# 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 |

**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/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.

| | |
|---|---|
| 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/m^2 on days 1, 22 and 43 of radiotherapy.

| | |
|---|---|
| **Arm title** | Chemoradiotherapy + Lapatinib, followed by Lapatinib |

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/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.

| | |
|---|---|
| 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/m^2 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 |
|---|---|

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.

| **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 | 56.5 | 55.8 | |
| standard deviation | ± 6.61 | ± 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 |
|---|---|

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 |
|---|---|

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 |

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 >=20% increase in the sum of the longest diameter of target lesions (TLs), or the appearance of >=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 |

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) |

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 |
|---|---|

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 |
|---|---|

End point description:

The number of participants who died due to progressive disease (a >=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 |
|---|---|

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 |
|---|---|

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 |
|---|---|

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 |
|---|---|

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 |
|---|---|

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 |
|---|---|

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 |
|---|---|

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 of 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 inter-quartile 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 |
|---|---|

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 |
|---|---|

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) |

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 >=2+ was considered positive.

| | |
|---|---|
| End point type | Secondary |

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 |
|---|---|

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 |
|---|---|

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 |
|---|---|

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 |
|---|---|

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 |
|---|---|

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 |
|---|---|

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

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 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) |
|---|---|

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 >=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 >=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 |
|---|---|

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 |
|---|---|

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 >=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 >=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 |
|---|---|

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 |
|---|---|

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 |
|---|---|

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 |

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 16.1 |

### 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.

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

| | | | |
|---|---|---|---|
| subjects affected / exposed | 6 / 31 (19.35%) | 6 / 35 (17.14%) | |
| occurrences (all) | 8 | 7 | |
| Lethargy | | | |
| subjects affected / exposed | 2 / 31 (6.45%) | 0 / 35 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Paraesthesia | | | |
| subjects affected / exposed | 2 / 31 (6.45%) | 3 / 35 (8.57%) | |
| occurrences (all) | 2 | 4 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 11 / 31 (35.48%) | 9 / 35 (25.71%) | |
| occurrences (all) | 11 | 10 | |
| Leukocytosis | | | |
| subjects affected / exposed | 0 / 31 (0.00%) | 2 / 35 (5.71%) | |
| occurrences (all) | 0 | 2 | |
| Leukopenia | | | |
| subjects affected / exposed | 7 / 31 (22.58%) | 5 / 35 (14.29%) | |
| occurrences (all) | 8 | 5 | |
| Lymphopenia | | | |
| subjects affected / exposed | 2 / 31 (6.45%) | 1 / 35 (2.86%) | |
| occurrences (all) | 2 | 1 | |
| Neutropenia | | | |
| subjects affected / exposed | 13 / 31 (41.94%) | 7 / 35 (20.00%) | |
| occurrences (all) | 16 | 9 | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 4 / 31 (12.90%) | 1 / 35 (2.86%) | |
| occurrences (all) | 4 | 1 | |
| Ear and labyrinth disorders | | | |
| Ear pain | | | |
| subjects affected / exposed | 4 / 31 (12.90%) | 2 / 35 (5.71%) | |
| occurrences (all) | 8 | 3 | |
| Hypoacusis | | | |
| subjects affected / exposed | 0 / 31 (0.00%) | 3 / 35 (8.57%) | |
| occurrences (all) | 0 | 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 | 3 / 31 (9.68%) | 1 / 35 (2.86%) | |
| occurrences (all) | 4 | 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.<br>Increase the required creatinine clearance of the subjects at entry.<br>Add CR/MRI scans of chest and upper abdomen throughout the study.<br>Add fiberoptic endoscopy during the maintenance period.<br>Implement the recording of alcohol and tobacco use. |
| 14 February 2008 | Allow enrollment of subjects with tumours with 2+ ErbB1 expression by immunohistochemistry.<br>Remove the confirmatory scans at 12 weeks.<br>Extend maintenance treatment until disease progression.<br>Allow the use of carboplatin for subjects who cannot tolerate cisplatin (after consultation with the medical monitor).<br>Clarify radiotherapy quality assurance process.<br>Clarify the intended dose of radiotherapy for subjects receiving 2D/3D or IMRT.<br>Clarify PET/CT scan requirements.<br>Clarify screening windows for bone scan and panendoscopy procedures.<br>Clarify the dose modifications required in the event of toxicities.<br>Clarify the dose of concurrent dexamethasone allowed.<br>Change the definition of the evaluable population.<br>Remove the requirement that only subjects in the evaluable population would be treated in the maintenance phase.<br>Remove the serum EGFR assessments.<br>Reduce the radiological assessments during the follow-up phase. |
| 03 July 2008 | Amend exclusion criteria to exclude patients with active hepatic disease.<br>Add additional SAE definition, reporting criteria and follow-up assessments for hepatic toxicity.<br>Add additional liver function assessments every 4 weeks.<br>Amend inclusion criteria to remove the requirement for EGFR overexpression.<br>Remove the requirement for a plasma sample for proteomic analysis to be taken at withdrawal from study medication.<br>Include interim analysis and amend sample size for decision making purposes.<br>Amend sample size for decision making purposes.<br>Add overall response rate as a secondary endpoint.<br>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.<br>Update to Prohibited Medications, regarding use of PPI.<br>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