somnolence			

subjects affected / exposed	0 / 31 (0.00%)	1 / 35 (2.86%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	1 / 31 (3.23%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 31 (9.68%)	2 / 35 (5.71%)	
occurrences causally related to treatment / all	0 / 3	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	2 / 31 (6.45%)	2 / 35 (5.71%)	
occurrences causally related to treatment / all	1 / 3	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	1 / 31 (3.23%)	2 / 35 (5.71%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			
subjects affected / exposed	1 / 31 (3.23%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphopenia			
subjects affected / exposed	0 / 31 (0.00%)	1 / 35 (2.86%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	1 / 31 (3.23%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			

Dysphagia			
subjects affected / exposed	2 / 31 (6.45%)	2 / 35 (5.71%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	0 / 31 (0.00%)	3 / 35 (8.57%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mouth haemorrhage			
subjects affected / exposed	1 / 31 (3.23%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parotid gland inflammation			
subjects affected / exposed	1 / 31 (3.23%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 31 (0.00%)	1 / 35 (2.86%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 31 (0.00%)	1 / 35 (2.86%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal tubular disorder			
subjects affected / exposed	0 / 31 (0.00%)	2 / 35 (5.71%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	0 / 31 (0.00%)	1 / 35 (2.86%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Renal failure acute			
subjects affected / exposed	0 / 31 (0.00%)	1 / 35 (2.86%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	3 / 31 (9.68%)	1 / 35 (2.86%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Bronchitis			
subjects affected / exposed	0 / 31 (0.00%)	1 / 35 (2.86%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal infection			
subjects affected / exposed	0 / 31 (0.00%)	1 / 35 (2.86%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parotitis			
subjects affected / exposed	1 / 31 (3.23%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngitis			
subjects affected / exposed	1 / 31 (3.23%)	0 / 35 (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 / 31 (3.23%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Staphylococcal infection			
subjects affected / exposed	0 / 31 (0.00%)	1 / 35 (2.86%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			

Dehydration			
subjects affected / exposed	1 / 31 (3.23%)	3 / 35 (8.57%)	
occurrences causally related to treatment / all	0 / 2	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	1 / 31 (3.23%)	1 / 35 (2.86%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Decreased appetite			
subjects affected / exposed	0 / 31 (0.00%)	1 / 35 (2.86%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperuricaemia			
subjects affected / exposed	0 / 31 (0.00%)	1 / 35 (2.86%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malnutrition			
subjects affected / exposed	0 / 31 (0.00%)	1 / 35 (2.86%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Chemoradiotherapy + Placebo, followed by Placebo	Chemoradiotherapy + Lapatinib, followed by Lapatinib	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	31 / 31 (100.00%)	34 / 35 (97.14%)	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	14 / 31 (45.16%)	4 / 35 (11.43%)	
occurrences (all)	16	6	
Chills			
subjects affected / exposed	1 / 31 (3.23%)	2 / 35 (5.71%)	
occurrences (all)	1	2	
Face oedema			

subjects affected / exposed	1 / 31 (3.23%)	3 / 35 (8.57%)	
occurrences (all)	1	3	
Fatigue			
subjects affected / exposed	2 / 31 (6.45%)	6 / 35 (17.14%)	
occurrences (all)	2	9	
Fibrosis			
subjects affected / exposed	0 / 31 (0.00%)	2 / 35 (5.71%)	
occurrences (all)	0	3	
Influenza like illness			
subjects affected / exposed	0 / 31 (0.00%)	2 / 35 (5.71%)	
occurrences (all)	0	2	
Localised oedema			
subjects affected / exposed	7 / 31 (22.58%)	4 / 35 (11.43%)	
occurrences (all)	9	6	
Mucosal inflammation			
subjects affected / exposed	14 / 31 (45.16%)	14 / 35 (40.00%)	
occurrences (all)	14	17	
Non-cardiac chest pain			
subjects affected / exposed	0 / 31 (0.00%)	2 / 35 (5.71%)	
occurrences (all)	0	2	
Oedema peripheral			
subjects affected / exposed	3 / 31 (9.68%)	2 / 35 (5.71%)	
occurrences (all)	3	2	
Pain			
subjects affected / exposed	3 / 31 (9.68%)	3 / 35 (8.57%)	
occurrences (all)	3	3	
Pyrexia			
subjects affected / exposed	6 / 31 (19.35%)	11 / 35 (31.43%)	
occurrences (all)	6	19	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	4 / 31 (12.90%)	4 / 35 (11.43%)	
occurrences (all)	6	12	
Dysphonia			

subjects affected / exposed	6 / 31 (19.35%)	5 / 35 (14.29%)	
occurrences (all)	7	7	
Dyspnoea			
subjects affected / exposed	3 / 31 (9.68%)	2 / 35 (5.71%)	
occurrences (all)	3	3	
Epiglottic oedema			
subjects affected / exposed	4 / 31 (12.90%)	0 / 35 (0.00%)	
occurrences (all)	4	0	
Haemoptysis			
subjects affected / exposed	2 / 31 (6.45%)	2 / 35 (5.71%)	
occurrences (all)	2	2	
Increased upper airway secretion			
subjects affected / exposed	3 / 31 (9.68%)	1 / 35 (2.86%)	
occurrences (all)	3	1	
Increased viscosity of bronchial secretion			
subjects affected / exposed	2 / 31 (6.45%)	2 / 35 (5.71%)	
occurrences (all)	3	2	
Laryngeal oedema			
subjects affected / exposed	2 / 31 (6.45%)	3 / 35 (8.57%)	
occurrences (all)	2	3	
Oropharyngeal pain			
subjects affected / exposed	7 / 31 (22.58%)	11 / 35 (31.43%)	
occurrences (all)	11	12	
Productive cough			
subjects affected / exposed	1 / 31 (3.23%)	2 / 35 (5.71%)	
occurrences (all)	1	2	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	4 / 31 (12.90%)	5 / 35 (14.29%)	
occurrences (all)	4	5	
Depressed mood			
subjects affected / exposed	2 / 31 (6.45%)	1 / 35 (2.86%)	
occurrences (all)	2	1	
Depression			

subjects affected / exposed	0 / 31 (0.00%)	2 / 35 (5.71%)	
occurrences (all)	0	2	
Insomnia			
subjects affected / exposed	2 / 31 (6.45%)	4 / 35 (11.43%)	
occurrences (all)	3	4	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	3 / 31 (9.68%)	4 / 35 (11.43%)	
occurrences (all)	7	5	
Aspartate aminotransferase increased			
subjects affected / exposed	7 / 31 (22.58%)	1 / 35 (2.86%)	
occurrences (all)	7	1	
Blood bilirubin increased			
subjects affected / exposed	3 / 31 (9.68%)	2 / 35 (5.71%)	
occurrences (all)	4	2	
Blood creatinine increased			
subjects affected / exposed	8 / 31 (25.81%)	2 / 35 (5.71%)	
occurrences (all)	9	3	
Blood sodium decreased			
subjects affected / exposed	1 / 31 (3.23%)	2 / 35 (5.71%)	
occurrences (all)	1	2	
Blood urea increased			
subjects affected / exposed	2 / 31 (6.45%)	1 / 35 (2.86%)	
occurrences (all)	2	1	
Creatinine renal clearance decreased			
subjects affected / exposed	4 / 31 (12.90%)	6 / 35 (17.14%)	
occurrences (all)	6	9	
Ejection fraction decreased			
subjects affected / exposed	0 / 31 (0.00%)	2 / 35 (5.71%)	
occurrences (all)	0	3	
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 31 (0.00%)	2 / 35 (5.71%)	
occurrences (all)	0	2	
Haemoglobin decreased			

subjects affected / exposed occurrences (all)	7 / 31 (22.58%) 9	7 / 35 (20.00%) 11	
Neutrophil count increased subjects affected / exposed occurrences (all)	3 / 31 (9.68%) 3	2 / 35 (5.71%) 2	
Weight decreased subjects affected / exposed occurrences (all)	12 / 31 (38.71%) 12	11 / 35 (31.43%) 11	
White blood cell count decreased subjects affected / exposed occurrences (all)	2 / 31 (6.45%) 2	1 / 35 (2.86%) 2	
Injury, poisoning and procedural complications Procedural pain subjects affected / exposed occurrences (all)	3 / 31 (9.68%) 3	0 / 35 (0.00%) 0	
Radiation mucositis subjects affected / exposed occurrences (all)	5 / 31 (16.13%) 5	4 / 35 (11.43%) 4	
Radiation skin injury subjects affected / exposed occurrences (all)	9 / 31 (29.03%) 9	5 / 35 (14.29%) 5	
Congenital, familial and genetic disorders Aplasia subjects affected / exposed occurrences (all)	2 / 31 (6.45%) 2	0 / 35 (0.00%) 0	
Nervous system disorders Aphonia subjects affected / exposed occurrences (all)	2 / 31 (6.45%) 2	0 / 35 (0.00%) 0	
Dizziness subjects affected / exposed occurrences (all)	2 / 31 (6.45%) 2	3 / 35 (8.57%) 3	
Dysgeusia subjects affected / exposed occurrences (all)	8 / 31 (25.81%) 8	5 / 35 (14.29%) 5	
Headache			

subjects affected / exposed occurrences (all)	6 / 31 (19.35%) 8	6 / 35 (17.14%) 7	
Lethargy subjects affected / exposed occurrences (all)	2 / 31 (6.45%) 2	0 / 35 (0.00%) 0	
Paraesthesia subjects affected / exposed occurrences (all)	2 / 31 (6.45%) 2	3 / 35 (8.57%) 4	
Blood and lymphatic system disorders			
Anaemia subjects affected / exposed occurrences (all)	11 / 31 (35.48%) 11	9 / 35 (25.71%) 10	
Leukocytosis subjects affected / exposed occurrences (all)	0 / 31 (0.00%) 0	2 / 35 (5.71%) 2	
Leukopenia subjects affected / exposed occurrences (all)	7 / 31 (22.58%) 8	5 / 35 (14.29%) 5	
Lymphopenia subjects affected / exposed occurrences (all)	2 / 31 (6.45%) 2	1 / 35 (2.86%) 1	
Neutropenia subjects affected / exposed occurrences (all)	13 / 31 (41.94%) 16	7 / 35 (20.00%) 9	
Thrombocytopenia subjects affected / exposed occurrences (all)	4 / 31 (12.90%) 4	1 / 35 (2.86%) 1	
Ear and labyrinth disorders			
Ear pain subjects affected / exposed occurrences (all)	4 / 31 (12.90%) 8	2 / 35 (5.71%) 3	
Hypoacusis subjects affected / exposed occurrences (all)	0 / 31 (0.00%) 0	3 / 35 (8.57%) 4	
Tinnitus			

subjects affected / exposed	3 / 31 (9.68%)	6 / 35 (17.14%)	
occurrences (all)	4	7	
Vertigo			
subjects affected / exposed	0 / 31 (0.00%)	2 / 35 (5.71%)	
occurrences (all)	0	2	
Gastrointestinal disorders			
Aphagia			
subjects affected / exposed	1 / 31 (3.23%)	2 / 35 (5.71%)	
occurrences (all)	1	2	
Aptyalism			
subjects affected / exposed	1 / 31 (3.23%)	2 / 35 (5.71%)	
occurrences (all)	1	2	
Cheilitis			
subjects affected / exposed	1 / 31 (3.23%)	2 / 35 (5.71%)	
occurrences (all)	1	2	
Constipation			
subjects affected / exposed	13 / 31 (41.94%)	9 / 35 (25.71%)	
occurrences (all)	16	12	
Dental caries			
subjects affected / exposed	0 / 31 (0.00%)	2 / 35 (5.71%)	
occurrences (all)	0	2	
Diarrhoea			
subjects affected / exposed	2 / 31 (6.45%)	18 / 35 (51.43%)	
occurrences (all)	2	53	
Dry mouth			
subjects affected / exposed	13 / 31 (41.94%)	15 / 35 (42.86%)	
occurrences (all)	19	25	
Dyspepsia			
subjects affected / exposed	2 / 31 (6.45%)	4 / 35 (11.43%)	
occurrences (all)	2	5	
Dysphagia			
subjects affected / exposed	11 / 31 (35.48%)	10 / 35 (28.57%)	
occurrences (all)	12	10	
Gastrooesophageal reflux disease			
subjects affected / exposed	3 / 31 (9.68%)	2 / 35 (5.71%)	
occurrences (all)	5	3	

Glossitis			
subjects affected / exposed	0 / 31 (0.00%)	2 / 35 (5.71%)	
occurrences (all)	0	3	
Mouth ulceration			
subjects affected / exposed	1 / 31 (3.23%)	3 / 35 (8.57%)	
occurrences (all)	1	3	
Nausea			
subjects affected / exposed	17 / 31 (54.84%)	22 / 35 (62.86%)	
occurrences (all)	25	40	
Odynophagia			
subjects affected / exposed	9 / 31 (29.03%)	7 / 35 (20.00%)	
occurrences (all)	10	11	
Oral mucosal erythema			
subjects affected / exposed	0 / 31 (0.00%)	2 / 35 (5.71%)	
occurrences (all)	0	4	
Oral pain			
subjects affected / exposed	8 / 31 (25.81%)	7 / 35 (20.00%)	
occurrences (all)	9	7	
Proctalgia			
subjects affected / exposed	2 / 31 (6.45%)	0 / 35 (0.00%)	
occurrences (all)	2	0	
Salivary gland disorder			
subjects affected / exposed	2 / 31 (6.45%)	2 / 35 (5.71%)	
occurrences (all)	2	2	
Stomatitis			
subjects affected / exposed	6 / 31 (19.35%)	5 / 35 (14.29%)	
occurrences (all)	7	5	
Tongue ulceration			
subjects affected / exposed	0 / 31 (0.00%)	3 / 35 (8.57%)	
occurrences (all)	0	3	
Vomiting			
subjects affected / exposed	10 / 31 (32.26%)	14 / 35 (40.00%)	
occurrences (all)	15	25	
Skin and subcutaneous tissue disorders			
Dry skin			

subjects affected / exposed	1 / 31 (3.23%)	3 / 35 (8.57%)	
occurrences (all)	1	3	
Nail disorder			
subjects affected / exposed	0 / 31 (0.00%)	2 / 35 (5.71%)	
occurrences (all)	0	2	
Pruritus			
subjects affected / exposed	2 / 31 (6.45%)	3 / 35 (8.57%)	
occurrences (all)	2	3	
Rash			
subjects affected / exposed	8 / 31 (25.81%)	17 / 35 (48.57%)	
occurrences (all)	12	34	
Skin reaction			
subjects affected / exposed	5 / 31 (16.13%)	8 / 35 (22.86%)	
occurrences (all)	5	8	
Swelling face			
subjects affected / exposed	0 / 31 (0.00%)	2 / 35 (5.71%)	
occurrences (all)	0	2	
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	4 / 31 (12.90%)	1 / 35 (2.86%)	
occurrences (all)	4	1	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	3 / 31 (9.68%)	1 / 35 (2.86%)	
occurrences (all)	3	1	
Neck pain			
subjects affected / exposed	6 / 31 (19.35%)	4 / 35 (11.43%)	
occurrences (all)	8	5	
Trismus			
subjects affected / exposed	1 / 31 (3.23%)	2 / 35 (5.71%)	
occurrences (all)	1	2	
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 31 (3.23%)	2 / 35 (5.71%)	
occurrences (all)	2	4	
Candida infection			

subjects affected / exposed	2 / 31 (6.45%)	0 / 35 (0.00%)
occurrences (all)	2	0
Catheter site infection		
subjects affected / exposed	2 / 31 (6.45%)	0 / 35 (0.00%)
occurrences (all)	2	0
Conjunctivitis		
subjects affected / exposed	0 / 31 (0.00%)	2 / 35 (5.71%)
occurrences (all)	0	2
Fungal infection		
subjects affected / exposed	2 / 31 (6.45%)	1 / 35 (2.86%)
occurrences (all)	2	1
Infection		
subjects affected / exposed	0 / 31 (0.00%)	2 / 35 (5.71%)
occurrences (all)	0	4
Influenza		
subjects affected / exposed	2 / 31 (6.45%)	1 / 35 (2.86%)
occurrences (all)	3	1
Nasopharyngitis		
subjects affected / exposed	1 / 31 (3.23%)	2 / 35 (5.71%)
occurrences (all)	1	6
Oral candidiasis		
subjects affected / exposed	6 / 31 (19.35%)	4 / 35 (11.43%)
occurrences (all)	7	4
Oral fungal infection		
subjects affected / exposed	5 / 31 (16.13%)	3 / 35 (8.57%)
occurrences (all)	6	3
Oral infection		
subjects affected / exposed	2 / 31 (6.45%)	2 / 35 (5.71%)
occurrences (all)	3	2
Rhinitis		
subjects affected / exposed	1 / 31 (3.23%)	2 / 35 (5.71%)
occurrences (all)	1	2
Sinusitis		
subjects affected / exposed	0 / 31 (0.00%)	2 / 35 (5.71%)
occurrences (all)	0	2
Upper respiratory tract infection		

subjects affected / exposed occurrences (all)	3 / 31 (9.68%) 4	1 / 35 (2.86%) 1	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	6 / 31 (19.35%)	4 / 35 (11.43%)	
occurrences (all)	7	4	
Dehydration			
subjects affected / exposed	3 / 31 (9.68%)	0 / 35 (0.00%)	
occurrences (all)	4	0	
Gout			
subjects affected / exposed	0 / 31 (0.00%)	2 / 35 (5.71%)	
occurrences (all)	0	2	
Hyperglycaemia			
subjects affected / exposed	2 / 31 (6.45%)	1 / 35 (2.86%)	
occurrences (all)	2	1	
Hyperkalaemia			
subjects affected / exposed	2 / 31 (6.45%)	0 / 35 (0.00%)	
occurrences (all)	2	0	
Hypokalaemia			
subjects affected / exposed	4 / 31 (12.90%)	7 / 35 (20.00%)	
occurrences (all)	4	7	
Hyponatraemia			
subjects affected / exposed	5 / 31 (16.13%)	4 / 35 (11.43%)	
occurrences (all)	5	4	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 September 2006	Exclude only patients with T1 or T2 disease and N1. Increase the required creatinine clearance of the subjects at entry. Add CR/MRI scans of chest and upper abdomen throughout the study. Add fiberoptic endoscopy during the maintenance period. Implement the recording of alcohol and tobacco use.
14 February 2008	Allow enrollment of subjects with tumours with 2+ ErbB1 expression by immunohistochemistry. Remove the confirmatory scans at 12 weeks. Extend maintenance treatment until disease progression. Allow the use of carboplatin for subjects who cannot tolerate cisplatin (after consultation with the medical monitor). Clarify radiotherapy quality assurance process. Clarify the intended dose of radiotherapy for subjects receiving 2D/3D or IMRT. Clarify PET/CT scan requirements. Clarify screening windows for bone scan and panendoscopy procedures. Clarify the dose modifications required in the event of toxicities. Clarify the dose of concurrent dexamethasone allowed. Change the definition of the evaluable population. Remove the requirement that only subjects in the evaluable population would be treated in the maintenance phase. Remove the serum EGFR assessments. Reduce the radiological assessments during the follow-up phase.
03 July 2008	Amend exclusion criteria 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. Amend inclusion criteria to remove the requirement for EGFR overexpression. Remove the requirement for a plasma sample for proteomic analysis to be taken at withdrawal from study medication. Include interim analysis and amend sample size for decision making purposes. Amend sample size for decision making purposes. Add overall response rate as a secondary endpoint. Change study medication dose reduction and delay instructions.
29 August 2012	Discontinue the blinded phase of the study. Stop the study for patients receiving placebo or in post treatment follow-up. Continue access to active clinical trial medication for subjects ongoing on lapatinib. Discontinue many study specific efficacy and safety assessments. Update to Prohibited Medications, regarding use of PPI. Describe the results of the efficacy and safety analyses of the blinded part of the study.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported