Protocol Registration Receipt
04/01/2010

Grantor: CDER IND/IDE Number: 61,362 Serial Number: 0477

A Study Of Lapatinib Versus Placebo Followed By Chemoradiation In Patients With Locally Advanced Head And Neck Cancer

This study has been completed.

Sponsor:	GlaxoSmithKline
Collaborators:	
Information provided by:	GlaxoSmithKline
ClinicalTrials.gov Identifier:	NCT00371566

Purpose

This is a study comparing the activity of lapatinib versus placebo followed by chemoradiation. This study is designed to explore the effects of lapatinib monotherapy on apoptosis/necrosis, in pre-treatment and post-treatment tumour tissue samples in subjects with locally advanced squamous cell carcinoma of head and neck.

Condition	Intervention	Phase
Squamous Cell Carcinoma of Head and	Drug: Lapatinib oral tablets	Phase 2

Condition	Intervention	Phase
Neck	Drug: Placebo	

Study Type: Interventional
Study Design: Treatment, Parallel Assignment, Single Blind, Randomized, Safety/Efficacy Study
Official Title: A Randomized, Single Blinded, Placebo-controlled, Multi-centre, Phase II Study of Lapatinib in Patients With Locally Advanced Squamous Cell Carcinoma of the Head and Neck (SCCHN)

Further study details as provided by GlaxoSmithKline:

Primary Outcome Measure:

- Change From Baseline of the Apoptotic Index During Treatment Phase [Time Frame: Baseline and Week 2] [Designated as safety issue: No]
  Apoptotic Index-TUNEL Assay is a method which counts a total of at least 1000 neoplastic nuclei(Cells with morphological changes defining cell death) subdivided in 10 fields chosen randomly at 400x magnification. A 'responder' was defined as having 20% cell death.

Secondary Outcome Measures:

- Change From Baseline of Cell Proliferation Rate of the Ki-67 Proliferative Index in Tumour Biopsy Samples During Treatment Phase [Time Frame: Baseline and Week 2] [Designated as safety issue: No]
  The Ki-67 protein is expressed in all phases of the cell cycle except G0 (low level phase) and serves as a good marker for cell proliferation. Scoring is assessed by point counting 500 to 1000 cells, and is reported as percent positive cells. 20% positive cells to define "positive" (i.e. high risk)
- Overall Radiological Response After Treatment Phase in mITT Population [Time Frame: Baseline and End of Treatment (Week 2 - 6)] [Designated as safety issue: No]
  Over all: Complete Response (CR)- absence of lesions. Partial Response (PR)- CR or PR of target lesions and incomplete response (IC) or stable disease (SD) in other lesions with no new lesions or progressive disease (PD). Stable Disease (SD)-no PD or Response. Progressive Disease (PD)-PD or new lesions. Not Evaluable(NE)- no other definitions. Number of subjects included those who had a scan immediately post lapatanib/placebo monotherapy.
- Overall Radiological Response After Follow-up Phase in mITT Population [Time Frame: Baseline and End of Follow-up (Week 19 - 25)] [Designated as safety issue: No]
  Over all: Complete Response(CR)-absence of lesions. Partial Response(PR)- CR or PR of target lesions and incomplete response (IC) or stable disease (SD)in other lesions with no new lesions or progressive disease (PD). Stable Disease(SD)-no PD or Response. Progressive Disease(PD)-PD or new lesions. Not Evaluable(NE)- no other definitions. Number of subjects included those who were considered evaluable if they completed a full course of chemoradiotherapy and were able to provide a baseline and follow-up scan following the completion of chemoradiation.
- Overall Radiological Response After Treatment Phase in ITT Population [Time Frame: Baseline and End of Treatment (Week 2 - 6)] [Designated as safety issue: No]
  Over all: Complete Response (CR)-absence of lesions. Partial Response (PR)- CR or PR of target lesions and incomplete response (IC) or stable

disease (SD) in other lesions with no new lesions or progressive disease (PD). Stable Disease (SD)-no PD or Response. Progressive Disease (PD)-PD or new lesions. Not Evaluable(NE)- no other definitions.

- Overall Radiological Response After Follow-up Phase in ITT Population [Time Frame: Baseline and End of Follow-up (week 19 - 25)] [Designated as safety issue: No]

  Over all: Complete Response (CR) - absence of lesions. Partial Response (PR) - CR or PR of target lesions and incomplete response (IC) or stable disease (SD) in other lesions with no new lesions or progressive disease (PD). Stable Disease (SD)- no PD or Response. Progressive Disease (PD)- PD or new lesions. Not Evaluable(NE)- no other definitions.
- Number of Circulating Tumor Cells at Baseline in mITT Population [Time Frame: Baseline] [Designated as safety issue: No]

  This measures the participants with Circulating Tumor Cells (CTC's)Pre-Treatment numbers of 0 to >= 4. CTC's are tumor cells that escape from the primary tumor into the bloodstream and travel through the circulation to distant sites where they develop into secondary tumors.
- Number of Participants With Circulating Tumor Cells After Treatment Phase in mITT Population [Time Frame: End of Treatment (week 2 - 6)] [Designated as safety issue: No]

  This measures the participants with Circulating Tumor Cells (CTC's) after treatment numbers of 0 to >= 4. CTC's are tumor cells that escape from the primary tumor into the bloodstream and travel through the circulation to distant sites where they develop into secondary tumors.
- Number of Participants With Circulating Tumor Cells After Chemoradiotherapy Phase in mITT Population [Time Frame: End of Chemoradiotherapy (week 10 - 13)] [Designated as safety issue: No]

  This measures the participants with Circulating Tumor Cells (CTC's) after chemoradiotherapy numbers of 0 to >= 4. CTC's are tumor cells that escape from the primary tumor into the bloodstream and travel through the circulation to distant sites where they develop into secondary tumors.
- Number of Biomarkers Including ErbB1, ErbB2, pErbB1, and pErb2 at Baseline and During Treatment Phase [Time Frame: Baseline and Week 2] [Designated as safety issue: No]

  Estrogen Receptor (ER) variants, ERB-B2 and ERB B-5 consist of the major proportion of ER expression both in normal and cancer tissues. The exact role of these markers are unknown. Acronyms defined: ICH (immunohistochemical) and FISH (fluorescence in situ hybridization).
- Number of Biomarkers Including Tumor Protein 53 and HPV During Treatment Phase [Time Frame: Week 2] [Designated as safety issue: No]

  Tumor Suppressor p53 is welcomed and described as "the guardian angel gene," it conserves stability by preventing genome mutation. Human Papillomavirus (HPV) biomarker is un-welcomed and is found to be an important precursor cancers of the head and neck. HPV biomarkers have the ability to bind to and inactivate the Tumor Suppressor p53 biomarker.
- Summary of Adverse Events by Maximum Toxicity Grade Started During Treatment Phase [Time Frame: Week 1 through Week 6] [Designated as safety issue: No]

  Toxicity Grading scale 0=none, 1=transient symptom, 2=mild symptom that does not interfere with activities of daily living (ADL's) 3=mild but interfers with ADL's w/o hospitalization. 4=requires hopitalization 5=Death.
- Summary of Adverse Events by Maximum Toxicity Grade (Grade 3 or Higher) Started During or After the Chemoradiotherapy Phase [Time Frame: Week 10 through 25] [Designated as safety issue: No]

  Toxicity Grading scale 0=none, 1= transient symptom, 2=mild symptom that does not interfere with activities of daily living (ADL's) 3=mild but interfers with ADL's w/o hospitalization. 4=requires hopitalization 5=Death.
- Comparison of Overall Response During Treatment Phase Using CT/MRI and PET Information [Time Frame: Week 2 - 4] [Designated as safety issue: No]

Position Emission Tomography (PET) scans 3-D images are read alongside CT or magnetic resonance imaging (MRI) scans, the combination gives both anatomic and metabolic information. CT = Computerized axial tomography; a type of x-ray for dense areas of the body. MRI = Magnetic Resonance Imaging which captures a picture using Magnets. Better = improvement in response, Worse = response was downgraded.

- Comparison of Overall Response During Follow up Phase Using CT/MRI and PET Information [Time Frame: weeks 19 - 25] [Designated as safety issue: No]

  Position Emission Tomography (PET) scans 3-D images are read alongside CT or magnetic resonance imaging (MRI) scans, the combination gives both anatomic and metabolic information. CT = Computerized axial tomography; a type of x-ray for dense areas of the body. MRI = Magnetic Resonance Imaging which captures a picture using Magnets. Better = improvement in response, Worse = response was downgraded.
- Summary of Adverse Events Experienced by 15% or More Subjects in Either Treatment Group [Time Frame: Week 1 through 25] [Designated as safety issue: No]

  Definition of an adverse event is any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.
- Summary of Fatal/Serious Adverse Events During or After Chemoradiotherapy Phase [Time Frame: Week 10 through 25] [Designated as safety issue: No]

  Events which started during or After the Chemoradiotherapy Phase. Definition of a serious adverse event is any untoward medicinal occurrence that, at any dose, results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in disability/incapacity, is a congenital anomaly/birth defect, other.
- Summary of Serious Adverse Events During or After Chemoradiotherapy Phase [Time Frame: Week 10 through 25] [Designated as safety issue: No]

  Events which started during or After Chemoradiotherapy Phase. Definition of a serious adverse event is any untoward medicinal occurrence that, at any dose, results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in disability/incapacity, is a congenital anomaly/birth defect, other.
- Adverse Events by Maximum Toxicity Grade 3 During or After Chemoradiotherapy Phase [Time Frame: Week 10 through 25] [Designated as safety issue: No]

  Events which started during or after Chemoradiotherapy Phase. "Grade 3" are severe and undesirable Adverse Event (significant symptoms requiring hospitalization or invasive intervention; transfusion; elective interventional radiological procedure; therapeutic endoscopy or operation).
- Adverse Events (AEs) by Maximum Toxicity Grade 4 During or After Chemoradiotherapy Phase [Time Frame: Week 10 through 25] [Designated as safety issue: No]

  Events which started during or after Chemoradiotherapy Phase. "Grade 4" are life-threatening or disabling Adverse Event (complicated by acute, life-threatening metabolic or cardiovascular complications such as circulatory failure, hemorrhage, sepsis. Life-threatening physiologic consequences; need for intensive care or emergent invasive procedure; emergent interventional radiological procedure, therapeutic endoscopy or operation).
- Adverse Events by Maximum Toxicity Grade 5 During or After Chemoradiotherapy Phase [Time Frame: Week 10 through 25] [Designated as safety issue: No]

  Events which started during or after Chemoradiotherapy Phase. "Grade 5" are death related to Adverse Event.
- Relative Change From Baseline of Ktrans Median (1/Min) After 2 - 4 Weeks of Treatment [Time Frame: Baseline, and Week 2 - 4] [Designated as safety issue: No]

  Dynamic Contrast enhanced Magnetic Resonance Imaging (DCE-MRI) tracks the diffusion of an administered contrast agent from -intra into the

extravascular tissue over time. Ktrans estimates blood flow and relates to the ease of exchange into extravascular spaces. A volume transfer (i.e, 1/min) constant of contrast agent is used to determine vascular permeability. By plugging DCE-MRI results into an appropriate pharmacokinetic model, physiological parameters of the tumor (e.g.,tissue perfusion, vessel permeability, vascular surface area, and extracellular/vascular volume fraction) are determined.

- Relative Change From Baseline of Kep Mean (1/Min) After 2 - 4 Weeks of Treatment [Time Frame: Baseline, and Week 2 - 4] [Designated as safety issue: No]

  DCE-MRI tracks the diffusion of an intravascularly administered contrast agent into the extravascular tissue over time. Over a period of time, the contrast agent diffuses back into the vasculature (described by the rate constant or Kep). The lower the Kep, the longer the contrast remains in the extravascular space and is more prolonged. A volume transfer (i.e, 1/min) constant of contrast agent is used to determine vascular permeability. By plugging DCE-MRI results into an appropriate pharmacokinetic model, physiological parameters of the tumor (e.g., vessel permeability, etc.) are determined.
- Relative Change From Baseline of Kep Perfused (1/Min) After 2 - 4 Weeks of Treatment [Time Frame: Baseline, and Week 2 - 4] [Designated as safety issue: No]

  DCE-MRI tracks the diffusion of an intravascularly administered contrast agent into the extravascular tissue over time. Over a period of time, the contrast agent diffuses back into the vasculature (described by the rate constant or Kep). The lower the Kep, the longer the contrast remains in the extravascular space and is more prolonged. A volume transfer (i.e, 1/min) constant of contrast agent is used to determine vascular permeability. By plugging DCE-MRI results into an appropriate pharmacokinetic model, physiological parameters of the tumor (e.g., vessel permeability, etc.) are determined.
- Relative Change From Baseline of Kep Whole (1/Min) After 2 - 4 Weeks of Treatment [Time Frame: Baseline, and Week 2 - 4] [Designated as safety issue: No]

  DCE-MRI tracks the diffusion of an intravascularly administered contrast agent into the extravascular tissue over time. Over a period of time, the contrast agent diffuses back into the vasculature (described by the rate constant or Kep). The lower the Kep, the longer the contrast remains in the extravascular space and is more prolonged. A volume transfer (i.e, 1/min) constant of contrast agent is used to determine vascular permeability. By plugging DCE-MRI results into an appropriate pharmacokinetic model, physiological parameters of the tumor (e.g., vessel permeability, etc.) are determined.
- Relative Change From Baseline of Ktrans Mean (1/Min) After 2 - 4 Weeks of Treatment [Time Frame: Baseline, and Week 2 - 4] [Designated as safety issue: No]

  Dynamic Contrast enhanced Magnetic Resonance Imaging (DCE-MRI) tracks the diffusion of an administered contrast agent from -intra into the extravascular tissue over time. Ktrans estimates blood flow and relates to the ease of exchange into extravascular spaces. A volume transfer (i.e, 1/min) constant of contrast agent is used to determine vascular permeability. By plugging DCE-MRI results into an appropriate pharmacokinetic model, physiological parameters of the tumor (e.g.,tissue perfusion, vessel permeability, vascular surface area, and extracellular/vascular volume fraction) are determined.
- Relative Change From Baseline of Ktrans Perfused (1/Min) After 2 - 4 Weeks of Treatment [Time Frame: Baseline, and Week 2 - 4] [Designated as safety issue: No]

  Dynamic Contrast enhanced Magnetic Resonance Imaging (DCE-MRI) tracks the diffusion of an administered contrast agent from -intra into the extravascular tissue over time. Ktrans estimates blood flow and relates to the ease of exchange into extravascular spaces. A volume transfer (i.e, 1/min) constant of contrast agent is used to determine vascular permeability. By plugging DCE-MRI results into an appropriate pharmacokinetic model, physiological parameters of the tumor (e.g.,tissue perfusion, vessel permeability, vascular surface area, and extracellular/vascular volume fraction) are

determined.

- Relative Change From Baseline of Ktrans Whole (1/Min) After 2 - 4 Weeks of Treatment [Time Frame: Baseline, and Week 2 - 4] [Designated as safety issue: No]

  Dynamic Contrast enhanced Magnetic Resonance Imaging (DCE-MRI) tracks the diffusion of an administered contrast agent from -intra into the extravascular tissue over time. Ktrans estimates blood flow and relates to the ease of exchange into extravascular spaces. A volume transfer (i.e, 1/min) constant of contrast agent is used to determine vascular permeability. By plugging DCE-MRI results into an appropriate pharmacokinetic model, physiological parameters of the tumor (e.g.,tissue perfusion, vessel permeability, vascular surface area, and extracellular/vascular volume fraction) are determined.

- Relative Change From Baseline of IAUC Median (90) After 2 - 4 Weeks of Treatment [Time Frame: Baseline, and Week 2 - 4] [Designated as safety issue: No]

  Dynamic Contrast - enhanced Magnetic Resonance Imaging (DCE-MRI) tracks the diffusion of an intravascularly administered contrast agent from intravascular into the extravascular tissue over time. Initial area under the contrast (IAUC), tracks the concentration versus time curve 90 seconds after contrast injection (IAUC90). By plugging DCE-MRI results into an appropriate pharmacokinetic model, physiological parameters of the tumor microenvironment (e.g., tissue perfusion, vessel permeability, vascular surface area, and extracellular-extra vascular volume fraction) are determined.

- Relative Change From Baseline of IAUC Mean (90) After 2 - 4 Weeks of Treatment [Time Frame: Baseline, and Week 2 - 4] [Designated as safety issue: No]

  Dynamic Contrast - enhanced Magnetic Resonance Imaging (DCE-MRI) tracks the diffusion of an intravascularly administered contrast agent from intravascular into the extravascular tissue over time. Initial area under the contrast (IAUC), tracks the concentration versus time curve 90 seconds after contrast injection (IAUC90). By plugging DCE-MRI results into an appropriate pharmacokinetic model, physiological parameters of the tumor microenvironment (e.g., tissue perfusion, vessel permeability, vascular surface area, and extracellular-extra vascular volume fraction) are determined.

- Relative Change From Baseline of Perfused IAUC (90) After 2 - 4 Weeks of Treatment [Time Frame: Baseline, and Week 2 - 4] [Designated as safety issue: No]

  Dynamic Contrast - enhanced Magnetic Resonance Imaging (DCE-MRI) tracks the diffusion of an intravascularly administered contrast agent from intravascular into the extravascular tissue over time. Initial area under the contrast (IAUC), tracks the concentration versus time curve 90 seconds after contrast injection (IAUC90). By plugging DCE-MRI results into an appropriate pharmacokinetic model, physiological parameters of the tumor microenvironment (e.g., tissue perfusion, vessel permeability, vascular surface area, and extracellular-extra vascular volume fraction) are determined.

- Relative Change From Baseline of Whole IAUC(90) After 2 - 4 Weeks of Treatment [Time Frame: Baseline, and Week 2 - 4] [Designated as safety issue: No]

  Dynamic Contrast - enhanced Magnetic Resonance Imaging (DCE-MRI) tracks the diffusion of an intravascularly administered contrast agent from intravascular into the extravascular tissue over time. Initial area under the contrast (IAUC), tracks the concentration versus time curve 90 seconds after contrast injection (IAUC90). By plugging DCE-MRI results into an appropriate pharmacokinetic model, physiological parameters of the tumor microenvironment (e.g., tissue perfusion, vessel permeability, vascular surface area, and extracellular-extra vascular volume fraction) are determined.

- Relative Change From Baseline of Kep Median (1/Min) After 2 - 4 Weeks of Treatment [Time Frame: Baseline, and Week 2 - 4] [Designated as safety issue: No]

  DCE-MRI tracks the diffusion of an intravascularly administered contrast agent into the extravascular tissue over time. Over a period of time, the contrast

agent diffuses back into the vasculature (described by the rate constant or Kep). The lower the Kep, the longer the contrast remains in the extravascular space and is more prolonged. A volume transfer (i.e, 1/min) constant of contrast agent is used to determine vascular permeability. By plugging DCE-MRI results into an appropriate pharmacokinetic model, physiological parameters of the tumor (e.g., vessel permeability, etc.) are determined.

Enrollment: 107
Study Start Date: March 2006
Study Completion Date: December 2007
Primary Completion Date: December 2007

Arms	Assigned Interventions
Experimental: Lapatinib	Drug: Lapatinib oral tablets Other Names: Lapatinib oral tablets platinum - based chemotherapy radiotherapy
Placebo Comparator: Placebo	Drug: Placebo

Eligibility

Ages Eligible for Study: 18 Years and older
Genders Eligible for Study: Both

Inclusion criteria:

- Willing and able to sign a written informed consent.
- Histologically or cytologically confirmed diagnosis of SCCHN.
- Stage III, IVA and IVB disease will be eligible, who are to receive chemoradiation therapy as primary treatment (total dose ≥ 65 Gy). Subjects with distant metastases (stage IVC) will be excluded.
- Willing and able to have a tumour biopsy taken at screening and a second tumour biopsy taken during lapatinib/placebo administration.
- Male or female ≥18 years of age.

Criteria for female subjects or female partners of male subjects: Non-child-bearing potential (i.e., women with functioning ovaries who have a current documented tubal ligation or hysterectomy, or women who are postmenopausal); Child-bearing potential (i.e., women with functioning ovaries and no documented impairment of oviductal or uterine function that would cause sterility.) This category includes women with oligomenorrhoea (severe), women who are perimenopausal, and

young women who have begun to menstruate. These subjects must have a negative serum pregnancy test at screening and agree to one of the following:

Complete abstinence from intercourse from 2 weeks prior to administration of the first dose of study medication until 28 days after the final dose of study medication; or

Consistent and correct use of one of the following acceptable methods of birth control:

male partner who is sterile prior to the female subject's entry into the study and is the sole sexual partner for that female subject; implants of levonorgestrel; injectable progestogen; any intrauterine device (IUD) with a documented failure rate of less than 1% per year; oral contraceptives (either combined or progestogen only); or barrier methods, including diaphragm or condom with a spermicide.

- Eastern Cooperative Oncology Group (ECOG) performance status 0, 1 or 2.
- Subjects must have adequate haematological, renal and hepatic function. Calculated creatinine clearance ≥50 ml/min as determined by the method of Cockcroft and Gault [Cockcroft, 1976] or by the EDTA method.

Absolute neutrophil count ≥1,500/µl, platelets ≥100,000/µl. Haemoglobin ≥9gm/dL (5mmol/L). Aspartate (AST) and alanine transaminase (ALT) less than three times the upper limit of the normal range (ULN).

Total bilirubin ≤2.0 mg/dL.

- Left ventricular ejection fraction (LVEF) within the institutional normal ranges as measured by echocardiogram (ECHO) or Multigated Acquisition (MUGA) scans.
- Able to swallow tablet whole or swallow a suspension of the tablet dissolved in water at study inclusion. If necessary, the suspension may be administered via percutaneous endoscopic gastrostomy (PEG), percutaneous jejunostomy tube (JTube), or a nasogastric tube (NG or Dobhoff type tube).
- Life expectancy of at least 6 months as judged by the investigator.

Exclusion criteria:

- Subjects with paranasal sinuses, nasopharyngeal and nasal cavity tumours;
- Subjects who have received prior systemic chemotherapy given with curative intent;
- Subjects who received prior radiotherapy;
- Prior or concurrent treatment with tyrosine kinase inhibitors;
- Use of any investigational agent within 30 days or 5 half-lives, whichever is longer, preceding the first dose of lapatinib;
- Concurrent use of CYP3A4 inducers or inhibitors;
- Subjects with known history of uncontrolled or symptomatic angina, arrhythmias, or congestive heart failure;
- History of another malignancy within the last 5 years, with the exception of completely resected basal or squamous cell skin cancer, or successfully treated in situ carcinoma. History of non-invasive lesion or in-situ carcinoma of head and neck that was successfully treated with surgery, photodynamics or laser, will be permitted;
- Distant metastases, ie Stage IVC;
- Females or males of child-bearing potential who are sexually active, if they do not agree to practice an effective method of contraception. (For example oral

contraceptives, IUD or diaphragm plus spermicide);

- Pregnant or lactating females (female patients of childbearing potential will undertake pregnancy testing at screening and during study completion/withdrawal visits);
- Malabsorption syndrome, disease significantly affecting GI function, that could affect absorption of lapatinib;
- History of allergic reactions to appropriate diuretics or antiemetics (e.g. 5-HT3 antagonists) to be administered with platinum-based chemotherapy;
- The investigator considers the patient unfit for the study as a result of the medical interview, physical examinations, or screening investigations;
- Subjects taking any prohibited medication (See Section 8.2)

Other Eligibility Criteria Considerations:

To assess any potential impact on subject eligibility with regard to safety, the investigator must refer to the following document(s) for detailed information regarding warnings,precautions, contraindications, adverse events, and other significant data pertaining to the investigational product(s) being used in this study: investigator's brochure IB and any IB supplements, and expedited investigator safety reports

Contacts and Locations

Locations

France

GSK Investigational Site
Caen, France, 14076

GSK Investigational Site
Montpellier Cedex 5, France, 34298

GSK Investigational Site
Villejuif Cedex, France, 94805

Greece

GSK Investigational Site
Athens, Greece, 142 33

India

GSK Investigational Site
Bangalore, India, 560029

GSK Investigational Site
Thiruvananthapuram, India, 695 011

Peru

GSK Investigational Site
Lima, Lima, Peru, Lima 34

Spain

GSK Investigational Site
Barcelona, Spain, 08035
GSK Investigational Site
Madrid, Spain, 28041

Investigators

Study Director:	GSK Clinical Trials, MD, PhD	GlaxoSmithKline

More Information

Responsible Party:	GSK (Study Director)
Study ID Numbers:	EGF104334
Health Authority:	United States: Food and Drug Administration Spain: Spanish Agency of Medicines

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Study Results

Participant Flow

Reporting Groups

	Description
Placebo	Subjects who were given Placebo for 2 to 6 weeks followed by 4 weeks of standard treatment of radiotherapy (of more than or equal to 65 Gy) and concurrent platinum-based Chemotherapy (based on the institutions standard of care)
Lapatinib	Subjects who were given once daily dose of oral lapatinib 1500 mg for 2 -6 weeks, followed by 4 weeks of standard treatment of radiotherapy (of more than or equal to 65 Gy) and concurrent platinum-based

	Description
	chemotherapy (based on the institutions standard care).

Treatment Phase

	Placebo	Lapatinib
Started	36	71
Completed	36	68 [1]
Not Completed	0	3
Withdrawal by Subject	0	1
Adverse Event	0	1
Protocol Violation	0	1

[1] 1 screen failure included in the ITT population

Chemoradiation Phase

	Placebo	Lapatinib
Started	36	68
Completed	31	65
Not Completed	5	3
Physician Decision	2	0
Withdrawal by Subject	0	1
Non compliant	0	1
Progressive Disease	1	1
Death	2	0

Follow Up Phase

	Placebo	Lapatinib
Started	31	65
Completed	28	58
Not Completed	3	7
Death	0	5
Disease progression	1	0
Withdrawal by Subject	0	1
Physician Decision	1	1
Lost to Follow-up	1	0

Baseline Characteristics

Reporting Groups

	Description
Placebo	Subjects who were given Placebo for 2 to 6 weeks followed by 4 weeks of standard treatment of radiotherapy (of more than or equal to 65 Gy) and concurrent platinum-based Chemotherapy (based on the intitutions standard of care)
Lapatinib	Subjects who were given once daily dose of oral lapatinib 1500 mg for 2 -6 weeks, followed by 4 weeks of standard treatment of radiotherapy (of more than or equal to 65 Gy) and concurrent platinum-based chemotherapy (based on the institutions standard care).

Baseline Measures

	Placebo	Lapatinib	Total
Number of Participants	36	71	107
Age, Continuous [units: years] Mean (Standard Deviation)	56.2 (10.47)	57.7 (11.01)	57.1 (10.83)
Gender, Male/Female [units: participants]			
Female	4	16	20
Male	32	55	87
Race/Ethnicity, Customized [units: participants]			
White	21	39	60
African American	0	0	0
American Indian or Alaska Native	3	11	14
Asian-Central and South Asian Heritage	9	19	28
Asian-Japanese East/South east Heritage	2	2	4
Asian-Mixed Heritage	1	0	1
Native Hawaiian or Pacific Islander	0	0	0

Outcome Measures

1. Primary Outcome Measure:

Measure Title	Change From Baseline of the Apoptotic Index During Treatment Phase
Measure Description	Apoptotic Index-TUNEL Assay is a method which counts a total of at least 1000 neoplastic nuclei(Cells with morphological changes defining cell death) subdivided in 10 fields chosen randomly at 400x magnification. A ‘responder’ was defined as having 20% cell death.
Time Frame	Baseline and Week 2
Safety Issue?	No

Analysis Population Description

The Intent-to-treat (ITT) population comprised of all subjects who were randomised to study treatment, regardless of whether they actually received study medication.

Reporting Groups

	Description
Placebo	Subjects who were given Placebo for 2 to 6 weeks followed by 4 weeks of standard treatment of radiotherapy (of more than or equal to 65 Gy) and concurrent platinum-based Chemotherapy (based on the intitutions standard of care)
Lapatinib	Subjects who were given once daily dose of oral lapatinib 1500 mg for 2 -6 weeks, followed by 4 weeks of standard treatment of radiotherapy (of more than or equal to 65 Gy) and concurrent platinum-based chemotherapy (based on the institutions standard care).

Measured Values

	Placebo	Lapatinib
Number of Participants Analyzed	27	57
Change From Baseline of the Apoptotic	6.2 (12.10)	4.2 (5.53)

	Placebo	Lapatinib
Index During Treatment Phase [units: Percentage of positive cells] Mean (Standard Deviation)		

Statistical Analysis 1 for Change From Baseline of the Apoptotic Index During Treatment Phase

Groups	Placebo, Lapatinib
Method	ANCOVA
P-Value	.394
Mean Difference (Net)	-1.7
Standard Deviation	± 1.93
95% Confidence Interval	-5.50 to 2.19

Additional details about the analysis, such as null hypothesis and power calculation:

The study was designed to provide evidence to support the null hypothesis: Delta equals 0% or reject it in favor of the two sided alternative hypothesis: Delta does not equal 0%, where Delta was the difference in the true response rate for the two treatment groups.

Additional information, such as whether or not the p-value is adjusted for multiple comparisons and the a priori threshold for statistical significance:

[Not specified.]

Other relevant information, such as adjustments or degrees of freedom:

Null hypothesis or reject it in favor of the two sided alternative hypothesis

2. Secondary Outcome Measure:

Measure Title	Change From Baseline of Cell Proliferation Rate of the Ki-67 Proliferative Index in Tumour Biopsy Samples During Treatment Phase

Measure Description	The Ki-67 protein is expressed in all phases of the cell cycle except G0 (low level phase) and serves as a good marker for cell proliferation. Scoring is assessed by point counting 500 to 1000 cells, and is reported as percent positive cells. 20% positive cells to define “positive” (i.e. high risk)
Time Frame	Baseline and Week 2
Safety Issue?	No

Analysis Population Description

The mITT (modified Intent-to-Treat) population consisted of all subjects who were randomised to study treatment, did not miss lapatinib/placebo treatment for more than 7 consecutive days and had provided sufficient tumor biopsy sample for the primary endpoint analysis.

Reporting Groups

	Description
Placebo	Subjects who were given Placebo for 2 to 6 weeks followed by 4 weeks of standard treatment of radiotherapy (of more than or equal to 65 Gy) and concurrent platinum-based Chemotherapy (based on the intitutions standard of care)
Lapatinib	Subjects who were given once daily dose of oral lapatinib 1500 mg for 2 -6 weeks, followed by 4 weeks of standard treatment of radiotherapy (of more than or equal to 65 Gy) and concurrent platinum-based chemotherapy (based on the institutions standard care).

Measured Values

	Placebo	Lapatinib
Number of Participants Analyzed	27	57
Change From Baseline of Cell Proliferation Rate of the Ki-67 Proliferative Index in Tumour Biopsy Samples During	-1.2 (7.90)	-5.6 (12.53)

	Placebo	Lapatinib
Treatment Phase [units: Percent of positive cells] Mean (Standard Deviation)		

3. Secondary Outcome Measure:

Measure Title	Overall Radiological Response After Treatment Phase in mITT Population
Measure Description	Over all: Complete Response (CR)– absence of lesions. Partial Response (PR)- CR or PR of target lesions and incomplete response (IC) or stable disease (SD) in other lesions with no new lesions or progressive disease (PD). Stable Disease (SD)–no PD or Response. Progressive Disease (PD)–PD or new lesions. Not Evaluable(NE)– no other definitions. Number of subjects included those who had a scan immediately post lapatanib/placebo monotherapy.
Time Frame	Baseline and End of Treatment (Week 2 - 6)
Safety Issue?	No

Analysis Population Description

The mITT population consisted of all subjects who were randomised to study treatment, did not miss lapatinib/placebo treatment for more than 7 consecutive days and had provided sufficient tumour biopsy sample for the primary endpoint analysis.

Reporting Groups

	Description
Placebo	Subjects who were given Placebo for 2 to 6 weeks followed by 4 weeks of standard treatment of radiotherapy (of more than or equal to 65 Gy) and concurrent platinum-based Chemotherapy (based on the intitutions standard of care)

	Description
Lapatinib	Subjects who were given once daily dose of oral lapatinib 1500 mg for 2 -6 weeks, followed by 4 weeks of standard treatment of radiotherapy (of more than or equal to 65 Gy) and concurrent platinum-based chemotherapy (based on the institutions standard care).

Measured Values

	Placebo	Lapatinib
Number of Participants Analyzed	12	20
Overall Radiological Response After Treatment Phase in mITT Population [units: Participants]		
Complete Response	0	1
Partial Response	0	3
Stable Disease	10	12
Progressive Disease	2	0
Non-Evaluable	0	4

4. Secondary Outcome Measure:

Measure Title	Overall Radiological Response After Follow-up Phase in mITT Population
Measure Description	Over all: Complete Response(CR)–absence of lesions. Partial Response(PR)- CR or PR of target lesions and incomplete response (IC) or stable disease (SD)in other lesions with no new lesions or progressive disease (PD). Stable Disease(SD)–no PD or Response. Progressive Disease(PD)–PD or new lesions. Not Evaluable(NE)– no other definitions. Number of subjects included those who were

	considered evaluable if they completed a full course of chemoradiotherapy and were able to provide a baseline and follow-up scan following the completion of chemoradiation.
Time Frame	Baseline and End of Follow-up (Week 19 - 25)
Safety Issue?	No

Analysis Population Description

The mITT population consisted of all subjects who were randomised to study treatment, did not miss lapatinib/placebo treatment for more than 7 consecutive days and had provided sufficient tumour biopsy sample for the primary endpoint analysis.

Reporting Groups

	Description
Placebo	Subjects who were given Placebo for 2 to 6 weeks followed by 4 weeks of standard treatment of radiotherapy (of more than or equal to 65 Gy) and concurrent platinum-based Chemotherapy (based on the intitutions standard of care)
Lapatinib	Subjects who were given once daily dose of oral lapatinib 1500 mg for 2 -6 weeks, followed by 4 weeks of standard treatment of radiotherapy (of more than or equal to 65 Gy) and concurrent platinum-based chemotherapy (based on the institutions standard care).

Measured Values

	Placebo	Lapatinib
Number of Participants Analyzed	23	47
Overall Radiological Response After Follow-up Phase in mITT Population [units: Participants]		
Complete Response	2	11

	Placebo	Lapatinib
Partial Response	13	29
Stable Disease	2	3
Progressive Disease	6	4

5. Secondary Outcome Measure:

Measure Title	Overall Radiological Response After Treatment Phase in ITT Population
Measure Description	Over all: Complete Response (CR)–absence of lesions. Partial Response (PR)- CR or PR of target lesions and incomplete response (IC) or stable disease (SD) in other lesions with no new lesions or progressive disease (PD). Stable Disease (SD)–no PD or Response. Progressive Disease (PD)–PD or new lesions. Not Evaluable(NE)– no other definitions.
Time Frame	Baseline and End of Treatment (Week 2 - 6)
Safety Issue?	No

Analysis Population Description

The Intent-to-treat (ITT) population comprised of all subjects who were randomised to study treatment, regardless of whether they actually received study medication.

Reporting Groups

	Description
Placebo	Subjects who were given Placebo for 2 to 6 weeks followed by 4 weeks of standard treatment of radiotherapy (of more than or equal to 65 Gy) and concurrent platinum-based Chemotherapy (based on the intitutions standard of care)

	Description
Lapatinib	Subjects who were given once daily dose of oral lapatinib 1500 mg for 2 -6 weeks, followed by 4 weeks of standard treatment of radiotherapy (of more than or equal to 65 Gy) and concurrent platinum-based chemotherapy (based on the institutions standard care).

Measured Values

	Placebo	Lapatinib
Number of Participants Analyzed	16	24
Overall Radiological Response After Treatment Phase in ITT Population [units: Participants]		
Complete Response	0	1
Partial Response	0	3
Stable Disease	12	15
Progressive Disease	4	0
Non-Evaluable	0	5

6. Secondary Outcome Measure:

Measure Title	Overall Radiological Response After Follow-up Phase in ITT Population
Measure Description	Over all: Complete Response (CR) – absence of lesions. Partial Response (PR) - CR or PR of target lesions and incomplete response (IC) or stable disease (SD) in other lesions with no new lesions or progressive disease (PD). Stable Disease (SD)– no PD or Response. Progressive Disease (PD)– PD or new lesions. Not Evaluable(NE)– no other definitions.

Time Frame	Baseline and End of Follow-up (week 19 - 25)
Safety Issue?	No

Analysis Population Description

The Intent-to-treat (ITT) population comprised of all subjects who were randomised to study treatment, regardless of whether they actually received study medication.

Reporting Groups

	Description
Placebo	Subjects who were given Placebo for 2 to 6 weeks followed by 4 weeks of standard treatment of radiotherapy (of more than or equal to 65 Gy) and concurrent platinum-based Chemotherapy (based on the intitutions standard of care)
Lapatinib	Subjects who were given once daily dose of oral lapatinib 1500 mg for 2 -6 weeks, followed by 4 weeks of standard treatment of radiotherapy (of more than or equal to 65 Gy) and concurrent platinum-based chemotherapy (based on the institutions standard care).

Measured Values

	Placebo	Lapatinib
Number of Participants Analyzed	30	58
Overall Radiological Response After Follow-up Phase in ITT Population [units: Participants]		
Complete Response	2	16
Partial Response	17	34
Stable Disease	2	4
Progressive Disease	9	4

7. Secondary Outcome Measure:

Measure Title	Number of Circulating Tumor Cells at Baseline in mITT Population
Measure Description	This measures the participants with Circulating Tumor Cells (CTC's)Pre-Treatment numbers of 0 to >= 4. CTC's are tumor cells that escape from the primary tumor into the bloodstream and travel through the circulation to distant sites where they develop into secondary tumors.
Time Frame	Baseline
Safety Issue?	No

Analysis Population Description

The mITT population consisted of all subjects who were randomised to study treatment, did not miss lapatinib/placebo treatment for more than 7 consecutive days and had provided sufficient tumour biopsy sample for the primary endpoint analysis. mITT FOLLOW-UP Population of Circulation Tumor Cells

Reporting Groups

	Description
Placebo	Subjects who were given Placebo for 2 to 6 weeks followed by 4 weeks of standard treatment of radiotherapy (of more than or equal to 65 Gy) and concurrent platinum-based Chemotherapy (based on the intitutions standard of care)
Lapatinib	Subjects who were given once daily dose of oral lapatinib 1500 mg for 2 -6 weeks, followed by 4 weeks of standard treatment of radiotherapy (of more than or equal to 65 Gy) and concurrent platinum-based chemotherapy (based on the institutions standard care).

Measured Values

	Placebo	Lapatinib
Number of Participants Analyzed	12	22
Number of Circulating Tumor Cells at Baseline in mITT Population [units: Participants]		
Number of CTC's 0	7	18
Number of CTC's 1	2	1
Number of CTC's 2	1	0
Number of CTC's 3	0	0
Number of CTC's ≥4	0	1
No result	2	2

8. Secondary Outcome Measure:

Measure Title	Number of Participants With Circulating Tumor Cells After Treatment Phase in mITT Population
Measure Description	This measures the participants with Circulating Tumor Cells (CTC's) after treatment numbers of 0 to >= 4. CTC's are tumor cells that escape from the primary tumor into the bloodstream and travel through the circulation to distant sites where they develop into secondary tumors.
Time Frame	End of Treatment (week 2 - 6)
Safety Issue?	No

Analysis Population Description

The mITT population consisted of all subjects who were randomised to study treatment, did not miss lapatinib/placebo treatment for more than 7 consecutive days and had provided sufficient tumour biopsy sample for the primary endpoint analysis.

Reporting Groups

	Description
Placebo	Subjects who were given Placebo for 2 to 6 weeks followed by 4 weeks of standard treatment of radiotherapy (of more than or equal to 65 Gy) and concurrent platinum-based Chemotherapy (based on the intitutions standard of care)
Lapatinib	Subjects who were given once daily dose of oral lapatinib 1500 mg for 2 -6 weeks, followed by 4 weeks of standard treatment of radiotherapy (of more than or equal to 65 Gy) and concurrent platinum-based chemotherapy (based on the institutions standard care).

Measured Values

	Placebo	Lapatinib
Number of Participants Analyzed	13	19
Number of Participants With Circulating Tumor Cells After Treatment Phase in mITT Population [units: Participants]		
Number of CTC's 0	12	13
Number of CTC's 1	0	3
Number of CTC's 2	0	1
Number of CTC's 3	0	0
Number of CTC's >=4	0	2
No result	1	0

9. Secondary Outcome Measure:

Measure Title	Number of Participants With Circulating Tumor Cells After Chemoradiotherapy Phase in mITT Population
Measure Description	This measures the participants with Circulating Tumor Cells (CTC's) after chemoradiotherapy numbers of 0 to >= 4. CTC's are tumor cells that escape from the primary tumor into the bloodstream and travel through the circulation to distant sites where they develop into secondary tumors.
Time Frame	End of Chemoradiotherapy (week 10 - 13)
Safety Issue?	No

Analysis Population Description

The mITT population consisted of all subjects who were randomised to study treatment, did not miss lapatinib/placebo treatment for more than 7 consecutive days and had provided sufficient tumour biopsy sample for the primary endpoint analysis.

Reporting Groups

	Description
Placebo	Subjects who were given Placebo for 2 to 6 weeks followed by 4 weeks of standard treatment of radiotherapy (of more than or equal to 65 Gy) and concurrent platinum-based Chemotherapy (based on the intitutions standard of care)
Lapatinib	Subjects who were given once daily dose of oral lapatinib 1500 mg for 2 -6 weeks, followed by 4 weeks of standard treatment of radiotherapy (of more than or equal to 65 Gy) and concurrent platinum-based chemotherapy (based on the institutions standard care).

Measured Values

	Placebo	Lapatinib
Number of Participants Analyzed	5	2

	Placebo	Lapatinib
Number of Participants With Circulating Tumor Cells After Chemoradiotherapy Phase in mITT Population [units: Participants]		
Number of CTC's 0	4	2
Number of CTC's 1	0	0
Number of CTC's 2	0	0
Number of CTC's 3	1	0
Number of CTC's >=4	0	0
No result	0	0

10. Secondary Outcome Measure:

Measure Title	Number of Biomarkers Including ErbB1, ErbB2, pErbB1, and pErb2 at Baseline and During Treatment Phase
Measure Description	Estrogen Receptor (ER) variants, ERB-B2 and ERB B-5 consist of the major proportion of ER expression both in normal and cancer tissues. The exact role of these markers are unknown. Acronyms defined: ICH (immunohistochemical) and FISH (fluorescence in situ hybridization).
Time Frame	Baseline and Week 2
Safety Issue?	No

Analysis Population Description

The mITT population consisted of all subjects who were randomised to study treatment, did not miss lapatinib/placebo treatment for more than 7 consecutive days and had provided sufficient tumour biopsy sample for the primary endpoint analysis.

Reporting Groups

	Description
Placebo	Subjects who were given Placebo for 2 to 6 weeks followed by 4 weeks of standard treatment of radiotherapy (of more than or equal to 65 Gy) and concurrent platinum-based Chemotherapy (based on the intitutions standard of care)
Lapatinib	Subjects who were given once daily dose of oral lapatinib 1500 mg for 2 -6 weeks, followed by 4 weeks of standard treatment of radiotherapy (of more than or equal to 65 Gy) and concurrent platinum-based chemotherapy (based on the institutions standard care).

Measured Values

	Placebo	Lapatinib
Number of Participants Analyzed	27	57
Number of Biomarkers Including ErbB1, ErbB2, pErbB1, and pErb2 at Baseline and During Treatment Phase [units: Participants]		
ErbB1 by IHC-Baseline 0 expressed	2	0
ErbB1 by IHC-Treatment 0 expressed	2	0
ErbB1 by IHC-Baseline 1+ expressed	2	2
ErbB1 by IHC-Treatment 1+ expressed	1	4
ErbB1 by IHC-Baseline 2+ expressed	0	10
ErbB1 by IHC-Treatment 2+ expressed	1	5
ErbB1 by IHC-Baseline 3+ expressed	23	45
ErbB1 by IHC-Treatment 3+ expressed	23	48
ErbB1 by FISH-Baseline Amplified	8	17

	Placebo	Lapatinib
ErbB1 by FISH-Treatment Amplified	0	0
ErbB1 by FISH-Baseline Non Amplified	19	40
ErbB1 by FISH-Treatment Non Amplified	0	0
ErbB2 by IHC-Baseline 0 expressed	19	42
ErbB2 by IHC-Treatment 0 expressed	15	26
ErbB2 by IHC-Baseline 1+ expressed	6	13
ErbB2 by IHC-Treatment 1+ expressed	11	29
ErbB2 by IHC-Baseline 2+ expressed	2	1
ErbB2 by IHC-Treatment 2+ expressed	1	1
ErbB2 by IHC-Baseline 3+ expressed	0	1
ErbB2 by IHC-Treatment 3+ expressed	0	1
ErbB2 by FISH-Baseline Amplified	2	1
ErbB2 by FISH-Treatment Amplified	0	0
ErbB2 by FISH-Baseline Non Amplified	25	54
ErbB2 by FISH-Treatment Non Amplified	0	2
pErbB1 by IHC-Baseline 0 expressed	0	3
pErbB1 by IHC-Baseline 1+ expressed	13	31
pErbB1 by IHC-Treatment 1+ expressed	14	38
pErbB1 by IHC-Baseline 2+ expressed	11	18

	Placebo	Lapatinib
pErbB1 by IHC-Treatment 2+ expressed	11	15
pErbB1 by IHC-Baseline 3+ expressed	3	5
pErbB1 by IHC-Treatment 3+ expressed	2	1
pErbB2 by IHC-Baseline 0 expressed	13	25
pErbB2 by IHC-Treatment 0 expressed	13	24
pErbB2 by IHC-Baseline 1+ expressed	12	30
pErbB2 by IHC-Treatment 1+ expressed	12	29
pErbB2 by IHC-Baseline 2+ expressed	1	1
pErbB2 by IHC-Treatment 2+ expressed	1	4
pErbB2 by IHC-Baseline 3+ expressed	0	0
pErbB2 by IHC-Treatment 3+ expressed	0	0
pErbB2 by IHC-Baseline - Missing expression	1	1
pErbB2 by IHC-Treatment Missing expression	1	0

11. Secondary Outcome Measure:

Measure Title	Number of Biomarkers Including Tumor Protein 53 and HPV During Treatment Phase

Measure Description	Tumor Suppressor p53 is welcomed and described as "the guardian angel gene," it conserves stability by preventing genome mutation. Human Papillomavirus (HPV) biomarker is un-welcomed and is found to be an important precursor cancers of the head and neck. HPV biomarkers have the ability to bind to and inactivate the Tumor Suppressor p53 biomarker.
Time Frame	Week 2
Safety Issue?	No

Analysis Population Description

The mITT population consisted of all subjects who were randomised to study treatment, did not miss lapatinib/placebo treatment for more than 7 consecutive days and had provided sufficient tumour biopsy sample for the primary endpoint analysis.

Reporting Groups

	Description
Placebo	Subjects who were given Placebo for 2 to 6 weeks followed by 4 weeks of standard treatment of radiotherapy (of more than or equal to 65 Gy) and concurrent platinum-based Chemotherapy (based on the intitutions standard of care)
Lapatinib	Subjects who were given once daily dose of oral lapatinib 1500 mg for 2 -6 weeks, followed by 4 weeks of standard treatment of radiotherapy (of more than or equal to 65 Gy) and concurrent platinum-based chemotherapy (based on the institutions standard care).

Measured Values

	Placebo	Lapatinib
Number of Participants Analyzed	36	71
Number of Biomarkers Including Tumor Protein 53 and HPV During Treatment		

	Placebo	Lapatinib
Phase [units: Participants]		
Tumor Protein 53 - 0 expression	14	25
Tumor Protein 53 - 1+ expression	5	14
Tumor Protein 53 - 2+ expression	3	11
Tumor Protein 53 - 3+ expression	14	19
Tumor Protein 53 - missing expression	0	0
HPV - Negative	36	64
HPV - Positive	0	5

12. Secondary Outcome Measure:

Measure Title	Summary of Adverse Events by Maximum Toxicity Grade Started During Treatment Phase
Measure Description	Toxicity Grading scale 0=none, 1=transient symptom, 2=mild symptom that does not interfere with activities of daily living (ADL's) 3=mild but interfers with ADL's w/o hospitalization. 4=requires hopitalization 5=Death.
Time Frame	Week 1 through Week 6
Safety Issue?	No

Analysis Population Description

The Intent-to-treat (ITT) population comprised of all subjects who were randomised to study treatment, regardless of whether they actually received study medication.

Reporting Groups

	Description
Placebo	Subjects who were given Placebo for 2 to 6 weeks followed by 4 weeks of standard treatment of radiotherapy (of more than or equal to 65 Gy) and concurrent platinum-based Chemotherapy (based on the intitutions standard of care)
Lapatinib	Subjects who were given once daily dose of oral lapatinib 1500 mg for 2 -6 weeks, followed by 4 weeks of standard treatment of radiotherapy (of more than or equal to 65 Gy) and concurrent platinum-based chemotherapy (based on the institutions standard care).

Measured Values

	Placebo	Lapatinib
Number of Participants Analyzed	36	69
Summary of Adverse Events by Maximum Toxicity Grade Started During Treatment Phase [units: Participants]		
Rash - Grade 3	0	1
Rash - Grade 4	0	0
Rash - Grade 5	0	0
Acne - Grade 3	0	1
Acne - Grade 4	0	0
Acne - Grade 5	0	0
Diarrhea - Grade 3	0	1
Diarrhea - Grade 4	0	0
Diarrhea - Grade 5	0	0

	Placebo	Lapatinib
Anaemia - Grade 3	0	1
Anaemia - Grade 4	0	0
Anaemia - Grade 5	0	0
Hyperglycaemia - Grade 3	1	0
Hyperglycaemia - Grade 4	0	0
Hyperglycaemia - Grade 5	0	0
Pain in jaw - Grade 3	1	0
Pain in jaw - Grade 4	0	0
Pain in jaw - Grade 5	0	0
Tumor Haemorrhage - Grade 3	1	0
Tumor Haemorrhage - Grade 4	0	0
Tumor Haemorrhage - Grade 5	0	0

13. Secondary Outcome Measure:

Measure Title	Summary of Adverse Events by Maximum Toxicity Grade (Grade 3 or Higher) Started During or After the Chemoradiotherapy Phase
Measure Description	Toxicity Grading scale 0=none, 1= transient symptom, 2=mild symptom that does not interfere with activities of daily living (ADL's) 3=mild but interfers with ADL's w/o hospitalization. 4=requires hopitalization 5=Death.
Time Frame	Week 10 through 25

Safety Issue?	No

Analysis Population Description

The Intent-to-treat (ITT) population comprised of all subjects who were randomised to study treatment, regardless of whether they actually received study medication.

Reporting Groups

	Description
Placebo	Subjects who were given Placebo for 2 to 6 weeks followed by 4 weeks of standard treatment of radiotherapy (of more than or equal to 65 Gy) and concurrent platinum-based Chemotherapy (based on the intitutions standard of care)
Lapatinib	Subjects who were given once daily dose of oral lapatinib 1500 mg for 2 -6 weeks, followed by 4 weeks of standard treatment of radiotherapy (of more than or equal to 65 Gy) and concurrent platinum-based chemotherapy (based on the institutions standard care).

Measured Values

	Placebo	Lapatinib
Number of Participants Analyzed	36	69
Summary of Adverse Events by Maximum Toxicity Grade (Grade 3 or Higher) Started During or After the Chemoradiotherapy Phase [units: Participants]		
Mucosal Inflamation-Grade 3	3	24
Mucosal Inflamation-Grade 4	0	2
Mucosal Inflamation-Grade 5	0	0
Skin Reaction-Grade 3	3	6

	Placebo	Lapatinib
Skin Reaction-Grade 4	0	1
Skin Reaction-Grade 5	0	0
Neutropenia-Grade 3	3	4
Neutropenia-Grade 4	1	0
Neutropenia-Grade 5	0	0
Asthenia-Grade 3	2	3
Asthenia-Grade 4	0	0
Asthenia-Grade 5	0	0
Soft Tissue Inflamation-Grade 3	1	2
Soft Tissue Inflamation-Grade 4	0	0
Soft Tissue Inflamation-Grade 5	0	0
Odynophagia-Grade 3	2	2
Odynophagia-Grade 4	0	0
Odynophagia-Grade 5	0	0
General Physical Health deterioration-Grade 3	0	2
General Physical Health deterioration-Grade 4	0	0
General Physical Health deterioration-Grade 5	0	0
Rash-Grade 3	0	2
Rash-Grade 4	0	0

	Placebo	Lapatinib
Rash-Grade 5	0	0
Radiation Skin Injury-Grade 3	0	2
Radiation Skin Injury-Grade 4	0	0
Radiation Skin Injury-Grade 5	0	0
Dysphagia-Grade 3	3	1
Dysphagia-Grade 4	0	0
Dysphagia-Grade 5	0	0
Nausea-Grade 3	1	1
Nausea-Grade 4	0	0
Nausea-Grade 5	0	0
Stomatitis-Grade 3	1	1
Stomatitis-Grade 4	0	0
Stomatitis-Grade 5	0	0
Radiation mucositis-Grade 3	2	1
Radiation mucositis-Grade 4	0	0
Radiation mucositis-Grade 5	0	0
Weight decrease-Grade 3	1	1
Weight decrease-Grade 4	0	0
Weight decrease-Grade 5	0	0
Pain-Grade 3	0	1
Pain-Grade 4	0	0

	Placebo	Lapatinib
Pain-Grade 5	0	0
Constipation-Grade 3	0	1
Constipation-Grade 4	0	0
Constipation-Grade 5	0	0
Skin Ulcer-Grade 3	0	1
Skin Ulcer-Grade 4	0	0
Skin Ulcer-Grade 5	0	0
Dysphonia-Grade 3	0	1
Dysphonia-Grade 4	0	0
Dysphonia-Grade 5	0	0
Leucopenia-Grade 3	2	1
Leucopenia-Grade 4	0	0
Leucopenia-Grade 5	0	0
AST increase-Grade 3	0	1
AST increase-Grade 4	0	0
AST increase-Grade 5	0	0
Trimus-Grade 3	0	1
Trimus-Grade 4	0	0
Trimus-Grade 5	0	0
Bipolar disorder-Grade 3	0	1
Bipolar disorder-Grade 4	0	0

	Placebo	Lapatinib
Bipolar disorder-Grade 5	0	0
Diplopia-Grade 3	0	1
Diplopia-Grade 4	0	0
Diplopia-Grade 5	0	0
Peripheral Embolism-Grade 3	0	1
Peripheral Embolism-Grade 4	0	0
Peripheral Embolism-Grade 5	0	0
Renal Failure-Grade 3	0	1
Renal Failure-Grade 4	0	0
Renal Failure-Grade 5	0	0
Localized edema-Grade 3	1	0
Localized edema-Grade 4	0	0
Localized edema-Grade 5	0	0
Vomiting-Grade 3	3	0
Vomiting-Grade 4	0	0
Vomiting-Grade 5	0	0
Respiratory failure-Grade 3	1	0
Respiratory failure-Grade 4	0	0
Respiratory failure-Grade 5	0	0
Respiratory tract infection-Grade 3	1	0
Respiratory tract infection-Grade 4	0	0

	Placebo	Lapatinib
Respiratory tract infection-Grade 5	0	0
Sepsis-Grade 3	1	0
Sepsis-Grade 4	0	0
Sepsis-Grade 5	0	0
Staphyloccocal sepsis-Grade 3	0	0
Staphyloccocal sepsis-Grade 4	0	0
Staphyloccocal sepsis-Grade 5	1	0
Hyponatraemia-Grade 3	2	0
Hyponatraemia-Grade 4	0	0
Hyponatraemia-Grade 5	0	0
Hypernatraemia-Grade 3	0	0
Hypernatraemia-Grade 4	0	1
Hypernatraemia-Grade 5	0	0
Ketoacidosis-Grade 3	1	0
Ketoacidosis-Grade 4	0	0
Ketoacidosis-Grade 5	0	0
Post Procedural Haemorrhage-Grade 3	1	0
Post Procedural Haemorrhage-Grade 4	0	0
Post Procedural Haemorrhage-Grade 5	0	0
Blood Creatinine Increased-Grade 3	1	0
Blood Creatinine Increased-Grade 4	0	0

	Placebo	Lapatinib
Blood Creatinine Increased-Grade 5	0	0
Haematocrit decreased-Grade 3	1	0
Haematocrit decreased-Grade 4	0	0
Haematocrit decreased-Grade 5	0	0
Haemoglobin decreased-Grade 3	1	0
Haemoglobin decreased-Grade 4	0	0
Haemoglobin decreased-Grade 5	0	0
Back Pain-Grade 3	1	0
Back Pain-Grade 4	0	0
Back Pain-Grade 5	0	0
Deep Vein Thrombosis-Grade 3	1	0
Deep Vein Thrombosis-Grade 4	0	0
Deep Vein Thrombosis-Grade 5	0	0
Ventricular Fibrillation-Grade 3	0	0
Ventricular Fibrillation-Grade 4	0	0
Ventricular Fibrillation-Grade 5	1	0
Intestinal Perforation-Grade 3	0	0
Intestinal Perforation-Grade 4	0	0
Intestinal Perforation-Grade 5	0	1
Dyspnoea-Grade 3	0	0
Dyspnoea-Grade 4	0	1

	Placebo	Lapatinib
Dyspnoea-Grade 5	0	0
Anaemia-Grade 3	0	0
Anaemia-Grade 4	0	2
Anaemia-Grade 5	0	0
Lymphopenia-Grade 3	1	0
Lymphopenia-Grade 4	0	0
Lymphopenia-Grade 5	0	0
Cardio-respiratory arrest-Grade 3	0	0
Cardio-respiratory arrest-Grade 4	0	0
Cardio-respiratory arrest-Grade 5	0	1
Sudden Death-Grade 3	0	0
Sudden Death-Grade 4	0	0
Sudden Death-Grade 5	0	1
Dry Mouth-Grade 3	1	0
Dry Mouth-Grade 4	0	0
Dry Mouth-Grade 5	0	0

14. Secondary Outcome Measure:

Measure Title	Comparison of Overall Response During Treatment Phase Using CT/MRI and PET Information
Measure Description	Position Emission Tomography (PET) scans 3-D images are read alongside CT or magnetic resonance imaging (MRI) scans, the

	combination gives both anatomic and metabolic information. CT = Computerized axial tomography; a type of x-ray for dense areas of the body. MRI = Magnetic Resonance Imaging which captures a picture using Magnets. Better = improvement in response, Worse = response was downgraded.
Time Frame	Week 2 - 4
Safety Issue?	No

Analysis Population Description

The mITT population consisted of all subjects who were randomised to study treatment, did not miss lapatinib/placebo treatment for more than 7 consecutive days and had provided sufficient tumour biopsy sample for the primary endpoint analysis.

Reporting Groups

	Description
Placebo	Subjects who were given Placebo for 2 to 6 weeks followed by 4 weeks of standard treatment of radiotherapy (of more than or equal to 65 Gy) and concurrent platinum-based Chemotherapy (based on the intitutions standard of care)
Lapatinib	Subjects who were given once daily dose of oral lapatinib 1500 mg for 2 -6 weeks, followed by 4 weeks of standard treatment of radiotherapy (of more than or equal to 65 Gy) and concurrent platinum-based chemotherapy (based on the institutions standard care).

Measured Values

	Placebo	Lapatinib
Number of Participants Analyzed	11	14
Comparison of Overall Response During Treatment Phase Using CT/MRI and PET Information		

	Placebo	Lapatinib
[units: Participants]		
Better	2	3
Same	8	6
Worse	0	3
Any Unknown	0	0
Missing	1	0
Not Evaluable	0	2

15. Secondary Outcome Measure:

Measure Title	Comparison of Overall Response During Follow up Phase Using CT/MRI and PET Information
Measure Description	Position Emission Tomography (PET) scans 3-D images are read alongside CT or magnetic resonance imaging (MRI) scans, the combination gives both anatomic and metabolic information. CT = Computerized axial tomography; a type of x-ray for dense areas of the body. MRI = Magnetic Resonance Imaging which captures a picture using Magnets. Better = improvement in response, Worse = response was downgraded.
Time Frame	weeks 19 - 25
Safety Issue?	No

Analysis Population Description

The mITT population consisted of all subjects who were randomised to study treatment, did not miss lapatinib/placebo treatment for more than 7 consecutive days and had provided sufficient tumour biopsy sample for the primary endpoint analysis.

Reporting Groups

	Description
Placebo	Subjects who were given Placebo for 2 to 6 weeks followed by 4 weeks of standard treatment of radiotherapy (of more than or equal to 65 Gy) and concurrent platinum-based Chemotherapy (based on the intitutions standard of care)
Lapatinib	Subjects who were given once daily dose of oral lapatinib 1500 mg for 2 -6 weeks, followed by 4 weeks of standard treatment of radiotherapy (of more than or equal to 65 Gy) and concurrent platinum-based chemotherapy (based on the institutions standard care).

Measured Values

	Placebo	Lapatinib
Number of Participants Analyzed	13	17
Comparison of Overall Response During Follow up Phase Using CT/MRI and PET Information [units: Participants]		
Better	0	2
Same	11	10
Worse	1	5
Any Unknown	0	0
Missing	1	0
Not Evaluable	0	0

16. Secondary Outcome Measure:

Measure Title	Summary of Adverse Events Experienced by 15% or More

	Subjects in Either Treatment Group
Measure Description	Definition of an adverse event is any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.
Time Frame	Week 1 through 25
Safety Issue?	No

Analysis Population Description

Safety population consisted of all randomized subjects who took at least one dose of study medication. This population was based on the actual treatment received, if different to the randomized treatment allocation.

Reporting Groups

	Description
Placebo	Subjects who were given Placebo for 2 to 6 weeks followed by 4 weeks of standard treatment of radiotherapy (of more than or equal to 65 Gy) and concurrent platinum-based Chemotherapy (based on the intitutions standard of care)
Lapatinib	Subjects who were given once daily dose of oral lapatinib 1500 mg for 2 -6 weeks, followed by 4 weeks of standard treatment of radiotherapy (of more than or equal to 65 Gy) and concurrent platinum-based chemotherapy (based on the institutions standard care).

Measured Values

	Placebo	Lapatinib
Number of Participants Analyzed	36	69
Summary of Adverse Events Experienced by 15% or More Subjects in Either Treatment Group		

	Placebo	Lapatinib
[units: Participants]		
Mucosal Inflammation	24	48
Odynophagia	13	23
Asthenia	17	21
Dysphagia	12	21
Nausea	8	20
Vomiting	13	17
Dry Mouth	8	15
Neutropenia	10	13
Radiation Skin Injury	8	13
Constipation	8	12
Skin Reaction	7	11
Pharyngolaryngeal Pain	6	11
Anorexia	11	10
Dysphonia	8	8
Pyrexia	6	6
Leukopenia	7	3

17. Secondary Outcome Measure:

Measure Title	Summary of Fatal/Serious Adverse Events During or After Chemoradiotherapy Phase

Measure Description	Events which started during or After the Chemoradiotherapy Phase. Definition of a serious adverse event is any untoward medicinal occurrence that, at any dose, results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in disability/incapacity, is a congenital anomaly/birth defect, other.
Time Frame	Week 10 through 25
Safety Issue?	No

Analysis Population Description

Safety population consisted of all randomized subjects who took at least one dose of study medication. This population was based on the actual treatment received, if different to the randomized treatment allocation.

Reporting Groups

	Description
Placebo	Subjects who were given Placebo for 2 to 6 weeks followed by 4 weeks of standard treatment of radiotherapy (of more than or equal to 65 Gy) and concurrent platinum-based Chemotherapy (based on the intitutions standard of care)
Lapatinib	Subjects who were given once daily dose of oral lapatinib 1500 mg for 2 -6 weeks, followed by 4 weeks of standard treatment of radiotherapy (of more than or equal to 65 Gy) and concurrent platinum-based chemotherapy (based on the institutions standard care).

Measured Values

	Placebo	Lapatinib
Number of Participants Analyzed	36	69
Summary of Fatal/Serious Adverse Events During or After Chemoradiotherapy Phase		

	Placebo	Lapatinib
[units: Participants]		
Cardio-respiratory arrest	0	1
Intestinal perforation	0	1
Respiratory tract infection	0	1
Sudden death	0	1
Ventricular fibrillation	1	0

18. Secondary Outcome Measure:

Measure Title	Summary of Serious Adverse Events During or After Chemoradiotherapy Phase
Measure Description	Events which started during or After Chemoradiotherapy Phase. Definition of a serious adverse event is any untoward medicinal occurrence that, at any dose, results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in disability/incapacity, is a congenital anomaly/birth defect, other.
Time Frame	Week 10 through 25
Safety Issue?	No

Analysis Population Description

Safety population consisted of all randomized subjects who took at least one dose of study medication. This population was based on the actual treatment received, if different to the randomized treatment allocation.

Reporting Groups

	Description
Placebo	Subjects who were given Placebo for 2 to 6 weeks followed by 4 weeks of standard treatment of radiotherapy (of more than or equal to 65 Gy) and concurrent platinum-based Chemotherapy (based on the intitutions standard of care)
Lapatinib	Subjects who were given once daily dose of oral lapatinib 1500 mg for 2 -6 weeks, followed by 4 weeks of standard treatment of radiotherapy (of more than or equal to 65 Gy) and concurrent platinum-based chemotherapy (based on the institutions standard care).

Measured Values

	Placebo	Lapatinib
Number of Participants Analyzed	36	69
Summary of Serious Adverse Events During or After Chemoradiotherapy Phase [units: Participants]		
Mucosal inflammation	2	3
Constipation	0	2
Asthenia	0	1
Bipolar disorder	0	1
Cardio-respiratory arrest	0	1
Chronic obstructive pulmonary disease	0	1
Dehydration	0	1
General physical health deterioration	0	1
Intestinal perforation	0	1

	Placebo	Lapatinib
Peripheral embolism	0	1
Renal failure	0	1
Respiratory tract infection	2	1
Skin ulcer	0	1
Sudden death	0	1
Electrolyte imbalance	1	0
Diabetic ketoacidosis	1	0
Ketoacidosis	1	0
Lobar pneumonia	1	0
Neutropenia	1	0
Parotitis	1	0
Pneumonia aspiration	1	0
Post procedural haemorrhage	1	0
Pyrexia	2	0
Renal Impairment	1	0
Sepsis	1	0
Septic shock	1	0
Upper respiratory tract infection	1	0
Ventricular fibrillation	1	0
Vomiting	2	0
Weight decreased	1	0

19. Secondary Outcome Measure:

Measure Title	Adverse Events by Maximum Toxicity Grade 3 During or After Chemoradiotherapy Phase
Measure Description	Events which started during or after Chemoradiotherapy Phase. "Grade 3" are severe and undesirable Adverse Event (significant symptoms requiring hospitalization or invasive intervention; transfusion; elective interventional radiological procedure; therapeutic endoscopy or operation).
Time Frame	Week 10 through 25
Safety Issue?	No

Analysis Population Description

Safety population consisted of all randomized subjects who took at least one dose of study medication. This population was based on the actual treatment received, if different to the randomized treatment allocation.

Reporting Groups

	Description
Placebo	Subjects who were given Placebo for 2 to 6 weeks followed by 4 weeks of standard treatment of radiotherapy (of more than or equal to 65 Gy) and concurrent platinum-based Chemotherapy (based on the intitutions standard of care)
Lapatinib	Subjects who were given once daily dose of oral lapatinib 1500 mg for 2 -6 weeks, followed by 4 weeks of standard treatment of radiotherapy (of more than or equal to 65 Gy) and concurrent platinum-based chemotherapy (based on the institutions standard care).

Measured Values

	Placebo	Lapatinib
Number of Participants Analyzed	36	69
Adverse Events by Maximum Toxicity Grade 3 During or After Chemoradiotherapy Phase [units: Participants]		
Mucosal inflammation	9	24
Skin reaction	3	6
Neutropenia	3	4
Asthenia	2	3
Soft tissue inflammation	1	2
Odynophagia	2	2
General physical health deterioration	0	2
Rash	0	2
Radiation skin injury	0	2
Dysphagia	3	1
Nausea	1	1
Stomatitis	1	1
Radiation mucositis	2	1
Weight decreased	1	1
Pain	0	1
Constipation	0	1
Skin ulcer	0	1
Dysphonia	0	1

	Placebo	Lapatinib
Leucopenia	2	1
Aspartate aminotransferase increased	0	1
Trismus	0	1
Bipolar disorder	0	1
Diplopia	0	1
Peripheral embolism	0	1
Renal failure	0	1
Localised oedema	1	0
Vomiting	3	0
Respiratory failure	1	0
Respiratory tract infection	1	0
Sepsis	1	0
Hyponatraemia	2	0
Ketoacidosis	1	0
Post procedural haemorrhage	1	0
Blood creatinine increased	1	0
Haematocrit decreased	1	0
Haemoglobin decreased	1	0
Back pain	1	0
Deep vein thrombosis	1	0
Lymphopenia	1	0

	Placebo	Lapatinib
Dry mouth	1	0

20. Secondary Outcome Measure:

Measure Title	Adverse Events (AEs) by Maximum Toxicity Grade 4 During or After Chemoradiotherapy Phase
Measure Description	Events which started during or after Chemoradiotherapy Phase. "Grade 4" are life-threatening or disabling Adverse Event (complicated by acute, life-threatening metabolic or cardiovascular complications such as circulatory failure, hemorrhage, sepsis. Life-threatening physiologic consequences; need for intensive care or emergent invasive procedure; emergent interventional radiological procedure, therapeutic endoscopy or operation).
Time Frame	Week 10 through 25
Safety Issue?	No

Analysis Population Description

Safety population consisted of all randomized subjects who took at least one dose of study medication. This population was based on the actual treatment received, if different to the randomized treatment allocation.

Reporting Groups

	Description
Placebo	Subjects who were given Placebo for 2 to 6 weeks followed by 4 weeks of standard treatment of radiotherapy (of more than or equal to 65 Gy) and concurrent platinum-based Chemotherapy (based on the intitutions standard of care)
Lapatinib	Subjects who were given once daily dose of oral lapatinib 1500 mg for 2 -6 weeks, followed by 4 weeks of standard treatment of radiotherapy

	Description
	(of more than or equal to 65 Gy) and concurrent platinum-based chemotherapy (based on the institutions standard care).

Measured Values

	Placebo	Lapatinib
Number of Participants Analyzed	36	69
Adverse Events (AEs) by Maximum Toxicity Grade 4 During or After Chemoradiotherapy Phase [units: Participants]		
Mucosal inflammation	0	2
Skin reaction	0	1
Neutropenia	1	0
Hypernatraemia	0	1
Dyspnoea	0	1
Anaemia	0	2

21. Secondary Outcome Measure:

Measure Title	Adverse Events by Maximum Toxicity Grade 5 During or After Chemoradiotherapy Phase
Measure Description	Events which started during or after Chemoradiotherapy Phase. "Grade 5" are death related to Adverse Event.
Time Frame	Week 10 through 25

Safety Issue?	No

Analysis Population Description

Safety population consisted of all randomized subjects who took at least one dose of study medication. This population was based on the actual treatment received, if different to the randomized treatment allocation.

Reporting Groups

	Description
Placebo	Subjects who were given Placebo for 2 to 6 weeks followed by 4 weeks of standard treatment of radiotherapy (of more than or equal to 65 Gy) and concurrent platinum-based Chemotherapy (based on the intitutions standard of care)
Lapatinib	Subjects who were given once daily dose of oral lapatinib 1500 mg for 2 -6 weeks, followed by 4 weeks of standard treatment of radiotherapy (of more than or equal to 65 Gy) and concurrent platinum-based chemotherapy (based on the institutions standard care).

Measured Values

	Placebo	Lapatinib
Number of Participants Analyzed	36	69
Adverse Events by Maximum Toxicity Grade 5 During or After Chemoradiotherapy Phase [units: Participants]		
Respiratory tract infection	0	1
Staphyloccocal sepsis	1	0
Ventricular fibrillation	1	0
Intestinal perforation	0	1

	Placebo	Lapatinib
Cardio-respiratory arrest	0	1
Sudden death	0	1

22. Secondary Outcome Measure:

Measure Title	Relative Change From Baseline of Ktrans Median (1/Min) After 2 - 4 Weeks of Treatment
Measure Description	Dynamic Contrast enhanced Magnetic Resonance Imaging (DCE-MRI) tracks the diffusion of an administered contrast agent from -intra into the extravascular tissue over time. Ktrans estimates blood flow and relates to the ease of exchange into extravascular spaces. A volume transfer (i.e, 1/min) constant of contrast agent is used to determine vascular permeability. By plugging DCE-MRI results into an appropriate pharmacokinetic model, physiological parameters of the tumor (e.g.,tissue perfusion, vessel permeability, vascular surface area, and extracellular/vascular volume fraction) are determined.
Time Frame	Baseline, and Week 2 - 4
Safety Issue?	No

Analysis Population Description

The mITT population consisted of all subjects who were randomised to study treatment, did not miss lapatinib/placebo treatment for more than 7 consecutive days and had provided sufficient tumour biopsy sample for the primary endpoint analysis. DCE-MRI population

Reporting Groups

	Description
Placebo	Subjects who were given Placebo for 2 to 6 weeks followed by 4 weeks of standard treatment of radiotherapy (of more than or equal to 65 Gy) and concurrent platinum-based Chemotherapy (based on the

	Description
	intitutions standard of care)
Lapatinib	Subjects who were given once daily dose of oral lapatinib 1500 mg for 2 -6 weeks, followed by 4 weeks of standard treatment of radiotherapy (of more than or equal to 65 Gy) and concurrent platinum-based chemotherapy (based on the institutions standard care).

Measured Values

	Placebo	Lapatinib
Number of Participants Analyzed	6	4
Relative Change From Baseline of Ktrans Median (1/Min) After 2 - 4 Weeks of Treatment [units: Percent change] Mean (Standard Deviation)	-2.70 (25.364)	6.15 (22.792)

23. Secondary Outcome Measure:

Measure Title	Relative Change From Baseline of Kep Mean (1/Min) After 2 - 4 Weeks of Treatment
Measure Description	DCE-MRI tracks the diffusion of an intravascularly administered contrast agent into the extravascular tissue over time. Over a period of time, the contrast agent diffuses back into the vasculature (described by the rate constant or Kep). The lower the Kep, the longer the contrast remains in the extravascular space and is more prolonged. A volume transfer (i.e, 1/min) constant of contrast agent is used to determine vascular permeability. By plugging DCE-MRI results into an appropriate pharmacokinetic model, physiological parameters of the tumor (e.g., vessel permeability, etc.) are determined.

Time Frame	Baseline, and Week 2 - 4
Safety Issue?	No

Analysis Population Description

The mITT population consisted of all subjects who were randomised to study treatment, did not miss lapatinib/placebo treatment for more than 7 consecutive days and had provided sufficient tumour biopsy sample for the primary endpoint analysis. DCE-MRI population

Reporting Groups

	Description
Placebo	Subjects who were given Placebo for 2 to 6 weeks followed by 4 weeks of standard treatment of radiotherapy (of more than or equal to 65 Gy) and concurrent platinum-based Chemotherapy (based on the intitutions standard of care)
Lapatinib	Subjects who were given once daily dose of oral lapatinib 1500 mg for 2 -6 weeks, followed by 4 weeks of standard treatment of radiotherapy (of more than or equal to 65 Gy) and concurrent platinum-based chemotherapy (based on the institutions standard care).

Measured Values

	Placebo	Lapatinib
Number of Participants Analyzed	6	4
Relative Change From Baseline of Kep Mean (1/Min) After 2 - 4 Weeks of Treatment [units: Percent change] Mean (Standard Deviation)	10.30 (33.630)	-14.54 (8.898)

24. Secondary Outcome Measure:

Measure Title	Relative Change From Baseline of Kep Perfused (1/Min)

	After 2 - 4 Weeks of Treatment
Measure Description	DCE-MRI tracks the diffusion of an intravascularly administered contrast agent into the extravascular tissue over time. Over a period of time, the contrast agent diffuses back into the vasculature (described by the rate constant or Kep). The lower the Kep, the longer the contrast remains in the extravascular space and is more prolonged. A volume transfer (i.e, 1/min) constant of contrast agent is used to determine vascular permeability. By plugging DCE-MRI results into an appropriate pharmacokinetic model, physiological parameters of the tumor (e.g., vessel permeability, etc.) are determined.
Time Frame	Baseline, and Week 2 - 4
Safety Issue?	No

Analysis Population Description

The mITT population consisted of all subjects who were randomised to study treatment, did not miss lapatinib/placebo treatment for more than 7 consecutive days and had provided sufficient tumour biopsy sample for the primary endpoint analysis. DCE-MRI population

Reporting Groups

	Description
Placebo	Subjects who were given Placebo for 2 to 6 weeks followed by 4 weeks of standard treatment of radiotherapy (of more than or equal to 65 Gy) and concurrent platinum-based Chemotherapy (based on the intitutions standard of care)
Lapatinib	Subjects who were given once daily dose of oral lapatinib 1500 mg for 2 -6 weeks, followed by 4 weeks of standard treatment of radiotherapy (of more than or equal to 65 Gy) and concurrent platinum-based chemotherapy (based on the institutions standard care).

Measured Values

	Placebo	Lapatinib
Number of Participants Analyzed	6	4
Relative Change From Baseline of Kep Perfused (1/Min) After 2 - 4 Weeks of Treatment [units: Percent change] Mean (Standard Deviation)	7.63 (26.965)	-19.96 (8.662)

25. Secondary Outcome Measure:

Measure Title	Relative Change From Baseline of Kep Whole (1/Min) After 2 - 4 Weeks of Treatment
Measure Description	DCE-MRI tracks the diffusion of an intravascularly administered contrast agent into the extravascular tissue over time. Over a period of time, the contrast agent diffuses back into the vasculature (described by the rate constant or Kep). The lower the Kep, the longer the contrast remains in the extravascular space and is more prolonged. A volume transfer (i.e, 1/min) constant of contrast agent is used to determine vascular permeability. By plugging DCE-MRI results into an appropriate pharmacokinetic model, physiological parameters of the tumor (e.g., vessel permeability, etc.) are determined.
Time Frame	Baseline, and Week 2 - 4
Safety Issue?	No

Analysis Population Description

The mITT population consisted of all subjects who were randomised to study treatment, did not miss lapatinib/placebo treatment for more than 7 consecutive days and had provided sufficient tumour biopsy sample for the primary endpoint analysis. DCE-MRI population

Reporting Groups

	Description
Placebo	Subjects who were given Placebo for 2 to 6 weeks followed by 4 weeks of standard treatment of radiotherapy (of more than or equal to 65 Gy) and concurrent platinum-based Chemotherapy (based on the intitutions standard of care)
Lapatinib	Subjects who were given once daily dose of oral lapatinib 1500 mg for 2 -6 weeks, followed by 4 weeks of standard treatment of radiotherapy (of more than or equal to 65 Gy) and concurrent platinum-based chemotherapy (based on the institutions standard care).

Measured Values

	Placebo	Lapatinib
Number of Participants Analyzed	6	4
Relative Change From Baseline of Kep Whole (1/Min) After 2 - 4 Weeks of Treatment [units: Percent change] Mean (Standard Deviation)	8.87 (29.875)	-19.64 (6.716)

26. Secondary Outcome Measure:

Measure Title	Relative Change From Baseline of Ktrans Mean (1/Min) After 2 - 4 Weeks of Treatment
Measure Description	Dynamic Contrast enhanced Magnetic Resonance Imaging (DCE-MRI) tracks the diffusion of an administered contrast agent from -intra into the extravascular tissue over time. Ktrans estimates blood flow and relates to the ease of exchange into extravascular spaces. A volume transfer (i.e, 1/min) constant of contrast agent is used to determine vascular permeability. By plugging DCE-MRI results into an appropriate pharmacokinetic model, physiological parameters of the

	tumor (e.g.,tissue perfusion, vessel permeability, vascular surface area, and extracellular/vascular volume fraction) are determined.
Time Frame	Baseline, and Week 2 - 4
Safety Issue?	No

Analysis Population Description

The mITT population consisted of all subjects who were randomised to study treatment, did not miss lapatinib/placebo treatment for more than 7 consecutive days and had provided sufficient tumour biopsy sample for the primary endpoint analysis. DCE-MRI population

Reporting Groups

	Description
Placebo	Subjects who were given Placebo for 2 to 6 weeks followed by 4 weeks of standard treatment of radiotherapy (of more than or equal to 65 Gy) and concurrent platinum-based Chemotherapy (based on the intitutions standard of care)
Lapatinib	Subjects who were given once daily dose of oral lapatinib 1500 mg for 2 -6 weeks, followed by 4 weeks of standard treatment of radiotherapy (of more than or equal to 65 Gy) and concurrent platinum-based chemotherapy (based on the institutions standard care).

Measured Values

	Placebo	Lapatinib
Number of Participants Analyzed	6	4
Relative Change From Baseline of Ktrans Mean (1/Min) After 2 - 4 Weeks of Treatment [units: Percent change] Mean (Standard Deviation)	-1.90 (27.965)	4.02 (17.683)

27. Secondary Outcome Measure:

Measure Title	Relative Change From Baseline of Ktrans Perfused (1/Min) After 2 - 4 Weeks of Treatment
Measure Description	Dynamic Contrast enhanced Magnetic Resonance Imaging (DCE-MRI) tracks the diffusion of an administered contrast agent from -intra into the extravascular tissue over time. Ktrans estimates blood flow and relates to the ease of exchange into extravascular spaces. A volume transfer (i.e, 1/min) constant of contrast agent is used to determine vascular permeability. By plugging DCE-MRI results into an appropriate pharmacokinetic model, physiological parameters of the tumor (e.g.,tissue perfusion, vessel permeability, vascular surface area, and extracellular/vascular volume fraction) are determined.
Time Frame	Baseline, and Week 2 - 4
Safety Issue?	No

Analysis Population Description

The mITT population consisted of all subjects who were randomised to study treatment, did not miss lapatinib/placebo treatment for more than 7 consecutive days and had provided sufficient tumour biopsy sample for the primary endpoint analysis. DCE-MRI population

Reporting Groups

	Description
Placebo	Subjects who were given Placebo for 2 to 6 weeks followed by 4 weeks of standard treatment of radiotherapy (of more than or equal to 65 Gy) and concurrent platinum-based Chemotherapy (based on the intitutions standard of care)
Lapatinib	Subjects who were given once daily dose of oral lapatinib 1500 mg for 2 -6 weeks, followed by 4 weeks of standard treatment of radiotherapy (of more than or equal to 65 Gy) and concurrent platinum-based chemotherapy (based on the institutions standard care).

Measured Values

	Placebo	Lapatinib
Number of Participants Analyzed	6	4
Relative Change From Baseline of Ktrans Perfused (1/Min) After 2 - 4 Weeks of Treatment [units: Percent change] Mean (Standard Deviation)	-1.44 (23.029)	0.69 (34.213)

28. Secondary Outcome Measure:

Measure Title	Relative Change From Baseline of Ktrans Whole (1/Min) After 2 - 4 Weeks of Treatment
Measure Description	Dynamic Contrast enhanced Magnetic Resonance Imaging (DCE-MRI) tracks the diffusion of an administered contrast agent from -intra into the extravascular tissue over time. Ktrans estimates blood flow and relates to the ease of exchange into extravascular spaces. A volume transfer (i.e, 1/min) constant of contrast agent is used to determine vascular permeability. By plugging DCE-MRI results into an appropriate pharmacokinetic model, physiological parameters of the tumor (e.g.,tissue perfusion, vessel permeability, vascular surface area, and extracellular/vascular volume fraction) are determined.
Time Frame	Baseline, and Week 2 - 4
Safety Issue?	No

Analysis Population Description

The mITT population consisted of all subjects who were randomised to study treatment, did not miss lapatinib/placebo treatment for more than 7 consecutive days and had provided sufficient tumour biopsy sample for the primary endpoint analysis. DCE-MRI population

Reporting Groups

	Description
Placebo	Subjects who were given Placebo for 2 to 6 weeks followed by 4 weeks of standard treatment of radiotherapy (of more than or equal to 65 Gy) and concurrent platinum-based Chemotherapy (based on the intitutions standard of care)
Lapatinib	Subjects who were given once daily dose of oral lapatinib 1500 mg for 2 -6 weeks, followed by 4 weeks of standard treatment of radiotherapy (of more than or equal to 65 Gy) and concurrent platinum-based chemotherapy (based on the institutions standard care).

Measured Values

	Placebo	Lapatinib
Number of Participants Analyzed	6	4
Relative Change From Baseline of Ktrans Whole (1/Min) After 2 - 4 Weeks of Treatment [units: Percent change] Mean (Standard Deviation)	-2.02 (20.971)	0.30 (31.783)

29. Secondary Outcome Measure:

Measure Title	Relative Change From Baseline of IAUC Median (90) After 2 - 4 Weeks of Treatment
Measure Description	Dynamic Contrast - enhanced Magnetic Resonance Imaging (DCE-MRI) tracks the diffusion of an intravascularly administered contrast agent from intravascular into the extravascular tissue over time. Initial area under the contrast (IAUC), tracks the concentration versus time curve 90 seconds after contrast injection (IAUC90). By plugging DCE-MRI results into an appropriate pharmacokinetic model, physiological parameters of the tumor microenvironment (e.g., tissue

	perfusion, vessel permeability, vascular surface area, and extracellular-extra vascular volume fraction) are determined.
Time Frame	Baseline, and Week 2 - 4
Safety Issue?	No

Analysis Population Description

The mITT population consisted of all subjects who were randomised to study treatment, did not miss lapatinib/placebo treatment for more than 7 consecutive days and had provided sufficient tumour biopsy sample for the primary endpoint analysis. DCE-MRI population

Reporting Groups

	Description
Placebo	Subjects who were given Placebo for 2 to 6 weeks followed by 4 weeks of standard treatment of radiotherapy (of more than or equal to 65 Gy) and concurrent platinum-based Chemotherapy (based on the intitutions standard of care)
Lapatinib	Subjects who were given once daily dose of oral lapatinib 1500 mg for 2 -6 weeks, followed by 4 weeks of standard treatment of radiotherapy (of more than or equal to 65 Gy) and concurrent platinum-based chemotherapy (based on the institutions standard care).

Measured Values

	Placebo	Lapatinib
Number of Participants Analyzed	6	4
Relative Change From Baseline of IAUC Median (90) After 2 - 4 Weeks of Treatment [units: Percent change] Mean (Standard Deviation)	-2.07 (30.188)	14.08 (23.998)

30. Secondary Outcome Measure:

Measure Title	Relative Change From Baseline of IAUC Mean (90) After 2 - 4 Weeks of Treatment
Measure Description	Dynamic Contrast - enhanced Magnetic Resonance Imaging (DCE-MRI) tracks the diffusion of an intravascularly administered contrast agent from intravascular into the extravascular tissue over time. Initial area under the contrast (IAUC), tracks the concentration versus time curve 90 seconds after contrast injection (IAUC90). By plugging DCE-MRI results into an appropriate pharmacokinetic model, physiological parameters of the tumor microenvironment (e.g., tissue perfusion, vessel permeability, vascular surface area, and extracellular-extra vascular volume fraction) are determined.
Time Frame	Baseline, and Week 2 - 4
Safety Issue?	No

Analysis Population Description

The mITT population consisted of all subjects who were randomised to study treatment, did not miss lapatinib/placebo treatment for more than 7 consecutive days and had provided sufficient tumour biopsy sample for the primary endpoint analysis. DCE-MRI population

Reporting Groups

	Description
Placebo	Subjects who were given Placebo for 2 to 6 weeks followed by 4 weeks of standard treatment of radiotherapy (of more than or equal to 65 Gy) and concurrent platinum-based Chemotherapy (based on the intitutions standard of care)
Lapatinib	Subjects who were given once daily dose of oral lapatinib 1500 mg for 2 -6 weeks, followed by 4 weeks of standard treatment of radiotherapy (of more than or equal to 65 Gy) and concurrent platinum-based chemotherapy (based on the institutions standard care).

Measured Values

	Placebo	Lapatinib
Number of Participants Analyzed	6	4
Relative Change From Baseline of IAUC Mean (90) After 2 - 4 Weeks of Treatment [units: Percent change] Mean (Standard Deviation)	-3.30 (28.415)	13.48 (20.763)

31. Secondary Outcome Measure:

Measure Title	Relative Change From Baseline of Perfused IAUC (90) After 2 - 4 Weeks of Treatment
Measure Description	Dynamic Contrast - enhanced Magnetic Resonance Imaging (DCE-MRI) tracks the diffusion of an intravascularly administered contrast agent from intravascular into the extravascular tissue over time. Initial area under the contrast (IAUC), tracks the concentration versus time curve 90 seconds after contrast injection (IAUC90). By plugging DCE-MRI results into an appropriate pharmacokinetic model, physiological parameters of the tumor microenvironment (e.g., tissue perfusion, vessel permeability, vascular surface area, and extracellular-extra vascular volume fraction) are determined.
Time Frame	Baseline, and Week 2 - 4
Safety Issue?	No

Analysis Population Description

The mITT population consisted of all subjects who were randomised to study treatment, did not miss lapatinib/placebo treatment for more than 7 consecutive days and had provided sufficient tumour biopsy sample for the primary endpoint analysis. DCE-MRI population

Reporting Groups

	Description
Placebo	Subjects who were given Placebo for 2 to 6 weeks followed by 4 weeks of standard treatment of radiotherapy (of more than or equal to 65 Gy) and concurrent platinum-based Chemotherapy (based on the intitutions standard of care)
Lapatinib	Subjects who were given once daily dose of oral lapatinib 1500 mg for 2 -6 weeks, followed by 4 weeks of standard treatment of radiotherapy (of more than or equal to 65 Gy) and concurrent platinum-based chemotherapy (based on the institutions standard care).

Measured Values

	Placebo	Lapatinib
Number of Participants Analyzed	6	4
Relative Change From Baseline of Perfused IAUC (90) After 2 - 4 Weeks of Treatment [units: Percent change] Mean (Standard Deviation)	-2.40 (29.521)	12.57 (28.722)

32. Secondary Outcome Measure:

Measure Title	Relative Change From Baseline of Whole IAUC(90) After 2 - 4 Weeks of Treatment
Measure Description	Dynamic Contrast - enhanced Magnetic Resonance Imaging (DCE-MRI) tracks the diffusion of an intravascularly administered contrast agent from intravascular into the extravascular tissue over time. Initial area under the contrast (IAUC), tracks the concentration versus time curve 90 seconds after contrast injection (IAUC90). By plugging DCE-MRI results into an appropriate pharmacokinetic model, physiological parameters of the tumor microenvironment (e.g., tissue

	perfusion, vessel permeability, vascular surface area, and extracellular-extra vascular volume fraction) are determined.
Time Frame	Baseline, and Week 2 - 4
Safety Issue?	No

Analysis Population Description

The mITT population consisted of all subjects who were randomised to study treatment, did not miss lapatinib/placebo treatment for more than 7 consecutive days and had provided sufficient tumour biopsy sample for the primary endpoint analysis. DCE-MRI population

Reporting Groups

	Description
Placebo	Subjects who were given Placebo for 2 to 6 weeks followed by 4 weeks of standard treatment of radiotherapy (of more than or equal to 65 Gy) and concurrent platinum-based Chemotherapy (based on the intitutions standard of care)
Lapatinib	Subjects who were given once daily dose of oral lapatinib 1500 mg for 2 -6 weeks, followed by 4 weeks of standard treatment of radiotherapy (of more than or equal to 65 Gy) and concurrent platinum-based chemotherapy (based on the institutions standard care).

Measured Values

	Placebo	Lapatinib
Number of Participants Analyzed	6	4
Relative Change From Baseline of Whole IAUC(90) After 2 - 4 Weeks of Treatment [units: Percent change] Mean (Standard Deviation)	-2.43 (29.313)	12.52 (28.974)

33. Secondary Outcome Measure:

Measure Title	Relative Change From Baseline of Kep Median (1/Min) After 2 - 4 Weeks of Treatment
Measure Description	DCE-MRI tracks the diffusion of an intravascularly administered contrast agent into the extravascular tissue over time. Over a period of time, the contrast agent diffuses back into the vasculature (described by the rate constant or Kep). The lower the Kep, the longer the contrast remains in the extravascular space and is more prolonged. A volume transfer (i.e, 1/min) constant of contrast agent is used to determine vascular permeability. By plugging DCE-MRI results into an appropriate pharmacokinetic model, physiological parameters of the tumor (e.g., vessel permeability, etc.) are determined.
Time Frame	Baseline, and Week 2 - 4
Safety Issue?	No

Analysis Population Description

The mITT population consisted of all subjects who were randomised to study treatment, did not miss lapatinib/placebo treatment for more than 7 consecutive days and had provided sufficient tumour biopsy sample for the primary endpoint analysis. DCE-MRI population

Reporting Groups

	Description
Placebo	Subjects who were given Placebo for 2 to 6 weeks followed by 4 weeks of standard treatment of radiotherapy (of more than or equal to 65 Gy) and concurrent platinum-based Chemotherapy (based on the intitutions standard of care)
Lapatinib	Subjects who were given once daily dose of oral lapatinib 1500 mg for 2 -6 weeks, followed by 4 weeks of standard treatment of radiotherapy (of more than or equal to 65 Gy) and concurrent platinum-based chemotherapy (based on the institutions standard care).

Measured Values

	Placebo	Lapatinib
Number of Participants Analyzed	6	4
Relative Change From Baseline of Kep Median (1/Min) After 2 - 4 Weeks of Treatment [units: Percent change] Mean (Standard Deviation)	2.88 (19.177)	-9.32 (10.002)

Reported Adverse Events

Reporting Groups

	Description
Placebo	Subjects who were given Placebo for 2 to 6 weeks followed by 4 weeks of standard treatment of radiotherapy (of more than or equal to 65 Gy) and concurrent platinum-based Chemotherapy (based on the intitutions standard of care)
Lapatinib	Subjects who were given once daily dose of oral lapatinib 1500 mg for 2 -6 weeks, followed by 4 weeks of standard treatment of radiotherapy (of mor than or equal to 65 Gy) and concurrent platinum-based chemotherapy (based on the institutions standard care).

Time Frame

Started prior to and during Lapatanib/Placebo phase, during or after chemoradiotherapy phase.

Additional Description

Safety population used in this analysis consisting of all randomized subjects who took at least one dose of study medication. This population was based on the actual treatment received, if different to the randomized treatment allocation.

Serious Adverse Events

	Placebo	Lapatinib
Total # participants affected/at risk	14/36 (38.89%)	14/69 (20.29%)
Blood and lymphatic system disorders		
Neutropenia †[A]		
# participants affected/at risk	1/36 (2.78%)	0/69 (0%)
# events		
Neutropenia		
# participants affected/at risk	1/36 (2.78%)	0/69 (0%)
# events		
Sepsis †[A]		
# participants affected/at risk	1/36 (2.78%)	0/69 (0%)
# events		
Septic Shock †[A]		
# participants affected/at risk	1/36 (2.78%)	0/69 (0%)
# events		
Cardiac disorders		
Cardio-respiratory arrest †[A]		
# participants affected/at risk	0/36 (0%)	1/69 (1.45%)

	Placebo	Lapatinib
# events		
Peripheral Embolism † [A]		
# participants affected/at risk	0/36 (0%)	1/69 (1.45%)
# events		
Ventricular Fibrillation † [A]		
# participants affected/at risk	1/36 (2.78%)	0/69 (0%)
# events		
Ventricular fibrillation		
# participants affected/at risk	1/36 (2.78%)	0/69 (0%)
# events		
Gastrointestinal disorders		
Constipation † [A]		
# participants affected/at risk	0/36 (0%)	2/69 (2.9%)
# events		
Intestinal perforation † [A]		
# participants affected/at risk	0/36 (0%)	1/69 (1.45%)
# events		

	Placebo	Lapatinib
Mucosal Inflammation †[A]		
# participants affected/at risk	2/36 (5.56%)	3/69 (4.35%)
# events		
Vomiting †[A]		
# participants affected/at risk	2/36 (5.56%)	0/69 (0%)
# events		
General disorders		
Dehydration †[A]		
# participants affected/at risk	0/36 (0%)	1/69 (1.45%)
# events		
General Physical Health deterioration †[A]		
# participants affected/at risk	0/36 (0%)	1/69 (1.45%)
# events		
Infections and infestations		
Parotitis †[A]		
# participants affected/at risk	1/36 (2.78%)	0/69 (0%)
# events		

	Placebo	Lapatinib
Pyrexia †[B]		
# participants affected/at risk	2/36 (5.56%)	1/69 (1.45%)
# events		
Injury, poisoning and procedural complications		
Post Procedural Haemorrhage †[A]		
# participants affected/at risk	1/36 (2.78%)	0/69 (0%)
# events		
Post procedural hemorrhage		
# participants affected/at risk	1/36 (2.78%)	0/69 (0%)
# events		
Investigations		
Sudden Death †[A]		
# participants affected/at risk	0/36 (0%)	1/69 (1.45%)
# events		
Weight decreased		
# participants affected/at risk	1/36 (2.78%)	0/69 (0%)
# events		

	Placebo	Lapatinib
Metabolism and nutrition disorders		
Diabetic Ketoacidosis †[A]		
# participants affected/at risk	1/36 (2.78%)	0/69 (0%)
# events		
Electrolyte Imbalance †[A]		
# participants affected/at risk	1/36 (2.78%)	0/69 (0%)
# events		
Ketoacidosis †[A]		
# participants affected/at risk	1/36 (2.78%)	0/69 (0%)
# events		
Ketoacidosis		
# participants affected/at risk	1/36 (2.78%)	0/69 (0%)
# events		
Weight Decrease †[A]		
# participants affected/at risk	1/36 (2.78%)	0/69 (0%)
# events		
Musculoskeletal and		

	Placebo	Lapatinib
connective tissue disorders		
Abdominal strangulated hernia † [A]		
# participants affected/at risk	1/36 (2.78%)	0/69 (0%)
# events		
Asthenia † [A]		
# participants affected/at risk	0/36 (0%)	1/69 (1.45%)
# events		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		
Tumour haemorrhage † [B]		
# participants affected/at risk	1/36 (2.78%)	0/69 (0%)
# events		
Psychiatric disorders		
Bipolar Disorder † [A]		
# participants affected/at risk	0/36 (0%)	1/69 (1.45%)
# events		

	Placebo	Lapatinib
Renal and urinary disorders		
Renal Failure † [A]		
# participants affected/at risk	0/36 (0%)	1/69 (1.45%)
# events		
Renal Impairment † [A]		
# participants affected/at risk	1/36 (2.78%)	0/69 (0%)
# events		
Renal impairment		
# participants affected/at risk	1/36 (2.78%)	0/69 (0%)
# events		
Respiratory, thoracic and mediastinal disorders		
Chronic Obstructive Pulmonary Disease † [A]		
# participants affected/at risk	0/36 (0%)	1/69 (1.45%)
# events		
Lobar Pneumonia † [A]		
# participants affected/at risk	1/36 (2.78%)	0/69 (0%)

	Placebo	Lapatinib
# events		
Pneumonia Aspirations † [A]		
# participants affected/at risk	1/36 (2.78%)	0/69 (0%)
# events		
Pneumonia aspiration		
# participants affected/at risk	1/36 (2.78%)	0/69 (0%)
# events		
Respiratory Tract Infection † [A]		
# participants affected/at risk	2/36 (5.56%)	1/69 (1.45%)
# events		
Upper Respiratory Tract Infection † [A]		
# participants affected/at risk	1/36 (2.78%)	0/69 (0%)
# events		
Skin and subcutaneous tissue disorders		
Skin Ulcer † [A]		
# participants affected/at risk	0/36 (0%)	1/69 (1.45%)

	Placebo	Lapatinib
# events		

† Indicates events were collected by systematic assessment.

A Term from vocabulary, MedDRA

B Term from vocabulary, MedDRA 10.0

Other Adverse Events

Frequency Threshold Above Which Other Adverse Events are Reported: 5%

	Placebo	Lapatinib
Total # participants affected/at risk	36/36 (100%)	69/69 (100%)
Blood and lymphatic system disorders		
Anemia		
# participants affected/at risk	5/36 (13.89%)	10/69 (14.49%)
# events		
Blood creatinine increased		
# participants affected/at risk	2/36 (5.56%)	2/69 (2.9%)
# events		
Leukopenia		
# participants affected/at risk	7/36 (19.44%)	4/69 (5.8%)
# events		
Neutropenia † [A]		

	Placebo	Lapatinib
# participants affected/at risk	10/36 (27.78%)	13/69 (18.84%)
# events		
Thrombocytopenia		
# participants affected/at risk	0/36 (0%)	5/69 (7.25%)
# events		
Weight decreased		
# participants affected/at risk	5/36 (13.89%)	9/69 (13.04%)
# events		
Ear and labyrinth disorders		
Ear pain		
# participants affected/at risk	4/36 (11.11%)	2/69 (2.9%)
# events		
Hypoacusis		
# participants affected/at risk	2/36 (5.56%)	7/69 (10.14%)
# events		
Tinnitus		
# participants affected/at risk	3/36 (8.33%)	1/69 (1.45%)

	Placebo	Lapatinib
# events		
Gastrointestinal disorders		
Aphthous stomatitis		
# participants affected/at risk	2/36 (5.56%)	3/69 (4.35%)
# events		
Aptyalism		
# participants affected/at risk	0/36 (0%)	5/69 (7.25%)
# events		
Constipation †[A]		
# participants affected/at risk	9/36 (25%)	12/69 (17.39%)
# events		
Diarrhoea †[A]		
# participants affected/at risk	2/36 (5.56%)	18/69 (26.09%)
# events		
Dry Mouth †[A]		
# participants affected/at risk	8/36 (22.22%)	15/69 (21.74%)
# events		

	Placebo	Lapatinib
Dyspepsia		
# participants affected/at risk	0/36 (0%)	4/69 (5.8%)
# events		
Dysphagia †[A]		
# participants affected/at risk	13/36 (36.11%)	22/69 (31.88%)
# events		
Mouth hemorrhage		
# participants affected/at risk	2/36 (5.56%)	1/69 (1.45%)
# events		
Mucosal inflammation †[A]		
# participants affected/at risk	24/36 (66.67%)	48/69 (69.57%)
# events		
Nausea †[A]		
# participants affected/at risk	9/36 (25%)	21/69 (30.43%)
# events		
Odynophagia †[A]		
# participants affected/at risk	13/36 (36.11%)	23/69 (33.33%)
# events		

	Placebo	Lapatinib
Oesophagitis		
# participants affected/at risk	2/36 (5.56%)	0/69 (0%)
# events		
Oral pain		
# participants affected/at risk	3/36 (8.33%)	10/69 (14.49%)
# events		
Stomatitis		
# participants affected/at risk	2/36 (5.56%)	5/69 (7.25%)
# events		
Toothache		
# participants affected/at risk	2/36 (5.56%)	3/69 (4.35%)
# events		
Vomiting †[A]		
# participants affected/at risk	14/36 (38.89%)	18/69 (26.09%)
# events		
General disorders		
Face oedema		
# participants affected/at	3/36 (8.33%)	1/69 (1.45%)

	Placebo	Lapatinib
risk		
# events		
Oedema		
# participants affected/at risk	2/36 (5.56%)	3/69 (4.35%)
# events		
Pain		
# participants affected/at risk	6/36 (16.67%)	8/69 (11.59%)
# events		
Pyrexia		
# participants affected/at risk	6/36 (16.67%)	7/69 (10.14%)
# events		
Soft tissue inflammation		
# participants affected/at risk	3/36 (8.33%)	5/69 (7.25%)
# events		
Infections and infestations		
Candidiasis		
# participants affected/at risk	4/36 (11.11%)	4/69 (5.8%)

	Placebo	Lapatinib
# events		
Oral candidiasis		
# participants affected/at risk	2/36 (5.56%)	5/69 (7.25%)
# events		
Oropharyngeal candidiasis		
# participants affected/at risk	3/36 (8.33%)	0/69 (0%)
# events		
Respiratory tract infection		
# participants affected/at risk	3/36 (8.33%)	1/69 (1.45%)
# events		
Injury, poisoning and procedural complications		
Radiation Skin Injury † [A]		
# participants affected/at risk	8/36 (22.22%)	13/69 (18.84%)
# events		
Radiation mucositis		
# participants affected/at risk	3/36 (8.33%)	5/69 (7.25%)
# events		

	Placebo	Lapatinib
Metabolism and nutrition disorders		
Anorexia †[A]		
# participants affected/at risk	11/36 (30.56%)	14/69 (20.29%)
# events		
Dehydration		
# participants affected/at risk	0/36 (0%)	7/69 (10.14%)
# events		
Hyperglycemia		
# participants affected/at risk	2/36 (5.56%)	2/69 (2.9%)
# events		
Hypoalbuminemia		
# participants affected/at risk	2/36 (5.56%)	1/69 (1.45%)
# events		
Hyponatremia		
# participants affected/at risk	2/36 (5.56%)	0/69 (0%)
# events		
Musculoskeletal and		

	Placebo	Lapatinib
connective tissue disorders		
Asthenia †[A]		
# participants affected/at risk	17/36 (47.22%)	23/69 (33.33%)
# events		
Neck pain		
# participants affected/at risk	3/36 (8.33%)	5/69 (7.25%)
# events		
Trismus		
# participants affected/at risk	0/36 (0%)	5/69 (7.25%)
# events		
Nervous system disorders		
Dysgeusia		
# participants affected/at risk	4/36 (11.11%)	11/69 (15.94%)
# events		
Headache		
# participants affected/at risk	2/36 (5.56%)	3/69 (4.35%)

	Placebo	Lapatinib
# events		
Paraesthesia		
# participants affected/at risk	4/36 (11.11%)	1/69 (1.45%)
# events		
Respiratory, thoracic and mediastinal disorders		
Cough		
# participants affected/at risk	5/36 (13.89%)	6/69 (8.7%)
# events		
Dysphonia †[A]		
# participants affected/at risk	8/36 (22.22%)	8/69 (11.59%)
# events		
Dyspnea		
# participants affected/at risk	4/36 (11.11%)	2/69 (2.9%)
# events		
Pharyngolaryngeal pain		
# participants affected/at risk	6/36 (16.67%)	12/69 (17.39%)
# events		

	Placebo	Lapatinib
Skin and subcutaneous tissue disorders		
Dermatitis		
# participants affected/at risk	3/36 (8.33%)	3/69 (4.35%)
# events		
Erythema		
# participants affected/at risk	0/36 (0%)	5/69 (7.25%)
# events		
Rash †[A]		
# participants affected/at risk	5/36 (13.89%)	21/69 (30.43%)
# events		
Skin reaction		
# participants affected/at risk	7/36 (19.44%)	11/69 (15.94%)
# events		
Vascular disorders		
Hypertension		
# participants affected/at risk	2/36 (5.56%)	0/69 (0%)
# events		

	Placebo	Lapatinib
Pallor		
# participants affected/at risk	2/36 (5.56%)	1/69 (1.45%)
# events		

† Indicates events were collected by systematic assessment.

A Term from vocabulary, MedDRA

More Information

Certain Agreements:

Principal Investigators are NOT employed by the organization sponsoring the study.

There IS an agreement between the Principal Investigator and the Sponsor (or its agents) that restricts the PI's rights to discuss or publish trial results after the trial is completed.

: GSK agreements may vary with individual investigators, but will not prohibit any investigator from publishing. GSK supports the publication of results from all centers of a multi-centre trial but requests that reports based on single-site data not precede the primary publication of the entire clinical trial.

Limitations and Caveats:

Results Point of Contact:

Name/Official Title: GSK Response Center

Organization: GlaxoSmithKline

Phone: 866-435-7343

Email: