ClinicalTrials.gov Protocol Registration and Results System (PRS) Receipt
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Study Identification

Unique Protocol ID:	VEG108838
Brief Title:	Pazopanib Plus Lapatinib Compared To Lapatinib Alone In Subjects With Inflammatory Breast Cancer
Official Title:	A Randomized, Multicenter, Phase III Study Comparing the Combination of Pazopanib and Lapatinib Versus Lapatinib Monotherapy in Patients With ErbB2 Over-expressing Inflammatory Breast Cancer
Secondary IDs:	

Study Status

Record Verification:	January 2013
Overall Status:	Completed
Study Start:	December 2007
Primary Completion:	May 2011 [Actual]
Study Completion:	December 2011 [Actual]

Sponsor/Collaborators

Sponsor:	GlaxoSmithKline
Responsible Party:	Sponsor
Collaborators:	

Oversight

FDA Regulated?:	Yes
Applicable Trial?:	Section 801 Clinical Trial? Yes

	Delayed Posting? No
IND/IDE Protocol?:	Yes
IND/IDE Information:	Grantor: CDER IND/IDE Number: 65,747 Serial Number: 0362 Has Expanded Access? No
Review Board:	Approval Status: Approved Board Name: Board Affiliation: Phone: Email:
Data Monitoring?:	Yes
Plan to Share Data?:	
Oversight Authorities:	United States: Food and Drug Administration

Study Description

Brief Summary:	The double blind part of the study is being conducted to compare the efficacy and safety of pazopanib in combination with lapatinib with that of lapatinib alone in subjects with inflammatory breast cancer whose tumors overexpress the ErbB2 protein. There is also an Open-label pazopanib arm to this study designed to test whether pazopanib given alone and lapatinib given alone would be safe and effective to treat patients with inflammatory breast cancer.
Detailed Description:	

Conditions

Conditions:	Neoplasms, Breast
Keywords:	GW572016 Breast Cancer RECIST Inflammatory Breast Cancer Pazopanib ErbB2 Cutaneous Disease Tykerb Inflammatory Skin Her2 Lapatinib

GW786034

Study Design

Study Type:	Interventional
Primary Purpose:	Treatment
Study Phase:	Phase 2
Intervention Model:	Parallel Assignment
Number of Arms:	3
Masking:	Double Blind (Subject, Investigator)
Allocation:	Randomized
Endpoint Classification:	Safety/Efficacy Study
Enrollment:	163 [Actual]

Arms and Interventions

Arms	Assigned Interventions
Active Comparator: arm 1 Lapatinib	Drug: lapatinib Oral administration Other Names: • Tykerb
Active Comparator: arm2 Pazopanib monotherapy (open label)	Drug: Pazopanib Oral administration Other Names: • Votrient
Experimental: arm3 Lapatinib+ pazopanib	Drug: lapatinib Oral administration Other Names: • Tykerb Drug: Pazopanib Oral administration Other Names: • Votrient

Outcome Measures

[See Results Section.]

Eligibility

Minimum Age: 18 Years

Maximum Age:

Gender: Female

Accepts Healthy Volunteers?: No

Criteria: Inclusion criteria:

Specific information regarding warnings, precautions, contraindications, adverse events, and other pertinent information on the investigational product that may impact patient eligibility is provided in the pazopanib IB and lapatinib prescribing information (or the lapatinib IB).

For Cohort 1 of this study, eligible patients met inclusion criteria outlined in the original version of the protocol and protocol amendment 1.

For Cohort 2 of this study, eligible patients must meet all of the following criteria:

- Patients must have evaluable Inflammatory Breast Cancer (IBC) substantiated by all of the following prior to randomization:
- History of invasive breast cancer documented by a biopsy and accompanying pathology report
- Current photographs* (global view and close-up views of all skin lesions) submitted at screening demonstrating unequivocal evidence of IBC as determined by either the medical monitor alone or in consultation with one or more of the study Principal Investigators.
- All patients must have photography at screening. Canfield Scientific Inc. will provide centralized monitoring, tracking, and collection of patients' photographs throughout the study. Screening photographs must be uploaded to the Canfield Scientific Inc website and approved by Canfield Scientific Inc, as the central photography vendor. The photographs, along with the completed Inflammatory Breast Cancer Skin Assessment Tool (IBSAT), must be reviewed and approved by GSK before a patient can be randomized. Sites should allow a minimum of 3 business days for this process. Sites submitting quality photographs and IBSATs on a regular basis will receive an exemption from this requirement for future patients.
- Patients with secondary IBC are eligible.
- Measurable lesions (cutaneous or radiographic) may be in the field of prior standard or palliative radiation therapy; however, there must be at least a 4 week period between the last radiation treatment and the baseline scan documenting disease status for the lesion to be measurable. If the irradiated lesion is the only site of disease, documented progression of the irradiated lesion is required.
- Disease progression or relapse following treatment for invasive breast cancer, which must have included a chemotherapy regimen. In regions where trastuzumab is available with no barriers to access*, patients must have received prior trastuzumab in addition to chemotherapy in order to be eligible. * (Barriers to access may include financial considerations.)
- Unequivocal ErbB2 overexpressing breast cancer, defined as 3+ staining by immunohistochemistry (IHC), or 2+ staining by IHC in conjunction with ErbB2 gene amplification by FISH/CISH, or ErbB2 gene amplification by FISH/CISH alone (in

subjects whose tumor blocks were not assessed by IHC). ErbB2 gene amplification is defined by: > six (6) ErbB2 gene copies/nucleus for test systems without an internal control probe or an ErbB2/CEP 17 ratio of more than 2.2.

Sites must submit a copy of the laboratory report demonstrating unequivocal ErbB2 overexpression, if testing performed at a local laboratory, with the screening worksheet. Archived tumor must be provided for all patients for ErbB2 FISH testing by the central laboratory. Patients will remain on study based on local ErbB2 expression results. If archived tumor is not available, a biopsy must be obtained at screening and sent to TMD Laboratories for ErbB2 FISH testing.

- Patients must provide written informed consent prior to performance of study-specific procedures or assessments, and must be willing to comply with treatment and follow up. Procedures conducted as part of the patient's routine clinical management (e.g., blood count, imaging study) and obtained prior to signing of informed consent may be utilized for screening or baseline purposes provided these procedures are conducted as specified in the protocol.

Note: Informed consent may be obtained prior to the protocol-specified screening window (i.e. Day -14 to Day -1).

- Females age ≥ 18 years, except in Tunisia. In Tunisia, patients must be ≥ 20 years to be eligible for this study.
- Adequate organ function as defined below:
- System (Laboratory Values)
- Hematologic:Absolute neutrophil count (ANC)(≥ 1.5 X 10^9/L)Hemoglobin1(≥9 g/dL)Platelets(≥100 X 10^9/L)International normalized ratio (INR)(≤ 1.2 X upper limit of normal (ULN))Partial thromboplastin time (PTT)(≤1.2 X ULN)
- Hepatic:Total bilirubin2 (≤ 1.5 X upper limit of normal (ULN))AST and ALT(≤ 2.5 X ULN)
- Renal:Serum Creatinine (≤ 1.5 mg/dL)Or, if serum creatinine >1.5 mg/dL,
- Calculated creatinine clearance(≥50 mL/min)
- Urine Protein to Creatinine Ratio(<1)
- Patients may not have had a transfusion within 7 days of screening assessment.
- Exception: Patients with elevated bilirubin levels due to Gilberts syndrome are eligible.
- Cardiac ejection fraction within the institutional range of normal as measured by echocardiogram. MUGA scans will be accepted in cases where an echocardiogram cannot be performed or is inconclusive or where MUGA scans are the accepted standard. Patients with known history of uncontrolled or symptomatic angina, arrhythmias, or congestive heart failure are not eligible.
- Eastern Cooperative Oncology Group (ECOG) performance status of 0-2.
- A female is eligible to enter and participate in this study if she is of:

Non-childbearing potential (i.e., physiologically incapable of becoming pregnant), including any female who has had:

- A hysterectomy
- A bilateral oophorectomy (ovariectomy)
- A bilateral tubal ligation
- Is post-menopausal
- Patients not using hormone replacement therapy (HRT) must have experienced total cessation of menses for ≥ 1 year and be greater than 45 years in age, OR, in questionable cases, have a follicle stimulating hormone (FSH) value >40 mIU/mL and an estradiol value < 40pg/mL (<140 pmol/L).

Patients must discontinue HRT prior to study enrollment due to the potential for inhibition of CYP enzymes that metabolize estrogens and progestins (See Section 8). For most forms of HRT, at least 2-4 weeks must elapse between the cessation of HRT and determination of menopausal status; length of this interval depends on the type and dosage of HRT. If a female patient is determined not to be post-menopausal, they must use adequate contraception, as defined immediately below.

Childbearing potential, including any female who has had a negative serum pregnancy test within 2 weeks prior to the first dose of study treatment, preferably as close to the first dose as possible, has used adequate contraception since the pregnancy test and agrees to use adequate contraception as described below. GSK acceptable contraceptive methods, when used consistently and in accordance with both the product label and the instructions of the physician, are as follow:

- An intrauterine device with a documented failure rate of less than 1% per year.
- Vasectomized partner who is sterile prior to the female patient's entry and is the sole sexual partner for that female.
- Complete abstinence from sexual intercourse for 14 days before exposure to investigational product, through the dosing period, and for at least 21 days after the last dose of investigational product.
- Double-barrier contraception (condom with spermicidal jelly, foam suppository, or film; diaphragm with spermicide; or male condom and diaphragm with spermicide).

Note: Oral contraceptives are not reliable due to potential drug drug interactions.

Female patients who are lactating should discontinue nursing prior to the first dose of investigational product and should refrain from nursing throughout the treatment period and for 14 days following the last dose of investigational product.

- French patients: In France, a patient will be eligible for inclusion in this study only if either affiliated to or a beneficiary of a social security category.

Exclusion Criteria:

- Patients meeting any of the following criteria must not be enrolled in the study:
- Treatment in the 14 days prior to randomization with any cancer therapy (tumor embolization, chemotherapy, immunotherapy, biological therapy, or hormonal therapy) or treatment with mitomycin within 6 weeks prior to randomization. Such treatment may not be resumed or begun after study entry. Note: Patients receiving LH-RH analogue therapy prior to the study may continue to receive LH-RH analogues for the duration of study participation. Bisphosphonates are permitted if started prior to Day 1.
- Any ongoing toxicity from prior anti-cancer therapy that is >Grade 1 and/or that is progressing in severity (with the exception of alopecia).
- Prior lapatinib therapy or other Her2/ErbB2 targeted therapy (except trastuzumab).
- Prior therapy with an anti-VEGF antibody or other VEGF/VEGF-R targeted therapy.
- Use of an investigational agent, including an investigational anti-cancer agent, within 28 days or 5 half-lives, whichever is longer, prior to the first dose of investigational product.
- Use of any prohibited medication within the timeframes listed in Section 8.1.3
- History of another malignancy.
- Note: Subjects who have had another malignancy and have been disease-free for 5 years, or subjects with a history of completely resected non-melanomatous skin carcinoma or successfully treated in situ carcinoma are eligible. If subject previously had breast cancer, it must have been HER2+ with either 3+ overexpression by IHC or unequivocal HER2 gene amplification by FISH or CISH.
- History or clinical evidence of central nervous system (CNS) metastases or leptomeningeal carcinomatosis, except for individuals who have previously-treated CNS metastases, are asymptomatic, and have had no requirement for steroids or anti-seizure medication for 2 months prior to first dose of study drug. Screening with CNS imaging studies (computed tomography [CT] or magnetic resonance imaging [MRI]) is required only if clinically indicated or if the subject has a history of CNS metastases.
- Clinically significant gastrointestinal abnormalities that may increase the risk for GI bleeding including, but not limited to:
- Active peptic ulcer disease

- Known intraluminal metastatic lesion/s with suspected bleeding
- Inflammatory bowel disease
- Ulcerative colitis, or other gastrointestinal conditions with increased risk of perforation
- History of abdominal fistula, gastrointestinal perforation, or intra abdominal abscess within 28 days prior to beginning study treatment.
- Clinically significant gastrointestinal abnormalities that may affect absorption of investigational product including, but limited to:
- Malabsorption syndrome
- Major resection of the stomach or small bowel.
- Presence of uncontrolled infection.
- Prolongation of corrected QT interval (QTc) > 480 msecs.
- History of any one or more of the following cardiovascular conditions within the past 6 months:
- Cardiac angioplasty or stenting
- Myocardial infarction
- Unstable angina
- Arterial thrombosis
- Symptomatic peripheral vascular disease
- Class III or IV congestive heart failure, as defined by the New York Heart Association (NYHA) (see Section 15.9 Appendix 9 for description).
- Poorly controlled hypertension [defined as systolic blood pressure (SBP) of ≥140mmHg or diastolic blood pressure (DBP) of ≥ 90mmHg].

Note: Initiation or adjustment of antihypertensive medication(s) is permitted during the screening period, in order to control a patient's BP prior to randomization. Blood pressure must be re-assessed on two occasions that are separated by a minimum of 1 hour. The mean SBP / DBP values from each blood pressure assessment must be < 140/90mmHg in order for a patient to be eligible for the study. See Section 6.2 and Section 6.4.2 for details on blood pressure control and reassessment prior to study enrollment.

- History of cerebrovascular accident, including TIA, pulmonary embolism or deep venous thrombosis (DVT).
- Prior major surgery or trauma within 28 days prior to first dose of investigational product and/or presence of any non-healing wound, fracture, or ulcer (other than ulcers due to inflammatory breast cancer).
- Evidence of active bleeding or bleeding diathesis.
- Hemoptysis within 6 weeks prior to first dose of investigational product.
- Known endobronchial lesions or involvement of large pulmonary vessels by tumor.
- Any serious and/or unstable pre-existing medical, psychiatric, or other condition that could interfere with patient's safety, provision of informed consent, or compliance to study procedures.
- Known immediate or delayed hypersensitivity reaction or idiosyncrasy to drugs chemically related to pazopanib or lapatinib.
- Have current active hepatic or biliary disease (with exception of patients with Gilbert's syndrome, asymptomatic gallstones, liver metastases or stable chronic liver disease per investigator assessment).

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References

Citations:

Links:

Study Data/Documents:

Study Results

Participant Flow

Recruitment Details	This study consisted of an initial randomized treatment phase; participants were randomized to receive lapatinib, pazopanib, or combination therapy. Participants who received pazopanib monotherapy in this initial phase and experienced disease progression were given the option to receive lapatinib monotherapy in an open-label extension phase.
Pre-Assignment Details	Enrollment in Cohort 1 was halted after 76 participants had been randomized based on safety data from Study VEG20007 (NCT00347919). The protocol was amended (Amendment 2) to change the combination therapy dose (Cohort 2); in addition, an open-label pazopanib arm (pazopanib 800 milligrams) was added (Cohort 2).

Reporting Groups

	Description
Cohort 1: Lapatinib 1500 mg + Pazopanib Placebo	Participants received oral lapatinib 1500 milligrams (mg) (6 x 250 mg tablets) in combination with placebo (matching to pazopanib; 2 tablets) once daily (QD).
Cohort 1: Lapatinib 1500 mg + Pazopanib 800 mg	Participants received oral lapatinib 1500 mg (6 x 250 mg tablets) in combination with pazopanib 800 mg (2 x 400 mg tablets) QD.
Cohort 2: Lapatinib 1500 mg + Pazopanib Placebo	Participants received oral lapatinib 1500 mg (6 x 250 mg tablets) in combination with placebo (matching to pazopanib; 2 tablets) QD. The study treatment continued until participants experienced disease progression, unacceptable toxicity, or death.
Cohort 2: Pazopanib 800 mg	Participants received oral pazopanib 800 mg (4 x 200 mg tablets) QD. The study treatment continued until participants experienced disease progression, unacceptable toxicity, or death. Participants who received pazopanib monotherapy and experienced unequivocal disease progression were given the option to receive lapatinib monotherapy in an open-label extension phase.

	Description
Cohort 2: Lapatinib 1000 mg + Pazopanib 400 mg	Participants received oral lapatinib 1000 mg (4 x 250 mg tablets) and 2 x 250 mg placebo tablets in combination with pazopanib 400 mg (2 x 200 mg tablets) QD. The study treatment continued until participants experienced disease progression, unacceptable toxicity, or death.
Open-label Lapatinib 1500 mg	Participants who received pazopanib 800 mg in the randomized treatment phase were given the option to receive oral lapatinib 1500 milligrams (mg) (6 x 250 mg tablets) QD.

Randomized Treatment Phase

	Cohort 1: Lapatinib 1500 mg + Pazopanib Placebo	Cohort 1: Lapatinib 1500 mg + Pazopanib 800 mg	Cohort 2: Lapatinib 1500 mg + Pazopanib Placebo	Cohort 2: Pazopanib 800 mg	Cohort 2: Lapatinib 1000 mg + Pazopanib 400 mg	Open-label Lapatinib 1500 mg
Started	38	38	36	13	38	0
Completed	33	34	33	11	33	0
Not Completed	5	4	3	2	5	0
Lost to Follow-up	2	2	2	1	3	0
Withdrawal by Subject	2	2	0	0	1	0
Disease Progression	1	0	1	0	0	0
Adverse Event	0	0	0	1	1	0

Monotherapy Extension Phase

	Cohort 1: Lapatinib 1500 mg + Pazopanib Placebo	Cohort 1: Lapatinib 1500 mg + Pazopanib 800 mg	Cohort 2: Lapatinib 1500 mg + Pazopanib Placebo	Cohort 2: Pazopanib 800 mg	Cohort 2: Lapatinib 1000 mg + Pazopanib 400 mg	Open-label Lapatinib 1500 mg
Started	0	0	0	0	0	9 [1]
Completed	0	0	0	0	0	0
Not Completed	0	0	0	0	0	9
Protocol Violation	0	0	0	0	0	1
Disease Progression	0	0	0	0	0	8

[1] 9/11 participants completing pazopanib monotherapy elected to receive lapatinib monotherapy.

Baseline Characteristics

Reporting Groups

	Description
Cohort 1: Lapatinib 1500 mg + Pazopanib Placebo	Participants received oral lapatinib 1500 milligrams (mg) (6 x 250 mg tablets) in combination with placebo (matching to pazopanib; 2 tablets) once daily (QD).
Cohort 1: Lapatinib 1500 mg + Pazopanib 800 mg	Participants received oral lapatinib 1500 mg (6 x 250 mg tablets) in combination with pazopanib 800 mg (2 x 400 mg tablets) QD.
Cohort 2: Lapatinib 1500 mg + Pazopanib Placebo	Participants received oral lapatinib 1500 mg (6 x 250 mg tablets) in combination with placebo (matching to pazopanib; 2 tablets) QD. The study treatment continued until participants experienced disease progression, unacceptable toxicity, or death.
Cohort 2: Pazopanib 800 mg	Participants received oral pazopanib 800 mg (4 x 200 mg tablets) QD. The study treatment continued until participants experienced disease progression, unacceptable toxicity, or death. Participants who received pazopanib monotherapy and experienced unequivocal disease progression were given the option to receive lapatinib monotherapy in an open-label extension phase.
Cohort 2: Lapatinib 1000 mg + Pazopanib 400 mg	Participants received oral lapatinib 1000 mg (4 x 250 mg tablets) and 2 x 250 mg placebo tablets in combination with pazopanib 400 mg (2 x 200 mg tablets) QD. The study treatment continued until participants experienced disease progression, unacceptable toxicity, or death.

Baseline Measures

	Cohort 1: Lapatinib 1500 mg + Pazopanib Placebo	Cohort 1: Lapatinib 1500 mg + Pazopanib 800 mg	Cohort 2: Lapatinib 1500 mg + Pazopanib Placebo	Cohort 2: Pazopanib 800 mg	Cohort 2: Lapatinib 1000 mg + Pazopanib 400 mg	Total
Number of Participants	38	38	36	13	38	163
Age, Continuous Years [units: Years] Mean (Standard Deviation)	51.9 (9.00)	52.4 (12.84)	53.0 (10.39)	54.7 (12.26)	53.9 (12.65)	53.0 (11.31)
Gender, Male/Female [units: Participants]						
Female	38	38	36	13	38	163
Male	0	0	0	0	0	0
Race/Ethnicity, Customized [units: participants]						
African American/African Heritage	1	1	0	0	0	2

	Cohort 1: Lapatinib 1500 mg + Pazopanib Placebo	Cohort 1: Lapatinib 1500 mg + Pazopanib 800 mg	Cohort 2: Lapatinib 1500 mg + Pazopanib Placebo	Cohort 2: Pazopanib 800 mg	Cohort 2: Lapatinib 1000 mg + Pazopanib 400 mg	Total
American Indian or Alaska Native	1	3	2	1	3	10
Central/South Asian Heritage	2	1	2	1	2	8
Japanese/East Asian /South East Asian Heritage	9	6	11	5	14	45
White	24	27	21	6	19	97
American Indian or Alaska Native and Asian	1	0	0	0	0	1

Outcome Measures

1. Primary Outcome Measure:

Measure Title	Number of Participants With Overall Response (OR), Defined as Those Participants Achieving Complete Response (CR) or Partial Response (PR), Assessed Per Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.0 and Cutaneous Lesions
Measure Description	RECIST-based response assessment was done at Weeks (Wks) 4 and 8 and every 8 weeks thereafter. Cutaneous disease assessment was done at Wk 4 and every 4 weeks thereafter. OR was evaluated when the skin and RECIST assessments coincided. Per RECIST, CR is the disappearance of all target and non-target lesions; PR is at least a 30 percent (%) decrease in the sum of the longest diameter (LD) of target lesions, taking as a reference the baseline sum LD. Cutaneous disease contained non-measurable and measurable skin disease, which was assessed by skin assessment tools.
Time Frame	Baseline until disease progression/recurrence was documented, assessed for up to 66 weeks
Safety Issue?	No

Analysis Population Description

Modified Intent-to-Treat (mITT) Population: all randomized participants who received at least one dose of study treatment. The mITT1 Population was used for cohort 1; the mITT2 Population used for cohort 2.

Reporting Groups

	Description
Cohort 1: Lapatinib 1500 mg + Pazopanib Placebo	Participants received oral lapatinib 1500 milligrams (mg) (6 x 250 mg tablets) in combination with placebo (matching to pazopanib; 2 tablets) once daily (QD).

	Description
Cohort 1: Lapatinib 1500 mg + Pazopanib 800 mg	Participants received oral lapatinib 1500 mg (6 x 250 mg tablets) in combination with pazopanib 800 mg (2 x 400 mg tablets) QD.
Cohort 2: Lapatinib 1500 mg + Pazopanib Placebo	Participants received oral lapatinib 1500 mg (6 x 250 mg tablets) in combination with placebo (matching to pazopanib; 2 tablets) QD. The study treatment continued until participants experienced disease progression, unacceptable toxicity, or death.
Cohort 2: Pazopanib 800 mg	Participants received oral pazopanib 800 mg (4 x 200 mg tablets) QD. The study treatment continued until participants experienced disease progression, unacceptable toxicity, or death. Participants who received pazopanib monotherapy and experienced unequivocal disease progression were given the option to receive lapatinib monotherapy in an open-label extension phase.
Cohort 2: Lapatinib 1000 mg + Pazopanib 400 mg	Participants received oral lapatinib 1000 mg (4 x 250 mg tablets) and 2 x 250 mg placebo tablets in combination with pazopanib 400 mg (2 x 200 mg tablets) QD. The study treatment continued until participants experienced disease progression, unacceptable toxicity, or death.

Measured Values

	Cohort 1: Lapatinib 1500 mg + Pazopanib Placebo	Cohort 1: Lapatinib 1500 mg + Pazopanib 800 mg	Cohort 2: Lapatinib 1500 mg + Pazopanib Placebo	Cohort 2: Pazopanib 800 mg	Cohort 2: Lapatinib 1000 mg + Pazopanib 400 mg
Number of Participants Analyzed	38	38	36	13	38
Number of Participants With Overall Response (OR), Defined as Those Participants Achieving Complete Response (CR) or Partial Response (PR), Assessed Per Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.0 and Cutaneous Lesions [units: participants]	11	17	17	4	22

Statistical Analysis 1 for Number of Participants With Overall Response (OR), Defined as Those Participants Achieving Complete Response (CR) or Partial Response (PR), Assessed Per Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.0 and Cutaneous Lesions

Statistical Analysis Overview	Comparison Groups	Cohort 1: Lapatinib 1500 mg + Pazopanib Placebo
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Other [Percentage of participants]

	Estimated Value	29
	Confidence Interval	(2-Sided) 90% 17.2 to 43.3
	Estimation Comments	The estimated value represents the percentage of participants with CR and PR.

Statistical Analysis 2 for Number of Participants With Overall Response (OR), Defined as Those Participants Achieving Complete Response (CR) or Partial Response (PR), Assessed Per Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.0 and Cutaneous Lesions

Statistical Analysis Overview	Comparison Groups	Cohort 1: Lapatinib 1500 mg + Pazopanib 800 mg
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Other [Percentage of participants]
	Estimated Value	45
	Confidence Interval	(2-Sided) 90% 30.9 to 59.3
	Estimation Comments	The estimated value represents the percentage of participants with CR and PR.

Statistical Analysis 3 for Number of Participants With Overall Response (OR), Defined as Those Participants Achieving Complete Response (CR) or Partial Response (PR), Assessed Per Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.0 and Cutaneous Lesions

Statistical Analysis Overview	Comparison Groups	Cohort 2: Lapatinib 1500 mg + Pazopanib Placebo
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	<0.001
	Comments	Comparision of participants receiving lapatanib 1500 mg + placebo to historical control of 10% response rate
	Method	t-test, 1 sided
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Other [Percentage of participants]
	Estimated Value	47

	Confidence Interval	(2-Sided) 90% 32.8 to 62.1
	Estimation Comments	The estimated value represents the percentage of participants receiving lapatanib 1500 mg + placebo with CR and PR.

Statistical Analysis 4 for Number of Participants With Overall Response (OR), Defined as Those Participants Achieving Complete Response (CR) or Partial Response (PR), Assessed Per Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.0 and Cutaneous Lesions

Statistical Analysis Overview	Comparison Groups	Cohort 2: Pazopanib 800 mg
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Other [Percentage of participants]
	Estimated Value	31
	Confidence Interval	(2-Sided) 90% 11.3 to 57.3
	Estimation Comments	The estimated value represents the percentage of participants with CR and PR.

Statistical Analysis 5 for Number of Participants With Overall Response (OR), Defined as Those Participants Achieving Complete Response (CR) or Partial Response (PR), Assessed Per Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.0 and Cutaneous Lesions

Statistical Analysis Overview	Comparison Groups	Cohort 2: Lapatinib 1000 mg + Pazopanib 400 mg
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	<0.001
	Comments	Comparision of participants receiving lapatanib 1000 mg + pazopanib 400 mg to 10% historical response rate
	Method	t-test, 1 sided
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Other [Percentage of participants]
	Estimated Value	58

	Confidence Interval	(2-Sided) 90% 43.3 to 71.5
	Estimation Comments	The estimated value represents the percentage of participants receiving lapatanib 1000 mg + pazopanib 400 mg with CR and PR.

Statistical Analysis 6 for Number of Participants With Overall Response (OR), Defined as Those Participants Achieving Complete Response (CR) or Partial Response (PR), Assessed Per Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.0 and Cutaneous Lesions

Statistical Analysis Overview	Comparison Groups	Cohort 2: Lapatinib 1500 mg + Pazopanib Placebo, Cohort 2: Lapatinib 1000 mg + Pazopanib 400 mg
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.485
	Comments	[Not specified]
	Method	Fisher Exact
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Other [Difference in percentage of participants]
	Estimated Value	11
	Confidence Interval	(2-Sided) 90% -8.3 to 29.7
	Estimation Comments	The estimated value represents the percent difference in the percentage of participants with CR and PR.

Statistical Analysis 7 for Number of Participants With Overall Response (OR), Defined as Those Participants Achieving Complete Response (CR) or Partial Response (PR), Assessed Per Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.0 and Cutaneous Lesions

Statistical Analysis Overview	Comparison Groups	Cohort 2: Pazopanib 800 mg, Cohort 2: Lapatinib 1000 mg + Pazopanib 400 mg
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.116
	Comments	[Not specified]
	Method	Fisher Exact
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Other [Difference in percentage of participants]
	Estimated Value	27
	Confidence Interval	(2-Sided) 90% 2.3 to 52.0
	Estimation Comments	The estimated value represents the percent difference in the percentage of participants with CR and PR.

2. Secondary Outcome Measure:

Measure Title	Median Duration of Response,Defined as the First Documented Evidence of CR or PR Until the First Documentation of Disease Progression
Measure Description	RECIST-based response assessment was done at Wks 4 and 8 and every 8 weeks thereafter. Cutaneous disease assessment was done at Wk 4 and every 4 weeks thereafter. OR was evaluated when the skin and RECIST assessments coincided. Per RECIST, PD is >=20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since treatment started or the appearance of >=1 new lesion and/or unequivocal progression of existing non-target lesions. Cutaneous disease contained non-measurable and measurable skin disease, which was assessed by skin assessment tools.
Time Frame	From the date of the first documented evidence of CR or PR until the date of the first documented disease progression or death, assessed for up to 62 weeks
Safety Issue?	No

Analysis Population Description

mITT1 and mITT2 Populations. Only participants who achieved a response of CR or PR during the study were analyzed. For participants who did not progress or die, duration of response was censored on the date of the last adequate assessment.

Reporting Groups

	Description
Cohort 1: Lapatinib 1500 mg + Pazopanib Placebo	Participants received oral lapatinib 1500 milligrams (mg) (6 x 250 mg tablets) in combination with placebo (matching to pazopanib; 2 tablets) once daily (QD).
Cohort 1: Lapatinib 1500 mg + Pazopanib 800 mg	Participants received oral lapatinib 1500 mg (6 x 250 mg tablets) in combination with pazopanib 800 mg (2 x 400 mg tablets) QD.

	Description
Cohort 2: Lapatinib 1500 mg + Pazopanib Placebo	Participants received oral lapatinib 1500 mg (6 x 250 mg tablets) in combination with placebo (matching to pazopanib; 2 tablets) QD. The study treatment continued until participants experienced disease progression, unacceptable toxicity, or death.
Cohort 2: Pazopanib 800 mg	Participants received oral pazopanib 800 mg (4 x 200 mg tablets) QD. The study treatment continued until participants experienced disease progression, unacceptable toxicity, or death. Participants who received pazopanib monotherapy and experienced unequivocal disease progression were given the option to receive lapatinib monotherapy in an open-label extension phase.
Cohort 2: Lapatinib 1000 mg + Pazopanib 400 mg	Participants received oral lapatinib 1000 mg (4 x 250 mg tablets) and 2 x 250 mg placebo tablets in combination with pazopanib 400 mg (2 x 200 mg tablets) QD. The study treatment continued until participants experienced disease progression, unacceptable toxicity, or death.

Measured Values

	Cohort 1: Lapatinib 1500 mg + Pazopanib Placebo	Cohort 1: Lapatinib 1500 mg + Pazopanib 800 mg	Cohort 2: Lapatinib 1500 mg + Pazopanib Placebo	Cohort 2: Pazopanib 800 mg	Cohort 2: Lapatinib 1000 mg + Pazopanib 400 mg
Number of Participants Analyzed	11	17	17	4	22
Median Duration of Response,Defined as the First Documented Evidence of CR or PR Until the First Documentation of Disease Progression [units: weeks] Median (90% Confidence Interval)	16.9 (12.4 to 21.0)	13.0 (9.1 to 28.1)	13.6 (10.0 to 19.9)	31.2 (3.4 to 33.1)	12.7 (8.0 to 16.1)

3. Secondary Outcome Measure:

Measure Title	Progression-free Survival, Defined as the Interval Between the Date of Randomization and the Earliest Date of Disease Progression (PD) or Death Due to Any Cause (Defined by an Investigator Review of Lesions Based on RECIST and Cutaneous Disease)
Measure Description	RECIST-based response assessment was done at Wks 4 and 8 and every 8 weeks thereafter. Cutaneous disease assessment was done at Wk 4 and every 4 weeks thereafter. OR was evaluated when the skin and RECIST assessments coincided. Per RECIST, PD is >=20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since treatment started or the appearance of >=1 new lesion and/or unequivocal progression of existing non-target lesions. Cutaneous disease contained non-measurable and measurable skin disease, which was assessed by skin assessment tools.
Time Frame	From the date of the randomization until the earliest date of disease progression or death due to any cause, assessed for up to 66 weeks

Safety Issue?	No

Analysis Population Description

mITT1 and mITT2 Populations

Reporting Groups

	Description
Cohort 1: Lapatinib 1500 mg + Pazopanib Placebo	Participants received oral lapatinib 1500 milligrams (mg) (6 x 250 mg tablets) in combination with placebo (matching to pazopanib; 2 tablets) once daily (QD).
Cohort 1: Lapatinib 1500 mg + Pazopanib 800 mg	Participants received oral lapatinib 1500 mg (6 x 250 mg tablets) in combination with pazopanib 800 mg (2 x 400 mg tablets) QD.
Cohort 2: Lapatinib 1500 mg + Pazopanib Placebo	Participants received oral lapatinib 1500 mg (6 x 250 mg tablets) in combination with placebo (matching to pazopanib; 2 tablets) QD. The study treatment continued until participants experienced disease progression, unacceptable toxicity, or death.
Cohort 2: Pazopanib 800 mg	Participants received oral pazopanib 800 mg (4 x 200 mg tablets) QD. The study treatment continued until participants experienced disease progression, unacceptable toxicity, or death. Participants who received pazopanib monotherapy and experienced unequivocal disease progression were given the option to receive lapatinib monotherapy in an open-label extension phase.
Cohort 2: Lapatinib 1000 mg + Pazopanib 400 mg	Participants received oral lapatinib 1000 mg (4 x 250 mg tablets) and 2 x 250 mg placebo tablets in combination with pazopanib 400 mg (2 x 200 mg tablets) QD. The study treatment continued until participants experienced disease progression, unacceptable toxicity, or death.

Measured Values

	Cohort 1: Lapatinib 1500 mg + Pazopanib Placebo	Cohort 1: Lapatinib 1500 mg + Pazopanib 800 mg	Cohort 2: Lapatinib 1500 mg + Pazopanib Placebo	Cohort 2: Pazopanib 800 mg	Cohort 2: Lapatinib 1000 mg + Pazopanib 400 mg
Number of Participants Analyzed	38	38	36	13	38
Progression-free Survival, Defined as the Interval Between the Date of Randomization and the Earliest Date of Disease Progression (PD) or Death Due to Any Cause (Defined by an Investigator Review of Lesions Based on RECIST and Cutaneous Disease) [units: weeks] Median (90% Confidence Interval)	16.1 (12.0 to 21.1)	14.3 (8.6 to 20.1)	16.0 (12.4 to 16.3)	11.4 (6.6 to 33.6)	16.0 (12.4 to 17.9)

4. Secondary Outcome Measure:

Measure Title	Overall Survival
Measure Description	Overall survival is defined as the time from randomization until death due to any cause. For participants who did not die, time to death was censored at the time of last contact.
Time Frame	From the date of randomization until the date of death due to any cause, assessed for up to 163 weeks
Safety Issue?	No

Analysis Population Description

mITT1 and mITT2 Populations

Reporting Groups

	Description
Cohort 1: Lapatinib 1500 mg + Pazopanib Placebo	Participants received oral lapatinib 1500 milligrams (mg) (6 x 250 mg tablets) in combination with placebo (matching to pazopanib; 2 tablets) once daily (QD).
Cohort 1: Lapatinib 1500 mg + Pazopanib 800 mg	Participants received oral lapatinib 1500 mg (6 x 250 mg tablets) in combination with pazopanib 800 mg (2 x 400 mg tablets) QD.
Cohort 2: Lapatinib 1500 mg + Pazopanib Placebo	Participants received oral lapatinib 1500 mg (6 x 250 mg tablets) in combination with placebo (matching to pazopanib; 2 tablets) QD. The study treatment continued until participants experienced disease progression, unacceptable toxicity, or death.
Cohort 2: Pazopanib 800 mg	Participants received oral pazopanib 800 mg (4 x 200 mg tablets) QD. The study treatment continued until participants experienced disease progression, unacceptable toxicity, or death. Participants who received pazopanib monotherapy and experienced unequivocal disease progression were given the option to receive lapatinib monotherapy in an open-label extension phase.
Cohort 2: Lapatinib 1000 mg + Pazopanib 400 mg	Participants received oral lapatinib 1000 mg (4 x 250 mg tablets) and 2 x 250 mg placebo tablets in combination with pazopanib 400 mg (2 x 200 mg tablets) QD. The study treatment continued until participants experienced disease progression, unacceptable toxicity, or death.

Measured Values

	Cohort 1: Lapatinib 1500 mg + Pazopanib Placebo	Cohort 1: Lapatinib 1500 mg + Pazopanib 800 mg	Cohort 2: Lapatinib 1500 mg + Pazopanib Placebo	Cohort 2: Pazopanib 800 mg	Cohort 2: Lapatinib 1000 mg + Pazopanib 400 mg
Number of Participants Analyzed	38	38	36	13	38
Overall Survival [units: months] Median (90% Confidence Interval)	14.7 (12.1 to 16.5)	16.2 (12.7 to 21.1)	15.9 (13.4 to NA) [1]	NA (9.8 to NA) [2]	NA (12.4 to NA) [2]

[1] Due to an insufficient number of events, the upper limit of the confidence interval could not be calculated.

[2] Due to an insufficient number of events, the median and the upper limit of the confidence interval could not be calculated.

Reported Adverse Events

Time Frame	[Not specified]
Additional Description	[Not specified]

Reporting Groups

	Description
Cohort 1: Lapatinib 1500 mg + Pazopanib Placebo	Participants received oral lapatinib 1500 milligrams (mg) (6 x 250 mg tablets) in combination with placebo (matching to pazopanib; 2 tablets) once daily (QD).
Cohort 1: Lapatinib 1500 mg + Pazopanib 800 mg	Participants received oral lapatinib 1500 mg (6 x 250 mg tablets) in combination with pazopanib 800 mg (2 x 400 mg tablets) QD.
Cohort 2: Lapatinib 1500 mg + Pazopanib Placebo	Participants received oral lapatinib 1500 mg (6 x 250 mg tablets) in combination with placebo (matching to pazopanib; 2 tablets) QD. The study treatment continued until participants experienced disease progression, unacceptable toxicity, or death.
Cohort 2: Pazopanib 800 mg	Participants received oral pazopanib 800 mg (4 x 200 mg tablets) QD. The study treatment continued until participants experienced disease progression, unacceptable toxicity, or death. Participants who received pazopanib monotherapy and experienced unequivocal disease progression were given the option to receive lapatinib monotherapy in an open-label extension phase.
Cohort 2: Lapatinib 1000 mg + Pazopanib 400 mg	Participants received oral lapatinib 1000 mg (4 x 250 mg tablets) and 2 x 250 mg placebo tablets in combination with pazopanib 400 mg (2 x 200 mg tablets) QD. The study treatment continued until participants experienced disease progression, unacceptable toxicity, or death.
Open-label Lapatinib 1500 mg	Participants who received pazopanib 800 mg in the randomized treatment phase were given the option to receive oral lapatinib 1500 milligrams (mg) (6 x 250 mg tablets) QD.

Serious Adverse Events

	Cohort 1: Lapatinib 1500 mg + Pazopanib Placebo	Cohort 1: Lapatinib 1500 mg + Pazopanib 800 mg	Cohort 2: Lapatinib 1500 mg + Pazopanib Placebo	Cohort 2: Pazopanib 800 mg	Cohort 2: Lapatinib 1000 mg + Pazopanib 400 mg	Open-label Lapatinib 1500 mg
	Affected/ At Risk (%)	Affected/ At Risk (%)	Affected/ At Risk (%)	Affected/ At Risk (%)	Affected/ At Risk (%)	Affected/ At Risk (%)
Total	6/38 (15.79%)	14/38 (36.84%)	4/36 (11.11%)	4/13 (30.77%)	9/38 (23.68%)	0/9 (0%)
Blood and lymphatic system disorders						
Neutropenia [A] †	1/38 (2.63%)	1/38 (2.63%)	0/36 (0%)	0/13 (0%)	0/38 (0%)	0/9 (0%)
Cardiac disorders						
Bradycardia [A] †	0/38 (0%)	0/38 (0%)	0/36 (0%)	1/13 (7.69%)	0/38 (0%)	0/9 (0%)
Cardiopulmonary failure [A] †	0/38 (0%)	0/38 (0%)	0/36 (0%)	1/13 (7.69%)	0/38 (0%)	0/9 (0%)
Sinus tachycardia [A] †	0/38 (0%)	0/38 (0%)	0/36 (0%)	0/13 (0%)	1/38 (2.63%)	0/9 (0%)
Gastrointestinal disorders						
Abdominal pain [A] †	0/38 (0%)	0/38 (0%)	0/36 (0%)	1/13 (7.69%)	1/38 (2.63%)	0/9 (0%)
Diarrhea [A] †	0/38 (0%)	2/38 (5.26%)	0/36 (0%)	0/13 (0%)	0/38 (0%)	0/9 (0%)
Nausea [A] †	1/38 (2.63%)	0/38 (0%)	0/36 (0%)	0/13 (0%)	0/38 (0%)	0/9 (0%)
Pancreatitis [A] †	0/38 (0%)	0/38 (0%)	0/36 (0%)	0/13 (0%)	1/38 (2.63%)	0/9 (0%)
Vomiting [A] †	1/38 (2.63%)	2/38 (5.26%)	0/36 (0%)	0/13 (0%)	0/38 (0%)	0/9 (0%)
General disorders						
Asthenia [A] †	0/38 (0%)	0/38 (0%)	0/36 (0%)	0/13 (0%)	1/38 (2.63%)	0/9 (0%)
Fatigue [A] †	0/38 (0%)	0/38 (0%)	1/36 (2.78%)	1/13 (7.69%)	1/38 (2.63%)	0/9 (0%)
Sudden death [A] †	1/38 (2.63%)	1/38 (2.63%)	0/36 (0%)	0/13 (0%)	0/38 (0%)	0/9 (0%)
Hepatobiliary disorders						
Cholestatic liver injury [A] †	1/38 (2.63%)	0/38 (0%)	0/36 (0%)	0/13 (0%)	0/38 (0%)	0/9 (0%)
Hepatic function abnormal [A] †	0/38 (0%)	0/38 (0%)	0/36 (0%)	0/13 (0%)	1/38 (2.63%)	0/9 (0%)

	Cohort 1: Lapatinib 1500 mg + Pazopanib Placebo	Cohort 1: Lapatinib 1500 mg + Pazopanib 800 mg	Cohort 2: Lapatinib 1500 mg + Pazopanib Placebo	Cohort 2: Pazopanib 800 mg	Cohort 2: Lapatinib 1000 mg + Pazopanib 400 mg	Open-label Lapatinib 1500 mg
	Affected/ At Risk (%)	Affected/ At Risk (%)	Affected/ At Risk (%)	Affected/ At Risk (%)	Affected/ At Risk (%)	Affected/ At Risk (%)
Hepatotoxicity [A] †	0/38 (0%)	1/38 (2.63%)	0/36 (0%)	0/13 (0%)	0/38 (0%)	0/9 (0%)
Infections and infestations						
Empyema [A] †	0/38 (0%)	1/38 (2.63%)	0/36 (0%)	0/13 (0%)	0/38 (0%)	0/9 (0%)
Pneumonia [A] †	0/38 (0%)	0/38 (0%)	0/36 (0%)	1/13 (7.69%)	1/38 (2.63%)	0/9 (0%)
Sepsis [A] †	0/38 (0%)	1/38 (2.63%)	0/36 (0%)	0/13 (0%)	0/38 (0%)	0/9 (0%)
Upper respiratory tract infection [A] †	1/38 (2.63%)	0/38 (0%)	0/36 (0%)	0/13 (0%)	0/38 (0%)	0/9 (0%)
Injury, poisoning and procedural complications						
Eye injury [A] †	0/38 (0%)	0/38 (0%)	0/36 (0%)	1/13 (7.69%)	0/38 (0%)	0/9 (0%)
Investigations						
Alanine aminotransferase increased [A] †	0/38 (0%)	1/38 (2.63%)	1/36 (2.78%)	0/13 (0%)	3/38 (7.89%)	0/9 (0%)
Blood bilirubin increased [A] †	0/38 (0%)	0/38 (0%)	0/36 (0%)	0/13 (0%)	1/38 (2.63%)	0/9 (0%)
Ejection fraction decreased [A] †	0/38 (0%)	1/38 (2.63%)	0/36 (0%)	0/13 (0%)	0/38 (0%)	0/9 (0%)
Gamma-glutamyltransferase increased [A] †	0/38 (0%)	0/38 (0%)	1/36 (2.78%)	0/13 (0%)	0/38 (0%)	0/9 (0%)
Liver function test abnormal [A] †	0/38 (0%)	1/38 (2.63%)	0/36 (0%)	0/13 (0%)	0/38 (0%)	0/9 (0%)
Metabolism and nutrition disorders						
Hyperuricemia [A] †	0/38 (0%)	0/38 (0%)	0/36 (0%)	0/13 (0%)	1/38 (2.63%)	0/9 (0%)
Musculoskeletal and connective tissue disorders						
Back pain [A] †	0/38 (0%)	1/38 (2.63%)	0/36 (0%)	0/13 (0%)	0/38 (0%)	0/9 (0%)
Musculoskeletal chest pain [A] †	0/38 (0%)	1/38 (2.63%)	0/36 (0%)	0/13 (0%)	0/38 (0%)	0/9 (0%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)						
Metastases to peritoneum [A] †	0/38 (0%)	0/38 (0%)	1/36 (2.78%)	0/13 (0%)	0/38 (0%)	0/9 (0%)

	Cohort 1: Lapatinib 1500 mg + Pazopanib Placebo	Cohort 1: Lapatinib 1500 mg + Pazopanib 800 mg	Cohort 2: Lapatinib 1500 mg + Pazopanib Placebo	Cohort 2: Pazopanib 800 mg	Cohort 2: Lapatinib 1000 mg + Pazopanib 400 mg	Open-label Lapatinib 1500 mg
	Affected/ At Risk (%)	Affected/ At Risk (%)	Affected/ At Risk (%)	Affected/ At Risk (%)	Affected/ At Risk (%)	Affected/ At Risk (%)
Nervous system disorders						
Headache [A] †	0/38 (0%)	1/38 (2.63%)	0/36 (0%)	0/13 (0%)	0/38 (0%)	0/9 (0%)
Subarachnoid hemorrhage [A] †	0/38 (0%)	0/38 (0%)	0/36 (0%)	0/13 (0%)	1/38 (2.63%)	0/9 (0%)
Respiratory, thoracic and mediastinal disorders						
Dyspnea [A] †	0/38 (0%)	0/38 (0%)	1/36 (2.78%)	0/13 (0%)	1/38 (2.63%)	0/9 (0%)
Hypoxia [A] †	0/38 (0%)	0/38 (0%)	0/36 (0%)	0/13 (0%)	1/38 (2.63%)	0/9 (0%)
Orthopnea [A] †	0/38 (0%)	0/38 (0%)	1/36 (2.78%)	0/13 (0%)	0/38 (0%)	0/9 (0%)
Pleural effusion [A] †	0/38 (0%)	0/38 (0%)	0/36 (0%)	0/13 (0%)	1/38 (2.63%)	0/9 (0%)
Pleurisy [A] †	1/38 (2.63%)	0/38 (0%)	0/36 (0%)	0/13 (0%)	0/38 (0%)	0/9 (0%)
Pulmonary edema [A] †	0/38 (0%)	0/38 (0%)	0/36 (0%)	1/13 (7.69%)	0/38 (0%)	0/9 (0%)
Pulmonary embolism [A] †	0/38 (0%)	1/38 (2.63%)	0/36 (0%)	0/13 (0%)	0/38 (0%)	0/9 (0%)
Respiratory failure [A] †	0/38 (0%)	1/38 (2.63%)	0/36 (0%)	0/13 (0%)	0/38 (0%)	0/9 (0%)
Skin and subcutaneous tissue disorders						
Skin hemorrhage [A] †	0/38 (0%)	0/38 (0%)	0/36 (0%)	0/13 (0%)	1/38 (2.63%)	0/9 (0%)
Skin ulcer [A] †	0/38 (0%)	0/38 (0%)	0/36 (0%)	0/13 (0%)	1/38 (2.63%)	0/9 (0%)
Vascular disorders						
Hypertension [A] †	0/38 (0%)	1/38 (2.63%)	0/36 (0%)	0/13 (0%)	0/38 (0%)	0/9 (0%)

† Indicates events were collected by systematic assessment.
A Term from vocabulary, MedDRA

Other Adverse Events

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

	Cohort 1: Lapatinib 1500 mg + Pazopanib Placebo	Cohort 1: Lapatinib 1500 mg + Pazopanib 800 mg	Cohort 2: Lapatinib 1500 mg + Pazopanib Placebo	Cohort 2: Pazopanib 800 mg	Cohort 2: Lapatinib 1000 mg + Pazopanib 400 mg	Open-label Lapatinib 1500 mg
	Affected/ At Risk (%)	Affected/ At Risk (%)	Affected/ At Risk (%)	Affected/ At Risk (%)	Affected/ At Risk (%)	Affected/ At Risk (%)
Total	31/38 (81.58%)	37/38 (97.37%)	34/36 (94.44%)	13/13 (100%)	35/38 (92.11%)	7/9 (77.78%)
Blood and lymphatic system disorders						
Anemia [A] †	2/38 (5.26%)	2/38 (5.26%)	4/36 (11.11%)	0/13 (0%)	1/38 (2.63%)	0/9 (0%)
Leukopenia [A] †	0/38 (0%)	2/38 (5.26%)	2/36 (5.56%)	1/13 (7.69%)	8/38 (21.05%)	1/9 (11.11%)
Neutropenia [A] †	0/38 (0%)	5/38 (13.16%)	0/36 (0%)	4/13 (30.77%)	7/38 (18.42%)	0/9 (0%)
Thrombocytopenia [A] †	0/38 (0%)	2/38 (5.26%)	0/36 (0%)	0/13 (0%)	0/38 (0%)	0/9 (0%)
Ear and labyrinth disorders						
Tinnitus [A] †	0/38 (0%)	0/38 (0%)	0/36 (0%)	0/13 (0%)	2/38 (5.26%)	0/9 (0%)
Endocrine disorders						
Hypothyroidism [A] †	1/38 (2.63%)	2/38 (5.26%)	0/36 (0%)	2/13 (15.38%)	4/38 (10.53%)	0/9 (0%)
Eye disorders						
Dry eye [A] †	0/38 (0%)	0/38 (0%)	0/36 (0%)	0/13 (0%)	2/38 (5.26%)	0/9 (0%)
Lacrimation increased [A] †	0/38 (0%)	0/38 (0%)	0/36 (0%)	0/13 (0%)	0/38 (0%)	1/9 (11.11%)
Ocular hyperaemia [A] †	0/38 (0%)	0/38 (0%)	0/36 (0%)	0/13 (0%)	0/38 (0%)	1/9 (11.11%)
Gastrointestinal disorders						
Abdominal discomfort [A] †	0/38 (0%)	0/38 (0%)	0/36 (0%)	1/13 (7.69%)	0/38 (0%)	0/9 (0%)
Abdominal distension [A] †	0/38 (0%)	0/38 (0%)	2/36 (5.56%)	1/13 (7.69%)	0/38 (0%)	0/9 (0%)
Abdominal pain [A] †	0/38 (0%)	3/38 (7.89%)	2/36 (5.56%)	2/13 (15.38%)	7/38 (18.42%)	0/9 (0%)
Abdominal pain upper [A] †	2/38 (5.26%)	4/38 (10.53%)	2/36 (5.56%)	0/13 (0%)	2/38 (5.26%)	0/9 (0%)

	Cohort 1: Lapatinib 1500 mg + Pazopanib Placebo	Cohort 1: Lapatinib 1500 mg + Pazopanib 800 mg	Cohort 2: Lapatinib 1500 mg + Pazopanib Placebo	Cohort 2: Pazopanib 800 mg	Cohort 2: Lapatinib 1000 mg + Pazopanib 400 mg	Open-label Lapatinib 1500 mg
	Affected/ At Risk (%)	Affected/ At Risk (%)	Affected/ At Risk (%)	Affected/ At Risk (%)	Affected/ At Risk (%)	Affected/ At Risk (%)
Constipation [A] †	2/38 (5.26%)	0/38 (0%)	3/36 (8.33%)	1/13 (7.69%)	1/38 (2.63%)	1/9 (11.11%)
Diarrhea [A] †	15/38 (39.47%)	33/38 (86.84%)	20/36 (55.56%)	6/13 (46.15%)	22/38 (57.89%)	2/9 (22.22%)
Dry mouth [A] †	0/38 (0%)	0/38 (0%)	0/36 (0%)	0/13 (0%)	2/38 (5.26%)	0/9 (0%)
Dyspepsia [A] †	0/38 (0%)	2/38 (5.26%)	0/36 (0%)	0/13 (0%)	0/38 (0%)	0/9 (0%)
Mouth ulceration [A] †	0/38 (0%)	0/38 (0%)	2/36 (5.56%)	1/13 (7.69%)	2/38 (5.26%)	0/9 (0%)
Nausea [A] †	5/38 (13.16%)	17/38 (44.74%)	6/36 (16.67%)	2/13 (15.38%)	9/38 (23.68%)	2/9 (22.22%)
Stomatitis [A] †	2/38 (5.26%)	4/38 (10.53%)	0/36 (0%)	1/13 (7.69%)	2/38 (5.26%)	0/9 (0%)
Vomiting [A] †	6/38 (15.79%)	15/38 (39.47%)	2/36 (5.56%)	4/13 (30.77%)	5/38 (13.16%)	1/9 (11.11%)
General disorders						
Asthenia [A] †	4/38 (10.53%)	8/38 (21.05%)	1/36 (2.78%)	0/13 (0%)	4/38 (10.53%)	1/9 (11.11%)
Edema peripheral [A] †	0/38 (0%)	0/38 (0%)	0/36 (0%)	1/13 (7.69%)	2/38 (5.26%)	0/9 (0%)
Fatigue [A] †	4/38 (10.53%)	14/38 (36.84%)	6/36 (16.67%)	3/13 (23.08%)	8/38 (21.05%)	0/9 (0%)
Hyperthermia [A] †	2/38 (5.26%)	2/38 (5.26%)	0/36 (0%)	0/13 (0%)	0/38 (0%)	0/9 (0%)
Malaise [A] †	0/38 (0%)	2/38 (5.26%)	0/36 (0%)	0/13 (0%)	0/38 (0%)	0/9 (0%)
Mucosal inflammation [A] †	0/38 (0%)	6/38 (15.79%)	1/36 (2.78%)	1/13 (7.69%)	0/38 (0%)	0/9 (0%)
Pyrexia [A] †	2/38 (5.26%)	3/38 (7.89%)	1/36 (2.78%)	0/13 (0%)	3/38 (7.89%)	0/9 (0%)
Hepatobiliary disorders						
Hyperbilirubinemia [A] †	2/38 (5.26%)	7/38 (18.42%)	0/36 (0%)	1/13 (7.69%)	1/38 (2.63%)	0/9 (0%)
Jaundice [A] †	0/38 (0%)	0/38 (0%)	0/36 (0%)	1/13 (7.69%)	0/38 (0%)	0/9 (0%)

	Cohort 1: Lapatinib 1500 mg + Pazopanib Placebo	Cohort 1: Lapatinib 1500 mg + Pazopanib 800 mg	Cohort 2: Lapatinib 1500 mg + Pazopanib Placebo	Cohort 2: Pazopanib 800 mg	Cohort 2: Lapatinib 1000 mg + Pazopanib 400 mg	Open-label Lapatinib 1500 mg
	Affected/ At Risk (%)	Affected/ At Risk (%)	Affected/ At Risk (%)	Affected/ At Risk (%)	Affected/ At Risk (%)	Affected/ At Risk (%)
Infections and infestations						
Nasopharyngitis [A] †	0/38 (0%)	0/38 (0%)	2/36 (5.56%)	0/13 (0%)	0/38 (0%)	0/9 (0%)
Staphylococcal skin infection [A] †	0/38 (0%)	0/38 (0%)	0/36 (0%)	1/13 (7.69%)	0/38 (0%)	1/9 (11.11%)
Urinary tract infection [A] †	3/38 (7.89%)	0/38 (0%)	0/36 (0%)	0/13 (0%)	0/38 (0%)	0/9 (0%)
Injury, poisoning and procedural complications						
Chemical eye injury [A] †	0/38 (0%)	0/38 (0%)	0/36 (0%)	0/13 (0%)	0/38 (0%)	1/9 (11.11%)
Investigations						
Alanine aminotransferase increased [A] †	4/38 (10.53%)	13/38 (34.21%)	8/36 (22.22%)	2/13 (15.38%)	8/38 (21.05%)	1/9 (11.11%)
Aspartate aminotransferase increased [A] †	5/38 (13.16%)	13/38 (34.21%)	8/36 (22.22%)	3/13 (23.08%)	10/38 (26.32%)	1/9 (11.11%)
Bilirubin conjugated increased [A] †	0/38 (0%)	0/38 (0%)	2/36 (5.56%)	0/13 (0%)	2/38 (5.26%)	0/9 (0%)
Blood alkaline phosphatase increased [A] †	2/38 (5.26%)	3/38 (7.89%)	3/36 (8.33%)	2/13 (15.38%)	4/38 (10.53%)	0/9 (0%)
Blood bicarbonate decreased [A] †	0/38 (0%)	0/38 (0%)	3/36 (8.33%)	0/13 (0%)	1/38 (2.63%)	0/9 (0%)
Blood bilirubin increased [A] †	0/38 (0%)	5/38 (13.16%)	5/36 (13.89%)	1/13 (7.69%)	6/38 (15.79%)	0/9 (0%)
Blood lactate dehydrogenase increased [A] †	0/38 (0%)	5/38 (13.16%)	0/36 (0%)	2/13 (15.38%)	4/38 (10.53%)	0/9 (0%)
Blood pressure increased [A] †	1/38 (2.63%)	2/38 (5.26%)	0/36 (0%)	0/13 (0%)	0/38 (0%)	0/9 (0%)
Blood sodium decreased [A] †	0/38 (0%)	0/38 (0%)	1/36 (2.78%)	1/13 (7.69%)	1/38 (2.63%)	0/9 (0%)
Blood thyroid stimulating hormone increased [A] †	0/38 (0%)	0/38 (0%)	1/36 (2.78%)	2/13 (15.38%)	3/38 (7.89%)	0/9 (0%)
Ejection fraction decreased [A] †	0/38 (0%)	0/38 (0%)	1/36 (2.78%)	1/13 (7.69%)	2/38 (5.26%)	0/9 (0%)
Electrocardiogram QT prolonged [A] †	0/38 (0%)	0/38 (0%)	1/36 (2.78%)	0/13 (0%)	2/38 (5.26%)	0/9 (0%)

	Cohort 1: Lapatinib 1500 mg + Pazopanib Placebo	Cohort 1: Lapatinib 1500 mg + Pazopanib 800 mg	Cohort 2: Lapatinib 1500 mg + Pazopanib Placebo	Cohort 2: Pazopanib 800 mg	Cohort 2: Lapatinib 1000 mg + Pazopanib 400 mg	Open-label Lapatinib 1500 mg
	Affected/ At Risk (%)	Affected/ At Risk (%)	Affected/ At Risk (%)	Affected/ At Risk (%)	Affected/ At Risk (%)	Affected/ At Risk (%)
Electrocardiogram ST segment depression [A] †	0/38 (0%)	0/38 (0%)	2/36 (5.56%)	0/13 (0%)	0/38 (0%)	0/9 (0%)
Gamma-glutamyltransferase increased [A] †	0/38 (0%)	0/38 (0%)	1/36 (2.78%)	0/13 (0%)	2/38 (5.26%)	0/9 (0%)
Hemoglobin decreased [A] †	0/38 (0%)	0/38 (0%)	0/36 (0%)	0/13 (0%)	3/38 (7.89%)	0/9 (0%)
Platelet count decreased [A] †	0/38 (0%)	0/38 (0%)	0/36 (0%)	2/13 (15.38%)	3/38 (7.89%)	0/9 (0%)
Platelet count increased [A] †	0/38 (0%)	0/38 (0%)	0/36 (0%)	0/13 (0%)	0/38 (0%)	1/9 (11.11%)
Weight decreased [A] †	1/38 (2.63%)	5/38 (13.16%)	2/36 (5.56%)	1/13 (7.69%)	0/38 (0%)	0/9 (0%)
Metabolism and nutrition disorders						
Decreased appetite [A] †	4/38 (10.53%)	9/38 (23.68%)	3/36 (8.33%)	2/13 (15.38%)	7/38 (18.42%)	1/9 (11.11%)
Enzyme abnormality [A] †	0/38 (0%)	0/38 (0%)	0/36 (0%)	1/13 (7.69%)	0/38 (0%)	0/9 (0%)
Hypokalemia [A] †	0/38 (0%)	0/38 (0%)	1/36 (2.78%)	0/13 (0%)	2/38 (5.26%)	0/9 (0%)
Musculoskeletal and connective tissue disorders						
Arthralgia [A] †	1/38 (2.63%)	3/38 (7.89%)	0/36 (0%)	1/13 (7.69%)	1/38 (2.63%)	0/9 (0%)
Back pain [A] †	2/38 (5.26%)	2/38 (5.26%)	0/36 (0%)	0/13 (0%)	0/38 (0%)	0/9 (0%)
Clubbing [A] †	0/38 (0%)	0/38 (0%)	0/36 (0%)	1/13 (7.69%)	0/38 (0%)	0/9 (0%)
Muscle spasms [A] †	1/38 (2.63%)	2/38 (5.26%)	0/36 (0%)	1/13 (7.69%)	0/38 (0%)	0/9 (0%)
Musculoskeletal chest pain [A] †	0/38 (0%)	2/38 (5.26%)	0/36 (0%)	0/13 (0%)	0/38 (0%)	0/9 (0%)
Musculoskeletal pain [A] †	0/38 (0%)	0/38 (0%)	0/36 (0%)	1/13 (7.69%)	0/38 (0%)	0/9 (0%)
Myalgia [A] †	1/38 (2.63%)	6/38 (15.79%)	1/36 (2.78%)	1/13 (7.69%)	1/38 (2.63%)	0/9 (0%)
Neck pain [A] †	0/38 (0%)	0/38 (0%)	0/36 (0%)	1/13 (7.69%)	0/38 (0%)	0/9 (0%)
Pain in extremity [A] †	4/38 (10.53%)	1/38 (2.63%)	0/36 (0%)	1/13 (7.69%)	2/38 (5.26%)	0/9 (0%)

	Cohort 1: Lapatinib 1500 mg + Pazopanib Placebo	Cohort 1: Lapatinib 1500 mg + Pazopanib 800 mg	Cohort 2: Lapatinib 1500 mg + Pazopanib Placebo	Cohort 2: Pazopanib 800 mg	Cohort 2: Lapatinib 1000 mg + Pazopanib 400 mg	Open-label Lapatinib 1500 mg
	Affected/ At Risk (%)	Affected/ At Risk (%)	Affected/ At Risk (%)	Affected/ At Risk (%)	Affected/ At Risk (%)	Affected/ At Risk (%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)						
Cancer pain [A] †	2/38 (5.26%)	2/38 (5.26%)	2/36 (5.56%)	0/13 (0%)	1/38 (2.63%)	0/9 (0%)
Nervous system disorders						
Dizziness [A] †	0/38 (0%)	2/38 (5.26%)	1/36 (2.78%)	1/13 (7.69%)	6/38 (15.79%)	0/9 (0%)
Dysgeusia [A] †	0/38 (0%)	2/38 (5.26%)	0/36 (0%)	0/13 (0%)	2/38 (5.26%)	0/9 (0%)
Headache [A] †	4/38 (10.53%)	7/38 (18.42%)	4/36 (11.11%)	0/13 (0%)	3/38 (7.89%)	1/9 (11.11%)
Hypoaesthesia [A] †	0/38 (0%)	0/38 (0%)	0/36 (0%)	2/13 (15.38%)	0/38 (0%)	0/9 (0%)
Neuralgia [A] †	0/38 (0%)	0/38 (0%)	0/36 (0%)	0/13 (0%)	0/38 (0%)	1/9 (11.11%)
Paraesthesia [A] †	2/38 (5.26%)	0/38 (0%)	0/36 (0%)	0/13 (0%)	0/38 (0%)	0/9 (0%)
Psychiatric disorders						
Insomnia [A] †	0/38 (0%)	0/38 (0%)	2/36 (5.56%)	0/13 (0%)	0/38 (0%)	0/9 (0%)
Renal and urinary disorders						
Dysuria [A] †	0/38 (0%)	2/38 (5.26%)	0/36 (0%)	0/13 (0%)	0/38 (0%)	0/9 (0%)
Proteinuria [A] †	0/38 (0%)	2/38 (5.26%)	2/36 (5.56%)	2/13 (15.38%)	4/38 (10.53%)	1/9 (11.11%)
Respiratory, thoracic and mediastinal disorders						
Cough [A] †	2/38 (5.26%)	1/38 (2.63%)	0/36 (0%)	0/13 (0%)	0/38 (0%)	0/9 (0%)
Dysphonia [A] †	0/38 (0%)	3/38 (7.89%)	0/36 (0%)	1/13 (7.69%)	0/38 (0%)	0/9 (0%)
Dyspnea [A] †	2/38 (5.26%)	3/38 (7.89%)	1/36 (2.78%)	0/13 (0%)	2/38 (5.26%)	0/9 (0%)
Epistaxis [A] †	3/38 (7.89%)	5/38 (13.16%)	1/36 (2.78%)	0/13 (0%)	3/38 (7.89%)	0/9 (0%)
Hemoptysis [A] †	0/38 (0%)	0/38 (0%)	0/36 (0%)	1/13 (7.69%)	0/38 (0%)	0/9 (0%)
Nasal discomfort [A] †	0/38 (0%)	0/38 (0%)	0/36 (0%)	0/13 (0%)	0/38 (0%)	1/9 (11.11%)

	Cohort 1: Lapatinib 1500 mg + Pazopanib Placebo	Cohort 1: Lapatinib 1500 mg + Pazopanib 800 mg	Cohort 2: Lapatinib 1500 mg + Pazopanib Placebo	Cohort 2: Pazopanib 800 mg	Cohort 2: Lapatinib 1000 mg + Pazopanib 400 mg	Open-label Lapatinib 1500 mg
	Affected/ At Risk (%)	Affected/ At Risk (%)	Affected/ At Risk (%)	Affected/ At Risk (%)	Affected/ At Risk (%)	Affected/ At Risk (%)
Skin and subcutaneous tissue disorders						
Acne [A] †	1/38 (2.63%)	5/38 (13.16%)	3/36 (8.33%)	0/13 (0%)	1/38 (2.63%)	1/9 (11.11%)
Alopecia [A] †	4/38 (10.53%)	3/38 (7.89%)	0/36 (0%)	0/13 (0%)	3/38 (7.89%)	0/9 (0%)
Dermatitis acneiform [A] †	2/38 (5.26%)	2/38 (5.26%)	0/36 (0%)	0/13 (0%)	0/38 (0%)	0/9 (0%)
Dry skin [A] †	2/38 (5.26%)	2/38 (5.26%)	0/36 (0%)	0/13 (0%)	2/38 (5.26%)	0/9 (0%)
Erythema [A] †	3/38 (7.89%)	3/38 (7.89%)	1/36 (2.78%)	1/13 (7.69%)	2/38 (5.26%)	0/9 (0%)
Hair color changes [A] †	0/38 (0%)	2/38 (5.26%)	1/36 (2.78%)	1/13 (7.69%)	6/38 (15.79%)	0/9 (0%)
Nail disorder [A] †	0/38 (0%)	0/38 (0%)	2/36 (5.56%)	0/13 (0%)	1/38 (2.63%)	0/9 (0%)
Palmar-plantar erythrodysaesthesia syndrome [A] †	3/38 (7.89%)	3/38 (7.89%)	2/36 (5.56%)	2/13 (15.38%)	2/38 (5.26%)	1/9 (11.11%)
Pruritis [A] †	4/38 (10.53%)	1/38 (2.63%)	4/36 (11.11%)	1/13 (7.69%)	3/38 (7.89%)	0/9 (0%)
Rash [A] †	5/38 (13.16%)	9/38 (23.68%)	11/36 (30.56%)	0/13 (0%)	12/38 (31.58%)	1/9 (11.11%)
Rash erythematous [A] †	2/38 (5.26%)	0/38 (0%)	0/36 (0%)	0/13 (0%)	0/38 (0%)	0/9 (0%)
Scab [A] †	0/38 (0%)	0/38 (0%)	0/36 (0%)	0/13 (0%)	0/38 (0%)	1/9 (11.11%)
Skin irritation [A] †	0/38 (0%)	0/38 (0%)	0/36 (0%)	1/13 (7.69%)	0/38 (0%)	1/9 (11.11%)
Skin ulcer [A] †	0/38 (0%)	0/38 (0%)	0/36 (0%)	2/13 (15.38%)	0/38 (0%)	0/9 (0%)
Vascular disorders						
Hematoma [A] †	0/38 (0%)	2/38 (5.26%)	0/36 (0%)	0/13 (0%)	0/38 (0%)	0/9 (0%)
Hot flush [A] †	2/38 (5.26%)	2/38 (5.26%)	0/36 (0%)	0/13 (0%)	0/38 (0%)	0/9 (0%)
Hypertension [A] †	1/38 (2.63%)	11/38 (28.95%)	1/36 (2.78%)	3/13 (23.08%)	9/38 (23.68%)	0/9 (0%)

† Indicates events were collected by systematic assessment.
A Term from vocabulary, MedDRA

Limitations and Caveats

[Not specified]

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-center trial but requests that reports based on single-site data not precede the primary publication of the entire clinical trial.

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