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

Unique Protocol ID:	VEG105281
Brief Title:	Pazopanib Plus Lapatinib Compared to Lapatinib Alone and Pazopanib Alone In Subjects With Metastatic Cervical Cancer
Official Title:	A Phase II, Open-Label, Randomized, Multicenter Trial of Pazopanib (GW786034) in Combination With Lapatinib (GW572016) Compared to Pazopanib Monotherapy and Lapatinib Monotherapy in Subjects With FIGO Stage IVB or Recurrent or Persistent Cervical Cancer With Zero or One Prior Chemotherapy Regimen
Secondary IDs:	

Study Status

Record Verification:	April 2015
Overall Status:	Completed
Study Start:	November 2006
Primary Completion:	July 2008 [Actual]
Study Completion:	July 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: 65747 Serial Number: 0192 Has Expanded Access? No
Review Board:	Approval Status: Approved Approval Number: 20061684 Board Name: Western Institutional Review Board Board Affiliation: Independent Phone: 3602522500 Email: clientservices@wirb.com
Data Monitoring?:	
Plan to Share Data?:	
Oversight Authorities:	Spain: Ministry of Health United States: Food and Drug Administration

Study Description

Brief Summary:	This study is being conducted to compare the efficacy and safety of pazopanib in combination with lapatinib with that of lapatinib alone or pazopanib alone in subjects with metastatic cervical cancer
Detailed Description:	A Phase II, Open-Label, Randomized, Multicenter Trial of Pazopanib (GW786034) in Combination with Lapatinib (GW572016) Compared to Pazopanib Monotherapy and Lapatinib Monotherapy in Subjects with International Federation of Gynecology (FIGO) Stage IVB or Recurrent or Persistent Cervical Cancer with Zero or One Prior Chemotherapy Regimen for Advanced/ Recurrent Disease

Conditions

Conditions:	Neoplasms, Uterine Cervix Metastatic Cervical Cancer
Keywords:	pazopanib ErB1/ErB2 lapatinib persistent VEGF recurrent metastatic cervical cancer advanced

FIGO Stage IVB

Study Design

Study Type:	Interventional
Primary Purpose:	Treatment
Study Phase:	Phase 2
Intervention Model:	Parallel Assignment
Number of Arms:	3
Masking:	Open Label
Allocation:	Randomized
Endpoint Classification:	Safety/Efficacy Study
Enrollment:	228 [Actual]

Arms and Interventions

Arms	Assigned Interventions
Experimental: Combination arm Pazopanib plus lapatinib	Drug: lapatinib (GW572016)
Active Comparator: Lapatinib monotherapy Lapatinib	Drug: lapatinib (GW572016)
Active Comparator: Pazopanib monotherapy Pazopanib	Drug: pazopanib (GW786034)

Outcome Measures

[See Results Section.]

Eligibility

Minimum Age:	18 Years
Maximum Age:	
Gender:	Female
Accepts Healthy Volunteers?:	No
Criteria:	Inclusion Criteria:

- A subject will be eligible for inclusion in this study only if all of the following criteria are met:
- Signed, written informed consent prior to performing any study-related procedures
- Female subjects ≥18 years of age
- FIGO Stage IVB, or recurrent or persistent cervical cancer
- Life expectancy of at least 12 weeks
- ECOG status of 0 or 1.
- Histologically confirmed FIGO Stage IVB, or recurrent or persistent squamous cell carcinoma, adenosquamous carcinoma, or adenocarcinoma of the cervix which is not amenable to curative treatment with surgery and/or radiation therapy
- Measurable disease, defined as at least one lesion that can be accurately measured in at least one dimension (longest dimension to be recorded). Each lesion must be ≥ 20 mm when measured by conventional techniques, including palpitation, plain x-ray, CT and MRI, or ≥10 mm when measured by spiral CT.
- At least one "target lesion" to be used to assess response as defined by Response Evaluation Criteria in Solid Tumors (RECIST; Terasse, 2000). Tumors within a previously irradiated field will be designated as "non-target" lesions unless progression is documented or a biopsy is obtained to confirm persistence at least 90 days following completion of radiation therapy.
- Received 0 or 1 prior chemotherapy regimen for metastatic disease.
- Note: Chemotherapy given in combination with radiation therapy as a radiosensitizer does not count toward this prior therapy limit
- Recovered from the effects of surgery or chemotherapy. At least three weeks must have elapsed from the last administration of chemotherapy.
- Adequate organ and bone marrow function as defined in Table 1.
- Table 1:(Definitions for Adequate Organ Function)
- System:(Laboratory Values)
- Hematologic: Absolute neutrophil count (ANC)(≥ 1.5 X 109/L)Hemoglobin1(≥9 g/dL)Platelets(≥100 X 109/L)
- Hepatic: Total bilirubin (≤1.5 X ULN)AST and ALT (≤2.5 X ULN)
- Renal: Calculated creatinine clearance2 (≥50 mL/min)
- Urine protein3 (Negative, trace or +1 by dipstick urinalysis or <1.0 gram determined by 24 hour urine protein analysis.)
- Subjects may not have had a transfusion within 7 days of screening assessment.
- Calculated by Cockcroft Gault formula See Appendix 7: Renal Function Tests
- A patient should first be screened with dipstick urinalysis. If urine protein by dipstick analysis is ≥2+, then a 24-hour urine protein must be assessed and 24 hour urine protein must be <1 g protein to be eligible.
- Ability to swallow and retain oral medication.
- 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 (total cessation of menses for ≥ 1 year)
- Childbearing potential, has 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, and agrees to use adequate contraception. GSK acceptable contraceptive methods, when used consistently and in accordance with both the product label and the instructions of the physician, are as follows:
- An intrauterine device with a documented failure rate of less than 1% per year.
- Vasectomized partner who is sterile prior to the female subject's entry and is the sole sexual partner for that female.

- Complete abstinence from sexual intercourse for 14 days before exposure to investigation 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.

- Subjects 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 as outlined in the protocol. Procedures conducted as apart of routine clinical management of the patient (e.g., blood count, imaging study) and obtained prior to signed informed consent may be utilized for screening purposes provided these tests are obtained as specified in the protocol

Exclusion Criteria:

- A subject will not be eligible for inclusion in this study if any of the following criteria apply:
- Neuroendocrine or small cell carcinoma of the cervix.
- Prior use of any biologic therapy with VEGF, VEGFR, or ErbB1/ErbB2 inhibitors.
- Concurrent cancer therapy (chemotherapy, radiation therapy, surgery, immunotherapy, biologic therapy, hormonal therapy, and tumor embolization).
- Concurrent treatment with an investigational agent or participation in another clinical trial.
- Use of an investigational anti-cancer drug within 28 days or 5 half-lives, whichever is longer, preceding the first dose of study medication.
- Has taken or is taking prohibited medications listed in the protocol.
- Any serious and/or unstable pre-existing medical, psychiatric, or other conditions that could interfere with patient's safety, obtaining informed consent or compliance to the study.
- History of another malignancy. Note: Patients who have had another malignancy and have been disease-free for 5 years, or patients with a history of completely resected non-melanomatous skin carcinoma or successfully treated in situ carcinoma are eligible.
- History or clinical evidence of central nervous system (CNS) metastases or leptomeningeal carcinomatosis. Routine screening with CNS imaging studies (computed tomography [CT] or magnetic resonance imaging [MRI]) is required only if clinically indicated.
- Malabsorption Syndrome, disease significantly affecting gastrointestinal function, or resection of the stomach or small bowel.
- Active peptic ulcer disease, inflammatory bowel disease, or other gastrointestinal condition increasing the risk of perforation; history of abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess within 4 weeks prior to beginning therapy.
- Presence of uncontrolled infection.
- Known immediate or delayed hypersensitivity reaction or idiosyncrasy to drugs chemically related to pazopanib.
- Corrected QT interval (QTc) prolongation defined as QTc interval > 470 msecs.
- History of any one of the following cardiac conditions within the past 6 months:
- Cardiac angioplasty or stenting
- Myocardial infarction
- Unstable angina
- History of cerebrovascular accident or pulmonary embolus within the past 6 months.
- Has Class III or IV heart failure as defined by the New York Heart Association (NYHA) functional classification system (See Appendix 6)

- Poorly controlled hypertension (systolic blood pressure (SBP) of ≥ 140mmHg, or diastolic blood pressure (DBP) of ≥ 90mmHg).
- Note: Initiation or adjustment of antihypertensive medication(s) is permitted prior to study entry. The blood pressure (BP) must be re-assessed on two occasions that are separated by a minimum of 24 hours. The mean SBP/DBP values from both BP assessments must be < 140/90mmHg in order for a subject to be eligible for the study.
- History of untreated deep venous thrombosis (DVT) within the past 6 months (e.g. calf vein thrombosis).
- Note: Patients with recent DVT who are treated with therapeutic anti-coagulant agents (excluding therapeutic warfarin) for at least 6 weeks are eligible.
- Presence of any non-healing, non-tumor related wound, fracture, or ulcer, or the presence of symptomatic peripheral vascular disease.
- Subjects with bilateral hydronephrosis which cannot be alleviated by ureteral stents or percutaneous drainage.
- Major surgical procedure, open biopsy, or significant traumatic injury within 4 weeks prior to beginning therapy, or anticipation of the need for a major surgical procedure during the course of the study; minor surgical procedures such as fine needle aspiration or core biopsy within 1 week prior to beginning therapy are also excluded.
- Unable to swallow and retain orally administered medication.
- Pregnant or lactating female.

Contacts/Locations

Study Officials: GSK Clinical Trials
Study Director
GlaxoSmithKline

Locations: France
GSK Investigational Site
Caen Cedex, France, 14076

Mexico
GSK Investigational Site
Mexico City, Mexico, CP 14080

Argentina
GSK Investigational Site
Quilmes, Argentina, 1878

India
GSK Investigational Site
Ahemdabad, India, 380016

Argentina
GSK Investigational Site
Santa Fe, Santa Fe, Argentina, 3000

Germany

GSK Investigational Site
Halle, Sachsen-Anhalt, Germany, 06120

GSK Investigational Site
Berlin, Berlin, Germany, 10367

India
GSK Investigational Site
Mangalore, India, 575001

Thailand
GSK Investigational Site
Khon Kaen, Thailand, 40002

Canada, Ontario
GSK Investigational Site
Toronto, Ontario, Canada, M5G 2M9

United States, Oklahoma
GSK Investigational Site
Oklahoma City, Oklahoma, United States, 73104

Italy
GSK Investigational Site
Milano, Lombardia, Italy, 20141

France
GSK Investigational Site
Lille Cedex, France, 59020

Spain
GSK Investigational Site
Barcelona, Spain, 08036

United States, California
GSK Investigational Site
Stanford, California, United States, 94305-5317

Italy
GSK Investigational Site
Campobasso, Molise, Italy, 86100

Thailand
GSK Investigational Site
Chiang Mai, Thailand, 50200

United States, Ohio
GSK Investigational Site
Columbus, Ohio, United States, 43214

Spain
GSK Investigational Site
La Laguna (Santa Cruz de Tenerife), Spain, 38320

Germany
GSK Investigational Site
Saarbruecken, Saarland, Germany, 66113

Belgium
GSK Investigational Site
Brussel, Belgium, 1000

United States, Tennessee
GSK Investigational Site
Chattanooga, Tennessee, United States, 37403

Germany
GSK Investigational Site
Magdeburg, Sachsen-Anhalt, Germany, 39108

United States, Georgia
GSK Investigational Site
Augusta, Georgia, United States, 30912

Argentina
GSK Investigational Site
Neuquen, Neuquén, Argentina, Q8300HDH

Italy
GSK Investigational Site
Bari, Puglia, Italy, 70124

France
GSK Investigational Site
Villejuif, France, 94805

Spain
GSK Investigational Site
Pamplona, Spain, 31008

France
GSK Investigational Site

Marseille Cedex 09, France, 13273

Canada, Ontario
GSK Investigational Site
Hamilton, Ontario, Canada, L8V 5C2

Argentina
GSK Investigational Site
Rosario, Santa Fe, Argentina, S2000KZE

Thailand
GSK Investigational Site
Bangkok, Thailand, 10330

Belgium
GSK Investigational Site
Gent, Belgium, 9000

France
GSK Investigational Site
Strasbourg, France, 67085

United States, New Mexico
GSK Investigational Site
Albuquerque, New Mexico, United States, 87131-5276

Germany
GSK Investigational Site
Berlin, Berlin, Germany, 10117

United States, Massachusetts
GSK Investigational Site
Boston, Massachusetts, United States, 02115

France
GSK Investigational Site
Bordeaux, France, 33076

Canada, British Columbia
GSK Investigational Site
Vancouver, British Columbia, Canada, V5Z 4E6

Germany
GSK Investigational Site
Muenchen, Bayern, Germany, 80337

United States, Texas
GSK Investigational Site
Dallas, Texas, United States, 75390

Ireland
GSK Investigational Site
Cork, Ireland

Estonia
GSK Investigational Site
Tartu, Estonia, 51003

Ireland
GSK Investigational Site
Dublin, Ireland, 7

Belgium
GSK Investigational Site
Leuven, Belgium, 3000

United States, California
GSK Investigational Site
Orange, California, United States, 92868

Argentina
GSK Investigational Site
Capital Federal, Buenos Aires, Argentina, C1405CUB

Estonia
GSK Investigational Site
Tallinn, Estonia, 11619

Spain
GSK Investigational Site
Barcelona, Spain, 08907

United States, Ohio
GSK Investigational Site
Cleveland, Ohio, United States, 44106

India
GSK Investigational Site
Trivandrum, India, 695011

Canada, Quebec
GSK Investigational Site

Montréal, Quebec, Canada, H2L 4M1

Spain
GSK Investigational Site
Marid, Spain, 28040

Belgium
GSK Investigational Site
Roeselare, Belgium, 8800

Spain
GSK Investigational Site
Madrid, Spain, 28007

Belgium
GSK Investigational Site
Bruxelles, Belgium, 1200

Italy
GSK Investigational Site
Napoli, Campania, Italy, 80131

India
GSK Investigational Site
New Delhi, India, 110096

United States, California
GSK Investigational Site
Los Angeles, California, United States, 90033

Canada, Alberta
GSK Investigational Site
Calgary, Alberta, Canada, T2N 4N2

Argentina
GSK Investigational Site
Ciudad Autonoma de Buenos Aires, Buenos Aires, Argentina, C1185AAT

United States, New York
GSK Investigational Site
New York, New York, United States, 10016

Argentina
GSK Investigational Site
Tucuman, Tucumán., Argentina, 4000

References

Citations: [Study Results] Monk BJ, Lopez LM, Zarba JJ, Oaknin A, Tarpin C, Termrungruanglert W, Alber J, Ding J, Stutts MW, Pandite LN. Phase II, open-label study of pazopanib or lapatinib monotherapy compared with pazopanib plus lapatinib combination therapy in patients with advanced and recurrent cervical cancer. J Clin Oncol, 2010;28(22):3562-3569.

[Study Results] Monk, BJ and Pandite, LN. Survival data from a phase II, open-label study of pazopanib or lapatinib monotherapy in patients with advanced and recurrent cervical cancer. J Clin Oncol, 2011; 29(36): 4845.

Links:

Study Data/Documents:

Study Results

Participant Flow

Recruitment Details	Participants (par.) continued to be enrolled into all three treatment arms after clinical data cutoff for the interim analysis, but before the results were evaluated. Final total enrollment was 228 participants: 76 in the combination arm, 78 in the lapatinib monotherapy arm, and 74 in the pazopanib monotherapy arm.
Pre-Assignment Details	Study was initially designed and started as a randomized, three-arm, controlled trial. Participants were randomized to the combination of pazopanib plus lapatinib, pazopanib monotherapy, or lapatinib monotherapy. Based on results from a planned interim analysis, the combination group was terminated, but the monotherapy groups continued as planned.

Reporting Groups

	Description
Combination Therapy: Lapatinib 1500 mg and Pazopanib 800 mg	Lapatinib 1500 mg (6 x 250 mg tablets) and pazopanib 800 mg (2 x 400 mg tablets) daily
Lapatinib Monotherapy	1500 mg (6 x 250 mg tablets) of oral lapatinib daily
Pazopanib Monotherapy	800 mg (2 x 400 mg tablets) of oral pazopanib daily

Interim Analysis; 11 February 2008

	Combination Therapy: Lapatinib 1500 mg and Pazopanib 800 mg	Lapatinib Monotherapy	Pazopanib Monotherapy
Started	59	58	60

	Combination Therapy: Lapatinib 1500 mg and Pazopanib 800 mg	Lapatinib Monotherapy	Pazopanib Monotherapy
Ongoing	23	20	25
Completed	0	0	0
Not Completed	59	58	60
Adverse Event	10	3	7
Lost to Follow-up	1	0	1
Protocol Violation	0	1	0
Withdrawal by Subject	4	0	2
Sponsor Terminated Study	1	0	0
Disease Progression	16	30	22
Death	0	1	0
Par. Withdrew; Followed for Survival	2	0	0
Physician Decision	2	3	3
Ongoing	23	20	25

Final Analysis; 31 July 2008

	Combination Therapy: Lapatinib 1500 mg and Pazopanib 800 mg	Lapatinib Monotherapy	Pazopanib Monotherapy
Started	0	78	74
Ongoing	0	29	32
Completed	0	39	26
Not Completed	0	39	48
Lost to Follow-up	0	0	3
Protocol Violation	0	1	0
Withdrawal by Subject	0	2	7
Physician Decision	0	6	6
Unknown	0	1	0

	Combination Therapy: Lapatinib 1500 mg and Pazopanib 800 mg	Lapatinib Monotherapy	Pazopanib Monotherapy
Ongoing	0	29	32

End-of-Study Analysis; 28 July 2011

	Combination Therapy: Lapatinib 1500 mg and Pazopanib 800 mg	Lapatinib Monotherapy	Pazopanib Monotherapy
Started	77 [1]	77 [2]	74
Completed	53	59	54
Not Completed	24	18	20
Lost to Follow-up	5	3	3
Protocol Violation	0	1	0
Withdrawal by Subject	7	2	7
Sponsor Terminated Study	4	5	4
Physician Decision	4	6	6
Unknown	4	1	0

[1] Enrollment continued in this arm after data cut for Interim Analysis and before arm closed.
[2] 1 participant randomized to lapatinib (final analysis table) actually received combination therapy.

Baseline Characteristics

Reporting Groups

	Description
Combination Therapy: Lapatinib 1500 mg and Pazopanib 800 mg	Lapatinib 1500 mg (6 x 250 mg tablets) and pazopanib 800 mg (2 x 400 mg tablets) daily
Lapatinib Monotherapy	1500 mg (6 x 250 mg tablets) of oral lapatinib daily
Pazopanib Monotherapy	800 mg (2 x 400 mg tablets) of oral pazopanib daily

Baseline Measures

	Combination Therapy: Lapatinib 1500 mg and Pazopanib 800 mg	Lapatinib Monotherapy	Pazopanib Monotherapy	Total
Number of Participants	59	58	60	177
Age, Continuous [1] [units: years] Mean (Standard Deviation)	50.4 (11.04)	48.7 (11.47)	49.6 (10.34)	49.5 (10.91)
Age, Continuous [2] [units: years] Mean (Standard Deviation)	NA (NA) [3]	49.2 (11.27)	50.8 (10.93)	50 (11.1)
Gender, Male/Female [4] [units: participants]				
Female	59	58	60	177
Male	0	0	0	0
Gender, Male/Female [5] [units: participants]				
Female	NA [3]	78	74	NA [6]
Male	NA [3]	0	0	NA [6]
Race/Ethnicity, Customized [7] [units: participants]				
African American	0	1	0	1
American Indian	10	4	12	26
Asian-South East	12	10	8	30
White	37	43	40	120
Race/Ethnicity, Customized [8] [units: participants]				
African American	NA [3]	1	0	NA [6]
American Indian	NA [3]	10	13	NA [6]
Asian-Central , South	NA [3]	2	0	NA [6]
Asian-South East	NA [3]	13	9	NA [6]

	Combination Therapy: Lapatinib 1500 mg and Pazopanib 800 mg	Lapatinib Monotherapy	Pazopanib Monotherapy	Total
White	NA [3]	52	52	NA [6]
Histology at diagnosis: Interim Analysis [units: participants]				
Adenocarcinoma	15	8	8	31
Adenosquamous carcinoma	0	4	3	7
Squamous cell carcinoma	32	38	43	113
Other	10	8	5	23
Missing	2	0	1	3
Histology at diagnosis: Final Anaysis [9] [units: participants]				
Adenocarcinoma	NA [3]	11	12	NA [6]
Adenosquamous carcinoma	NA [3]	4	3	NA [6]
Squamous cell carcinoma	NA [3]	55	53	NA [6]
Other	NA [3]	8	6	NA [6]

[1] Age at Interim Analysis

[2] Age at Final Analysis (n=0, 78, 74)

[3] There are no participants for this analysis subgroup.

[4] Gender at Interim Analysis

[5] Gender at Final Analysis (n=0, 78, 74)

[6] Total not calculated because data are not available (NA) in one or more arms.

[7] Race at Interim Analysis

[8] Race at Final Analysis (n=0, 78, 74)

[9] (n=0, 78, 74)

Outcome Measures

1. Primary Outcome Measure:

Measure Title	Progression-free Survival (PFS) in Interim Analysis
Measure Description	PFS is defined as the interval between the date of randomization and the date of disease progression or death due to any cause. The study was designed to test Combination vs. Lapatinib first. The result indicated that Combination would not show improvement over Lapatinib even if followed until the final analysis and the Combination arm was terminated. The monotherapy arms continued to the final analysis. Data shown here are from this interim analysis.
Time Frame	From randomization until at least 35 PFS events in pairwise comparison of the three treatment arms (Interim Analysis; up to 52.14 weeks)
Safety Issue?	No

Analysis Population Description

Intent to Treat (ITT) Population: all randomized participants

Reporting Groups

	Description
Combination Therapy: Lapatinib 1500 mg and Pazopanib 800 mg	Lapatinib 1500 mg (6 x 250 mg tablets) and pazopanib 800 mg (2 x 400 mg tablets) daily
Lapatinib Monotherapy	1500 mg (6 x 250 mg tablets) of oral lapatinib daily
Pazopanib Monotherapy	800 mg (2 x 400 mg tablets) of oral pazopanib daily

Measured Values

	Combination Therapy: Lapatinib 1500 mg and Pazopanib 800 mg	Lapatinib Monotherapy	Pazopanib Monotherapy
Number of Participants Analyzed	59	58	60
Progression-free Survival (PFS) in Interim Analysis [units: Weeks] Median (90% Confidence Interval)	12.6 (11.7 to 14.1)	12.6 (11.6 to 18.3)	17.9 (12.1 to 23.9)

Statistical Analysis 1 for Progression-free Survival (PFS) in Interim Analysis

Statistical Analysis Overview	Comparison Groups	Combination Therapy: Lapatinib 1500 mg and Pazopanib 800 mg, Lapatinib Monotherapy
	Comments	[Not specified]

	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.535
	Comments	Stratified log-rank test with one-sided p-value. p<=0.0037 required for significance, and p>0.4956 indicated futility.
	Method	Log Rank
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Hazard Ratio (HR)
	Estimated Value	1.05
	Confidence Interval	(2-Sided) 90% 0.65 to 1.7
	Estimation Comments	The estimated value is the hazard ratio comparing combination to lapatinib monotherapy

2. Primary Outcome Measure:

Measure Title	Progression-free Survival (PFS) in Final Analysis
Measure Description	PFS is defined as the interval between the date of randomization and the date of disease progression or death due to any cause. This study began as a 3-arm study. The combination arm was terminated at the interim analysis. The monotherapy arms continued to final analysis. Data shown here are from the final analysis.
Time Frame	From Randomization until 105 total PFS events in combined population of two monotherapy arms (up to 85.57 weeks)
Safety Issue?	No

Analysis Population Description
ITT Population

Reporting Groups

	Description
Lapatinib Monotherapy	1500 mg (6 x 250 mg tablets) of oral lapatinib daily
Pazopanib Monotherapy	800 mg (2 x 400 mg tablets) of oral pazopanib daily

Measured Values

	Lapatinib Monotherapy	Pazopanib Monotherapy
Number of Participants Analyzed	78	74
Progression-free Survival (PFS) in Final Analysis [units: Weeks] Median (90% Confidence Interval)	17.1 (12.1 to 18.1)	18.1 (15.1 to 24.6)

Statistical Analysis 1 for Progression-free Survival (PFS) in Final Analysis

Statistical Analysis Overview	Comparison Groups	Lapatinib Monotherapy, Pazopanib Monotherapy
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.013
	Comments	Stratified log-rank test with one-sided p-value.
	Method	Log Rank
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Hazard Ratio, log
	Estimated Value	0.66
	Confidence Interval	(2-Sided) 90% 0.48 to 0.91
	Estimation Comments	[Not specified]

3. Secondary Outcome Measure:

Measure Title	Overall Survival
Measure Description	Overall survival is defined as the time from randomization until death due to any cause.
Time Frame	From Randomization (11 December 2006) until approximately 78% overall survival events at the time of the second overall survival update (3 March 2010) (up to 168.29 weeks)
Safety Issue?	No

Analysis Population Description
ITT Population

Reporting Groups

	Description
Lapatinib Monotherapy	1500 mg (6 x 250 mg tablets) of oral lapatinib daily
Pazopanib Monotherapy	800 mg (2 x 400 mg tablets) of oral pazopanib daily

Measured Values

	Lapatinib Monotherapy	Pazopanib Monotherapy
Number of Participants Analyzed	78	74
Overall Survival [units: Weeks] Median (90% Confidence Interval)	44.1 (35.6 to 48.9)	49.7 (42.0 to 55.9)

4. Secondary Outcome Measure:

Measure Title	Clinical Benefit Response
Measure Description	Clinical benefit response is defined as the number of participants with evidence of complete (CR) or partial (PR) tumor response or stable disease (SD) for at least 6 months (183 days). Per Response Evaluation Criteria In Solid Tumors (RECIST): CR, all detectable tumor has disappeared; PR, a >=30% decrease in the sum of the longest dimensions of the target lesions taking as a reference the baseline sum; Stable Disease, small changes that do not meet previously given criteria. Confirmation requires at least 2 assessments of CR/PR with at least 4 weeks between assessments.
Time Frame	From Randomization until 105 total PFS events in combined population of two monotherapy arms (up to 85.57 weeks)
Safety Issue?	No

Analysis Population Description
ITT Population

Reporting Groups

	Description
Lapatinib Monotherapy	1500 mg (6 x 250 mg tablets) of oral lapatinib daily
Pazopanib Monotherapy	800 mg (2 x 400 mg tablets) of oral pazopanib daily

Measured Values

	Lapatinib Monotherapy	Pazopanib Monotherapy
Number of Participants Analyzed	78	74
Clinical Benefit Response [units: participants]	7	15

5. Secondary Outcome Measure:

Measure Title	Response
Measure Description	Response is defined as the number of participants achieving either a complete or partial tumor response per RECIST criteria. CR, all detectable tumor has disappeared; PR, a >=30% decrease in the sum of the longest dimensions of the target lesions taking as a reference the baseline sum.
Time Frame	From Randomization until 105 total PFS events in combined population of two monotherapy arms (up to 85.57 weeks)
Safety Issue?	No

Analysis Population Description

ITT Population

Reporting Groups

	Description
Lapatinib Monotherapy	1500 mg (6 x 250 mg tablets) of oral lapatinib daily
Pazopanib Monotherapy	800 mg (2 x 400 mg tablets) of oral pazopanib daily

Measured Values

	Lapatinib Monotherapy	Pazopanib Monotherapy
Number of Participants Analyzed	78	74
Response [units: participants]	4	7

Statistical Analysis 1 for Response

Statistical Analysis Overview	Comparison Groups	Lapatinib Monotherapy, Pazopanib Monotherapy
	Comments	[Not specified]

	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.237
	Comments	One-sided p-value.
	Method	Fisher Exact
	Comments	[Not specified]

6. Secondary Outcome Measure:

Measure Title	Time to Response
Measure Description	For the subset of participants who showed a confirmed CR or PR, time to response was defined as the time from randomization until the first documented evidence of CR or PR (whichever status was recorded first). CR, all detectable tumor has disappeared; PR, a >=30% decrease in the sum of the longest dimensions of the target lesions taking as a reference the baseline sum.
Time Frame	From Randomization until 105 total PFS events in combined population of two monotherapy arms (up to 85.57 weeks)
Safety Issue?	No

Analysis Population Description
ITT Population

Reporting Groups

	Description
Lapatinib Monotherapy	1500 mg (6 x 250 mg tablets) of oral lapatinib daily
Pazopanib Monotherapy	800 mg (2 x 400 mg tablets) of oral pazopanib daily

Measured Values

	Lapatinib Monotherapy	Pazopanib Monotherapy
Number of Participants Analyzed	4	7
Time to Response [units: weeks] Mean (90% Confidence Interval)	18.2 (6.0 to 24.1)	6.9 (5.6 to 11.9)

7. Secondary Outcome Measure:

Measure Title	Duration of Response
Measure Description	For participants who had a CR or PR, the duration of response was defined as the time from first documented evidence of PR or CR until the first documented sign of disease progression or death. CR, all detectable tumor has disappeared; PR, a >=30% decrease in the sum of the longest dimensions of the target lesions taking as a reference the baseline sum.
Time Frame	From Randomization until 105 total PFS events in combined population of two monotherapy arms (up to 85.57 weeks)
Safety Issue?	No

Analysis Population Description

ITT Population. The median for lapatinib was not reached at the time of data cut-off. No formal analysis of this endpoint was conducted for this group due to a very small number of responding participants.

Reporting Groups

	Description
Lapatinib Monotherapy	1500 mg (6 x 250 mg tablets) of oral lapatinib daily
Pazopanib Monotherapy	800 mg (2 x 400 mg tablets) of oral pazopanib daily

Measured Values

	Lapatinib Monotherapy	Pazopanib Monotherapy
Number of Participants Analyzed	0	7
Duration of Response [units: weeks] Mean (90% Confidence Interval)		48.1 (12.0 to 48.1)

8. Secondary Outcome Measure:

Measure Title	Safety and Tolerability of Pazopanib, Lapatinib and the Combination of Pazopanib and Lapatinib
Measure Description	Safety was assessed as the number of participants experiencing a serious adverse event (SAE) or an adverse event (AE). See the adverse event module for safety data.
Time Frame	From Randomization (11 December 2006) until last participant had last visit (28 July 2011) in combined population of two monotherapy arms (up to 241.43 weeks)
Safety Issue?	No

Analysis Population Description

Safety Population: all participants who received at least one dose of study drug

Reporting Groups

	Description
Lapatinib Monotherapy	1500 mg (6 x 250 mg tablets) of oral lapatinib daily
Pazopanib Monotherapy	800 mg (2 x 400 mg tablets) of oral pazopanib daily
Combination Therapy: Lapatinib 1500 mg and Pazopanib 800	Lapatinib 1500 mg (6 x 250 mg tablets) and pazopanib 800 mg (2 x 400 mg tablets) daily

Measured Values

	Lapatinib Monotherapy	Pazopanib Monotherapy	Combination Therapy: Lapatinib 1500 mg and Pazopanib 800
Number of Participants Analyzed	76	74	76
Safety and Tolerability of Pazopanib, Lapatinib and the Combination of Pazopanib and Lapatinib [units: participants]			
Serious adverse events	22	28	32
Other adverse events with >5% occurrence	66	69	71

Reported Adverse Events

Time Frame	SAEs/AEs were assessed in par. receiving >=1 dose of study treatment at time of final PFS analysis (From Randomization [11 December 2006] until last par. had last visit [28 July 2011] in combined population of two monotherapy arms [up to 241.43 weeks])
Additional Description	Serious adverse events (SAEs) and adverse events (AEs) are reported for the Safety Population (all participants who received at least one dose of study drug).

Reporting Groups

	Description
Combination Therapy: Lapatinib 1500 mg and Pazopanib 800 mg	Lapatinib 1500 mg (6 x 250 mg tablets) and pazopanib 800 mg (2 x 400 mg tablets) daily
Lapatinib Monotherapy	1500 mg (6 x 250 mg tablets) of oral lapatinib daily

	Description
Pazopanib Monotherapy	800 mg (2 x 400 mg tablets) of oral pazopanib daily

Serious Adverse Events

	Combination Therapy: Lapatinib 1500 mg and Pazopanib 800 mg	Lapatinib Monotherapy	Pazopanib Monotherapy
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Total	32/76 (42.11%)	22/76 (28.95%)	28/74 (37.84%)
Blood and lymphatic system disorders			
Anaemia [A] †	4/76 (5.26%)	1/76 (1.32%)	2/74 (2.7%)
Febrile neutropenia [A] †	1/76 (1.32%)	0/76 (0%)	0/74 (0%)
Cardiac disorders			
Cardiac arrest [A] †	0/76 (0%)	0/76 (0%)	1/74 (1.35%)
Myocardial infarction [A] †	0/76 (0%)	1/76 (1.32%)	0/74 (0%)
Tachycardia [A] †	0/76 (0%)	0/76 (0%)	1/74 (1.35%)
Gastrointestinal disorders			
Abdominal pain [A] †	3/76 (3.95%)	1/76 (1.32%)	4/74 (5.41%)
Ascites [A] †	0/76 (0%)	0/76 (0%)	1/74 (1.35%)
Colitis [A] †	0/76 (0%)	1/76 (1.32%)	0/74 (0%)
Diarrhoea [A] †	1/76 (1.32%)	4/76 (5.26%)	4/74 (5.41%)
Enteritis [A] †	0/76 (0%)	0/76 (0%)	1/74 (1.35%)
Enterovesical fistula [A] †	0/76 (0%)	0/76 (0%)	1/74 (1.35%)
Intestinal obstruction [A] †	1/76 (1.32%)	2/76 (2.63%)	0/74 (0%)
Intestinal perforation [A] †	2/76 (2.63%)	0/76 (0%)	0/74 (0%)
Large intestine perforation [A] †	0/76 (0%)	1/76 (1.32%)	0/74 (0%)
Rectal haemorrhage [A] †	1/76 (1.32%)	0/76 (0%)	0/74 (0%)

	Combination Therapy: Lapatinib 1500 mg and Pazopanib 800 mg	Lapatinib Monotherapy	Pazopanib Monotherapy
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Rectal ulcer [A] †	0/76 (0%)	0/76 (0%)	1/74 (1.35%)
Small intestinal obstruction [A] †	0/76 (0%)	0/76 (0%)	2/74 (2.7%)
Subileus [A] †	0/76 (0%)	1/76 (1.32%)	0/74 (0%)
Upper gastrointestinal haemorrhage [A] †	1/76 (1.32%)	0/76 (0%)	0/74 (0%)
Vomiting [A] †	0/76 (0%)	0/76 (0%)	1/74 (1.35%)
General disorders			
Asthenia [A] †	1/76 (1.32%)	0/76 (0%)	0/74 (0%)
Chest pain [A] †	1/76 (1.32%)	1/76 (1.32%)	0/74 (0%)
Fatigue [A] †	1/76 (1.32%)	1/76 (1.32%)	0/74 (0%)
General physical health deterioration [A] †	0/76 (0%)	0/76 (0%)	1/74 (1.35%)
Pain [A] †	0/76 (0%)	1/76 (1.32%)	0/74 (0%)
Performance status decreased [A] †	1/76 (1.32%)	0/76 (0%)	0/74 (0%)
Pyrexia [A] †	0/76 (0%)	2/76 (2.63%)	0/74 (0%)
Sudden death [A] †	1/76 (1.32%)	0/76 (0%)	0/74 (0%)
Hepatobiliary disorders			
Jaundice [A] †	0/76 (0%)	1/76 (1.32%)	0/74 (0%)
Infections and infestations			
Cellulitis [A] †	1/76 (1.32%)	0/76 (0%)	0/74 (0%)
Gangrene [A] †	1/76 (1.32%)	0/76 (0%)	0/74 (0%)
Gastroenteritis [A] †	0/76 (0%)	1/76 (1.32%)	0/74 (0%)
Pneumonia [A] †	1/76 (1.32%)	0/76 (0%)	0/74 (0%)
Pneumonia primary atypical [A] †	0/76 (0%)	0/76 (0%)	1/74 (1.35%)

	Combination Therapy: Lapatinib 1500 mg and Pazopanib 800 mg	Lapatinib Monotherapy	Pazopanib Monotherapy
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Pyelonephritis [A] †	1/76 (1.32%)	0/76 (0%)	1/74 (1.35%)
Pyonephrosis [A] †	0/76 (0%)	0/76 (0%)	1/74 (1.35%)
Septic Shock [A] †	1/76 (1.32%)	0/76 (0%)	0/74 (0%)
Urinary tract infection [A] †	0/76 (0%)	1/76 (1.32%)	1/74 (1.35%)
Injury, poisoning and procedural complications			
Toxicity to various agents [A] †	0/76 (0%)	1/76 (1.32%)	0/74 (0%)
Wound [A] †	0/76 (0%)	0/76 (0%)	1/74 (1.35%)
Investigations			
Ejection fraction decreased [A] †	2/76 (2.63%)	0/76 (0%)	0/74 (0%)
Forced expiratory volume decreased [A] †	0/76 (0%)	0/76 (0%)	1/74 (1.35%)
Metabolism and nutrition disorders			
Decreased appetite [A] †	0/76 (0%)	1/76 (1.32%)	1/74 (1.35%)
Dehydration [A] †	2/76 (2.63%)	0/76 (0%)	1/74 (1.35%)
Failure to thrive [A] †	0/76 (0%)	1/76 (1.32%)	0/74 (0%)
Hypercalcaemia [A] †	0/76 (0%)	1/76 (1.32%)	0/74 (0%)
Hyperkalaemia [A] †	0/76 (0%)	0/76 (0%)	1/74 (1.35%)
Hypoglycaemia [A] †	1/76 (1.32%)	1/76 (1.32%)	0/74 (0%)
Hypokalaemia [A] †	0/76 (0%)	0/76 (0%)	1/74 (1.35%)
Hyponatraemia [A] †	0/76 (0%)	0/76 (0%)	1/74 (1.35%)
Musculoskeletal and connective tissue disorders			
Bone pain [A] †	0/76 (0%)	1/76 (1.32%)	0/74 (0%)
Groin pain [A] †	0/76 (0%)	0/76 (0%)	1/74 (1.35%)

	Combination Therapy: Lapatinib 1500 mg and Pazopanib 800 mg	Lapatinib Monotherapy	Pazopanib Monotherapy
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Intervertebral disc protrusion [A] †	0/76 (0%)	1/76 (1.32%)	0/74 (0%)
Muscular weakness [A] †	0/76 (0%)	0/76 (0%)	1/74 (1.35%)
Osteonecrosis [A] †	1/76 (1.32%)	0/76 (0%)	0/74 (0%)
Pain in extremity [A] †	0/76 (0%)	1/76 (1.32%)	0/74 (0%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cardiac neoplasm unspecified [A] †	0/76 (0%)	1/76 (1.32%)	0/74 (0%)
Tumour haemorrhage [A] †	0/76 (0%)	1/76 (1.32%)	0/74 (0%)
Tumour pain [A] †	1/76 (1.32%)	1/76 (1.32%)	0/74 (0%)
Nervous system disorders			
Convulsion [A] †	0/76 (0%)	0/76 (0%)	1/74 (1.35%)
Dizziness [A] †	0/76 (0%)	0/76 (0%)	1/74 (1.35%)
Peripheral sensory neuropathy [A] †	0/76 (0%)	1/76 (1.32%)	0/74 (0%)
Spinal cord compression [A] †	0/76 (0%)	0/76 (0%)	1/74 (1.35%)
Psychiatric disorders			
Confusional state [A] †	0/76 (0%)	0/76 (0%)	1/74 (1.35%)
Insomnia [A] †	0/76 (0%)	1/76 (1.32%)	0/74 (0%)
Renal and urinary disorders			
Haematuria [A] †	2/76 (2.63%)	0/76 (0%)	0/74 (0%)
Proteinuria [A] †	0/76 (0%)	1/76 (1.32%)	0/74 (0%)
Renal failure [A] †	0/76 (0%)	0/76 (0%)	1/74 (1.35%)
Renal failure acute [A] †	1/76 (1.32%)	0/76 (0%)	0/74 (0%)
Ureteric stenosis [A] †	1/76 (1.32%)	0/76 (0%)	0/74 (0%)

	Combination Therapy: Lapatinib 1500 mg and Pazopanib 800 mg	Lapatinib Monotherapy	Pazopanib Monotherapy
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Urethral fistula [A] †	1/76 (1.32%)	0/76 (0%)	0/74 (0%)
Urinary bladder haemorrhage [A] †	1/76 (1.32%)	0/76 (0%)	0/74 (0%)
Urinary retention [A] †	1/76 (1.32%)	0/76 (0%)	0/74 (0%)
Reproductive system and breast disorders			
Cervix disorder [A] †	1/76 (1.32%)	0/76 (0%)	0/74 (0%)
Female genital tract fistula [A] †	4/76 (5.26%)	0/76 (0%)	2/74 (2.7%)
Genital hemorrhage [A] †	0/76 (0%)	0/76 (0%)	1/74 (1.35%)
Pelvic pain [A] †	0/76 (0%)	1/76 (1.32%)	1/74 (1.35%)
Vaginal haemorrhage [A] †	2/76 (2.63%)	0/76 (0%)	1/74 (1.35%)
Respiratory, thoracic and mediastinal disorders			
Bronchial obstruction [A] †	0/76 (0%)	1/76 (1.32%)	0/74 (0%)
Cough [A] †	1/76 (1.32%)	0/76 (0%)	0/74 (0%)
Dyspnoea [A] †	1/76 (1.32%)	4/76 (5.26%)	0/74 (0%)
Epistaxis [A] †	0/76 (0%)	0/76 (0%)	1/74 (1.35%)
Pulmonary embolism [A] †	0/76 (0%)	1/76 (1.32%)	2/74 (2.7%)
Pulmonary haemorrhage [A] †	1/76 (1.32%)	0/76 (0%)	0/74 (0%)
Respiratory Failure [A] †	1/76 (1.32%)	0/76 (0%)	0/74 (0%)
Respiratory distress [A] †	1/76 (1.32%)	0/76 (0%)	0/74 (0%)
Tachypnoea [A] †	1/76 (1.32%)	0/76 (0%)	0/74 (0%)
Vascular disorders			
Arterial thrombosis limb [A] †	1/76 (1.32%)	0/76 (0%)	0/74 (0%)
Deep vein thrombosis [A] †	0/76 (0%)	0/76 (0%)	2/74 (2.7%)

	Combination Therapy: Lapatinib 1500 mg and Pazopanib 800 mg	Lapatinib Monotherapy	Pazopanib Monotherapy
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Hypertension [A] †	1/76 (1.32%)	0/76 (0%)	2/74 (2.7%)
Hypotension [A] †	1/76 (1.32%)	0/76 (0%)	0/74 (0%)
Iliac artery occlusion [A] †	1/76 (1.32%)	0/76 (0%)	0/74 (0%)
Shock haemorrhagic [A] †	1/76 (1.32%)	0/76 (0%)	0/74 (0%)
Venous thrombosis [A] †	0/76 (0%)	0/76 (0%)	1/74 (1.35%)

† 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%

	Combination Therapy: Lapatinib 1500 mg and Pazopanib 800 mg	Lapatinib Monotherapy	Pazopanib Monotherapy
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Total	71/76 (93.42%)	66/76 (86.84%)	69/74 (93.24%)
Blood and lymphatic system disorders			
Anaemia [A] †	12/76 (15.79%)	12/76 (15.79%)	8/74 (10.81%)
Leukopenia [A] †	6/76 (7.89%)	0/76 (0%)	5/74 (6.76%)
Lymphopenia [A] †	0/76 (0%)	3/76 (3.95%)	4/74 (5.41%)
Neutropenia [A] †	3/76 (3.95%)	1/76 (1.32%)	9/74 (12.16%)
Gastrointestinal disorders			
Abdominal pain [A] †	15/76 (19.74%)	9/76 (11.84%)	14/74 (18.92%)
Abdominal pain upper [A] †	5/76 (6.58%)	7/76 (9.21%)	13/74 (17.57%)
Constipation [A] †	8/76 (10.53%)	8/76 (10.53%)	17/74 (22.97%)
Diarrhoea [A] †	58/76 (76.32%)	42/76 (55.26%)	40/74 (54.05%)
Dry mouth [A] †	3/76 (3.95%)	4/76 (5.26%)	2/74 (2.7%)

	Combination Therapy: Lapatinib 1500 mg and Pazopanib 800 mg	Lapatinib Monotherapy	Pazopanib Monotherapy
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Dyspepsia [A] †	4/76 (5.26%)	3/76 (3.95%)	2/74 (2.7%)
Flatulence [A] †	1/76 (1.32%)	4/76 (5.26%)	0/74 (0%)
Nausea [A] †	28/76 (36.84%)	25/76 (32.89%)	28/74 (37.84%)
Rectal haemorrhage [A] †	7/76 (9.21%)	3/76 (3.95%)	2/74 (2.7%)
Stomatitis [A] †	4/76 (5.26%)	5/76 (6.58%)	2/74 (2.7%)
Vomiting [A] †	32/76 (42.11%)	18/76 (23.68%)	15/74 (20.27%)
General disorders			
Asthenia [A] †	19/76 (25%)	17/76 (22.37%)	13/74 (17.57%)
Fatigue [A] †	14/76 (18.42%)	15/76 (19.74%)	10/74 (13.51%)
Oedema peripheral [A] †	5/76 (6.58%)	8/76 (10.53%)	6/74 (8.11%)
Pain [A] †	3/76 (3.95%)	1/76 (1.32%)	5/74 (6.76%)
Pyrexia [A] †	5/76 (6.58%)	6/76 (7.89%)	3/74 (4.05%)
Hepatobiliary disorders			
Hyperbilirubinaemia [A] †	5/76 (6.58%)	1/76 (1.32%)	4/74 (5.41%)
Infections and infestations			
Pharyngitis [A] †	0/76 (0%)	0/76 (0%)	4/74 (5.41%)
Urinary tract infection [A] †	9/76 (11.84%)	10/76 (13.16%)	6/74 (8.11%)
Investigations			
Alanine aminotransferase increased [A] †	5/76 (6.58%)	1/76 (1.32%)	11/74 (14.86%)
Aspartate aminotransferase increased [A] †	9/76 (11.84%)	2/76 (2.63%)	11/74 (14.86%)
Blood alkaline phosphatase increased [A] †	7/76 (9.21%)	5/76 (6.58%)	14/74 (18.92%)
Blood lactate dehydrogenase increased [A] †	5/76 (6.58%)	1/76 (1.32%)	8/74 (10.81%)

	Combination Therapy: Lapatinib 1500 mg and Pazopanib 800 mg	Lapatinib Monotherapy	Pazopanib Monotherapy
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Haemoglobin decreased [A] †	2/76 (2.63%)	1/76 (1.32%)	4/74 (5.41%)
Weight decreased [A] †	6/76 (7.89%)	4/76 (5.26%)	3/74 (4.05%)
Metabolism and nutrition disorders			
Decreased appetite [A] †	29/76 (38.16%)	25/76 (32.89%)	20/74 (27.03%)
Musculoskeletal and connective tissue disorders			
Arthralgia [A] †	5/76 (6.58%)	3/76 (3.95%)	4/74 (5.41%)
Back pain [A] †	8/76 (10.53%)	11/76 (14.47%)	9/74 (12.16%)
Myalgia [A] †	5/76 (6.58%)	6/76 (7.89%)	5/74 (6.76%)
Pain in extremity [A] †	4/76 (5.26%)	7/76 (9.21%)	8/74 (10.81%)
Nervous system disorders			
Dizziness [A] †	3/76 (3.95%)	5/76 (6.58%)	5/74 (6.76%)
Dysgeusia [A] †	11/76 (14.47%)	3/76 (3.95%)	5/74 (6.76%)
Headache [A] †	10/76 (13.16%)	7/76 (9.21%)	20/74 (27.03%)
Somnolence [A] †	0/76 (0%)	4/76 (5.26%)	3/74 (4.05%)
Psychiatric disorders			
Insomnia [A] †	3/76 (3.95%)	5/76 (6.58%)	5/74 (6.76%)
Renal and urinary disorders			
Dysuria [A] †	5/76 (6.58%)	4/76 (5.26%)	3/74 (4.05%)
Haematuria [A] †	3/76 (3.95%)	5/76 (6.58%)	3/74 (4.05%)
Proteinuria [A] †	9/76 (11.84%)	11/76 (14.47%)	6/74 (8.11%)
Urinary incontinence [A] †	0/76 (0%)	5/76 (6.58%)	2/74 (2.7%)
Reproductive system and breast disorders			

	Combination Therapy: Lapatinib 1500 mg and Pazopanib 800 mg	Lapatinib Monotherapy	Pazopanib Monotherapy
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Pelvic pain [A] †	4/76 (5.26%)	5/76 (6.58%)	5/74 (6.76%)
Vaginal haemorrhage [A] †	8/76 (10.53%)	2/76 (2.63%)	5/74 (6.76%)
Respiratory, thoracic and mediastinal disorders			
Cough [A] †	4/76 (5.26%)	7/76 (9.21%)	7/74 (9.46%)
Dyspnoea [A] †	9/76 (11.84%)	8/76 (10.53%)	3/74 (4.05%)
Epistaxis [A] †	6/76 (7.89%)	1/76 (1.32%)	2/74 (2.7%)
Skin and subcutaneous tissue disorders			
Acne [A] †	6/76 (7.89%)	4/76 (5.26%)	0/74 (0%)
Alopecia [A] †	7/76 (9.21%)	1/76 (1.32%)	6/74 (8.11%)
Dermatitis acneiform [A] †	3/76 (3.95%)	5/76 (6.58%)	1/74 (1.35%)
Dry skin [A] †	3/76 (3.95%)	5/76 (6.58%)	5/74 (6.76%)
Erythema [A] †	0/76 (0%)	3/76 (3.95%)	5/74 (6.76%)
Hair colour changes [A] †	8/76 (10.53%)	0/76 (0%)	11/74 (14.86%)
Pruritus [A] †	1/76 (1.32%)	8/76 (10.53%)	2/74 (2.7%)
Rash [A] †	12/76 (15.79%)	22/76 (28.95%)	4/74 (5.41%)
Skin hypopigmentation [A] †	4/76 (5.26%)	0/76 (0%)	2/74 (2.7%)
Vascular disorders			
Hypertension [A] †	24/76 (31.58%)	2/76 (2.63%)	23/74 (31.08%)

† 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.

Results Point of Contact:

Name/Official Title: GSK Response Center
Organization: GlaxoSmithKline
Phone: 866-435-7343
Email: