Protocol Registration Receipt
08/15/2013

Grantor: CDER IND/IDE Number: 61362 Serial Number: 00392

Lapatinib In Combination With Trastuzumab Versus Lapatinib Monotherapy In Subjects With HER2-positive Metastatic Breast Cancer

This study has been completed.

Sponsor:	GlaxoSmithKline
Collaborators:	
Information provided by (Responsible Party):	GlaxoSmithKline
ClinicalTrials.gov Identifier:	NCT00320385

Purpose

This study will evaluate and compare the safety and efficacy of lapatinib in combination with trastuzumab versus lapatinib monotherapy in subjects with HER2-positive metastatic breast cancer.

Condition	Intervention	Phase
Neoplasms, Breast	Drug: Lapatinib	Phase 3

Condition	Intervention	Phase
	Biological/Vaccine: Trastuzumab	

Study Type: Interventional
Study Design: Treatment, Parallel Assignment, Open Label, Randomized, Safety/Efficacy Study
Official Title: A Randomized, Multicenter, Open-Label, Phase III Study of Lapatinib in Combination With Trastuzumab Versus Lapatinib Monotherapy in Subjects With HER2-positive Metastatic Breast Cancer Whose Disease Has Progressed on Trastuzumab-Containing Regimens

Further study details as provided by GlaxoSmithKline:

Primary Outcome Measure:

- Progression-Free Survival (PFS) [Time Frame: Baseline to disease progression or death due to any cause or 30 days after last dose (up to 216 weeks)] [Designated as safety issue: No]

  PFS was defined as the time from randomization until the first documented sign of disease progression or death due to any cause.

Secondary Outcome Measures:

- Overall Survival (OS) [Time Frame: Baseline to death or 30 days after last dose for the last participant (up to 216 weeks)] [Designated as safety issue: No]

  OS was defined as the time from randomization until death due to any cause. For participants who did not die, OS was censored at the time of last contact.
- Overall Tumor Response (OR) [Time Frame: Baseline to disease progression or death or discontinuation from study or 30 days after last dose (up to 216 weeks)] [Designated as safety issue: No]

  OR was defined as the percentage of participants experiencing either a confirmed complete response (CR) or a confirmed partial response (PR) according to Response Evaluation Criteria in Solid Tumors (RECIST) criteria 1.0. CR was defined as the disappearance of all lesions (target and/or non-target). PR was defined as at least a 30% decrease in the sum of the longest dimensions (LD) of target lesions taking as a reference the baseline sum LD, with non-target lesions not increased or absent.
- Clinical Benefit Response (CBR) [Time Frame: Baseline to disease progression or death or discontinuation from study or 30 days after last dose (up to 216 weeks)] [Designated as safety issue: No]

  CBR: percentage of participants with confirmed CR or PR or stable disease (SD) for at least 24 weeks according to RECIST criteria. CR: disappearance of all lesions (target and/or non-target). PR: at least a 30% decrease in the sum of the LD of target lesions taking as reference baseline sum LD, with non-target lesions not increased or absent. SD: neither had sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease (PD) in target lesions, taking as reference the smallest sum LD since treatment started; persistence of 1 or more non-target lesions.
- Time to Response (TTR) [Time Frame: Baseline until first documented evidence of CR or PR or 30 days after last dose (up to 216 weeks)] [Designated as safety issue: No]

  TTR was defined as the time from randomization until the first documented evidence of CR or PR (whichever status was recorded first). TTR could not be analyzed because too few participants experienced a confirmed CR or PR.

- Duration of Response (DR) [Time Frame: Time from first documented evidence of CR or PR until the first documented sign of disease progression or death or 30 days after last dose (up to 216 weeks)] [Designated as safety issue: No]

  DR was defined for the subset of participants who showed a confirmed CR or PR, as the time from the first documented evidence of CR or PR until the first documented sign of disease progression or death. Because of the low number of participants experiencing a confirmed response in both treatment arms, analysis for this outcome measure was not performed.
- Time to Progression (TTP) [Time Frame: Baseline to disease progression or death or 30 days after last dose (up to 216 weeks)] [Designated as safety issue: No]

  TTP was defined as the interval between the date of randomization and the earlier of the date of disease progression or death due to breast cancer. Because this outcome measure was confounded by death due to other causes and was similar to PFS, it was not analyzed.
- Change From Baseline in Functional Assessment of Cancer Therapy-Breast (FACT-B) Scores at Week 4, Week 12, Week 16, Week 24, and Conclusion or Withdrawal From Study [Time Frame: Baseline, Week 4, Week 12, Week 16, Week 24, and conclusion or withdrawal from study (up to Week 108)] [Designated as safety issue: No]

  Quality of Life (QOL) was assessed using the FACT-B questionnaire, which was a 37-item (27 general and 10 breast cancer-specific questions) self-reporting instrument consisting of 5 dimensions: physical-, social/family-, emotional-, functional-well being, and a breast cancer subscale. Higher scores on the FACT-B scales indicate a higher QOL; each ranging from 0 (not at all) to 4 (very much). The score is transformed for FACT-B and results in a total score ranging from 0 to 144.

Enrollment: 296
Study Start Date: November 2005
Study Completion Date: October 2010
Primary Completion Date: June 2007

Arms	Assigned Interventions
Experimental: Arm 1: Lapatinib plus Trastuzumab Lapatinib 1000mg once daily in combination with trastuzumab 4mg/kg loading dose followed by 2mg/kg weekly	Drug: Lapatinib oral lapatinib once daily Other Names: Tyverb Tykerb Biological/Vaccine: Trastuzumab IV trastuzumab 2mg/kg weekly after 4mg/kg loading dose Other Names: Herceptin

Arms	Assigned Interventions
Experimental: Arm 2: Lapatinib Lapatinib 1500mg once daily	Drug: Lapatinib oral lapatinib once daily Other Names: Tyverb Tykerb

Eligibility

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

Inclusion Criteria:

- Signed informed consent.
- Female ≥18 years. Women of childbearing potential must have a negative serum pregnancy test at screening and must use an approved contraceptive method, if appropriate (for example, intrauterine device [IUD], birth control pills, or barrier device) beginning 2 weeks before the first dose of investigational product and for 28 days after the final dose of investigational product.
- Metastatic breast cancer, histologically/cytologically confirmed. If the disease is restricted to a solitary lesion, its neoplastic nature must be confirmed by cytology or histology.
- Subjects must have stage IV breast cancer whereby their disease has progressed in either the adjuvant or metastatic setting. Prior therapies must include, but are not limited to:
- Taxane-containing regimen for at least 4 cycles, or 2 cycles provided disease progression occurred while on taxane.
- Anthracycline-containing regimen for at least 4 cycles, or 2 cycles provided disease progression occurred while on anthracycline.
- Subjects must have documented progression following at least ONE trastuzumab plus cytotoxic chemotherapy or anti-hormonal regimen in the metastatic setting.
- Note: The most recent treatment must have contained trastuzumab, either alone or in combination with other therapy in the metastatic setting, and subjects must have progressed while on this regimen. Progression is defined as either new lesions or a ≥20% increase in the sum of longest diameter (LD) on the progression radiologic scan.
- Subjects must have archived tumor tissue available for testing.
- Documented amplification of the ErbB2 gene by fluorescence in situ hybridization (FISH) or documented overexpression of the ErbB2 protein by IHC in primary or metastatic tumor tissue. The IHC or FISH amplification may be documented by a local or central laboratory for randomization into the study. Subjects may be randomized on the basis of ErbB2 positivity by IHC 3+ overexpression or FISH amplification.
- Lesion eligibility is as follows:

- at least one measurable lesion(s) according to Response Evaluation Criteria in Solid Tumors [RECIST; Therasse, 2000], or
- bone-only disease.
- Note: Tumor lesions which are situated in a previously irradiated field, and have well-defined margins which are located in soft tissue will be defined as measurable disease.
- Subjects with stable CNS metastases defined as asymptomatic and off systemic steroids and anticonvulsants for at least 1 month. Treatment with prophylactic anticonvulsants is permitted, unless listed within the Prohibited Medications (Section 8.2).
- Radiotherapy if received within 2 weeks prior to initiation of investigational product to a limited area (e.g., palliative treatment for painful disease) other than the sole site of measurable disease is allowed; however, subject must have completed treatment and recovered from all treatment-related toxicities prior to administration of the first dose of investigational product.
- With the single exception of prior trastuzumab treatment, all prior chemotherapy, immunotherapy, biologic therapy, or surgery (except for minor surgical procedures) must be discontinued at least 3 weeks prior to the first dose of investigational product. Subjects must have recovered or stabilized sufficiently from treatment-related toxicities prior to administration of the first dose of investigational product.
- Bisphosphonate therapy for bone metastases is allowed; however, treatment must be initiated prior to the first dose of investigational product. Prophylactic use of bisphosphonates is permitted only for the treatment of osteoporosis.
- ECOG Performance Status of 0 to 2.
- Able to swallow and retain oral medication.
- Cardiac ejection fraction within institutional range of normal as measured by echocardiogram. MUGA scans will be accepted in cases where an echocardiogram cannot be performed or is inconclusive. Same modality used at baseline must be used for repeat assessments throughout study.
- Subject must have adequate organ function as defined in Table 1 :
- Table 1 (Definitions for Adequate Hematologic and Hepatic Function)
- SYSTEM (LABORATORY VALUES)
- Hematologic:
- ANC (absolute neutrophil count) (≥ 1x10^9/ L)
- Hemoglobin (≥ 9 g / dL)
- Platelets (≥75x10^9/ L)
- Hepatic
- Albumin (≥ 2.5 g / dL)
- Serum bilirubin (≤ 2 mg / dL)
- AST and ALT (≤ 3 x ULN without liver metastases) (≤ 5 xULN if documented liver metastases)
- Renal
- Serum Creatinine (≤1.5 mg / dL)
- OR -
- Calculated Creatinine Clearance1 (≥40 mL / min)
- Calculated by the Cockcroft and Gault Method.
- Subjects may continue anti-estrogen therapy only if treatment was initiated at least 1 month prior to the first dose of investigational product (IP). After

randomization, no anti-hormonal therapy may be initiated.

Exclusion Criteria:

- Pregnant or lactating females.
- Prior therapy with an ErbB1 and/or ErbB2 inhibitor other than trastuzumab.
- Malabsorption syndrome, disease significantly affecting gastrointestinal function, or resection of the stomach or small bowel. Subjects with ulcerative colitis are also excluded.
- History of other malignancy. However, subjects who have been disease-free for 5 years, or subjects with a history of completely resected non-melanoma skin cancer or successfully treated in situ carcinoma are eligible.
- Concurrent disease or condition that would make the subject inappropriate for study participation or any serious medical disorder that would interfere with the subject's safety.
- Unresolved or unstable, serious toxicity from prior administration of another investigational drug and/or of prior cancer treatment.
- Active or uncontrolled infection.
- Dementia, altered mental status, or any psychiatric condition that would prohibit the understanding or rendering of informed consent.
- Known history of uncontrolled or symptomatic angina, arrhythmias, or congestive heart failure.
- Known history or clinical evidence of leptomeningeal carcinomatosis.
- Concurrent cancer therapy (chemotherapy, radiation therapy, immunotherapy, biologic therapy).
- Concurrent treatment with an investigational agent or participation in another clinical trial.
- Used an investigational drug within 3 weeks or 5 half-lives, whichever is longer, preceding the first dose of investigational product.
- Known immediate or delayed hypersensitivity reaction or idiosyncrasy to drugs chemically related to trastuzumab or lapatinib or their excipients.
- 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).

Contacts and Locations

Locations

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Investigators

Study Director:	GSK Clinical Trials	GlaxoSmithKline

More Information

Publications:

Wu Y, Amonkar M, Sherrill B, Ellis C. Impact of Lapatinib Plus Trastuzumab Versus Single-Agent Lapatinib on Quality of Life of Patients With Trastuzumab-Refractory HER2+ Metastatic Breast Cancer. [Ann Oncol]. 2011;

Blackwell K, Burstein H, Storniolo A, Rugo H, Sledge G, Aktan G, Ellis C, Florance A, Vukelja S, Bischoff J, Baselga J, O'Shaughnessy J. Overall Survival Benefit with Lapatinib in Combination with Trastuzumab for Patients with HER2-Positive Metastatic Breast Cancer: Final Results from the EGF104900 Study. [J Clin Oncol]. 2012;

Responsible Party: GlaxoSmithKline
Study ID Numbers: EGF104900
Health Authority: United States: Food and Drug Administration

Study Results

Participant Flow

Reporting Groups

	Description
Trastuzumab + Lapatinib	Participants received Lapatinib 1000 milligram (mg) tablets orally daily 1 hour before or after breakfast along with Trastuzumab infusion at a loading dose of 4 milligrams/kilogram (mg/kg) body weight intravenously (IV) over 90 minutes on Day 1, followed by 2 mg/kg IV over 30 minutes weekly, in a 4 week cycle.
Lapatinib	Participants received Lapatinib 1500 mg tablets orally daily 1 hour before or after breakfast.

Overall Study

	Trastuzumab + Lapatinib	Lapatinib
Started	148	148
Completed	130	126
Not Completed	18	22
Lost to Follow-up	7	10
Withdrawal by Subject	6	7
Sponsor Terminated Study	2	1
Investigator Decision	0	1
Death	1	2

	Trastuzumab + Lapatinib	Lapatinib
Serious Adverse Event	1	0
Withdrew Consent	1	0
Adverse Event	0	1

Baseline Characteristics

Reporting Groups

	Description
Trastuzumab + Lapatinib	Participants received Lapatinib 1000 milligram (mg) tablets orally daily 1 hour before or after breakfast along with Trastuzumab infusion at a loading dose of 4 milligrams/kilogram (mg/kg) body weight intravenously (IV) over 90 minutes on Day 1, followed by 2 mg/kg IV over 30 minutes weekly, in a 4 week cycle.
Lapatinib	Participants received Lapatinib 1500 mg tablets orally daily 1 hour before or after breakfast.

Baseline Measures

	Trastuzumab + Lapatinib	Lapatinib	Total
Number of Participants	148	148	296
Age, Continuous [units: Years] Mean (Standard Deviation)	52.1 (11.60)	51.0 (10.40)	51.5 (11.01)
Gender, Male/Female [units: Participants]			

	Trastuzumab + Lapatinib	Lapatinib	Total
Female	148	148	296
Male	0	0	0
Race/Ethnicity, Customized [units: participants]			
White	137	140	277
African American/African Heritage	6	5	11
Asian	2	3	5
American Indian or Alaska Native	1	0	1
Native Hawaiian or other Pacific Islander	2	0	2

Outcome Measures

1. Primary Outcome Measure:

Measure Title	Progression-Free Survival (PFS)
Measure Description	PFS was defined as the time from randomization until the first documented sign of disease progression or death due to any cause.
Time Frame	Baseline to disease progression or death due to any cause or 30 days after last dose (up to 216 weeks)
Safety Issue?	No

Analysis Population Description

Intent-to-Treat (ITT) Population: all randomized participants irrespective of whether or not they actually received study treatment. Only participants with progesterone receptor status were considered for evaluation.

Reporting Groups

	Description
Trastuzumab + Lapatinib	Participants received Lapatinib 1000 milligram (mg) tablets orally daily 1 hour before or after breakfast along with Trastuzumab infusion at a loading dose of 4 milligrams/kilogram (mg/kg) body weight intravenously (IV) over 90 minutes on Day 1, followed by 2 mg/kg IV over 30 minutes weekly, in a 4 week cycle.
Lapatinib	Participants received Lapatinib 1500 mg tablets orally daily 1 hour before or after breakfast.

Measured Values

	Trastuzumab + Lapatinib	Lapatinib
Number of Participants Analyzed	146	145
Progression-Free Survival (PFS) [units: weeks] Median (95% Confidence Interval)	12.0 (8.1 to 16.0)	8.1 (7.6 to 9.0)

Statistical Analysis 1 for Progression-Free Survival (PFS)

Groups	Trastuzumab + Lapatinib, Lapatinib
Method	Log Rank
P-Value	0.008
Hazard Ratio (HR)	0.73
95% Confidence Interval	0.57 to 0.93

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

[Not specified.]

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

[Not specified.]

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

[Not specified.]

Other relevant estimation information:

The Pike estimator of the treatment hazard ratio based on the log-rank test was provided, together with a 95% confidence interval.

2. Secondary Outcome Measure:

Measure Title	Overall Survival (OS)
Measure Description	OS was defined as the time from randomization until death due to any cause. For participants who did not die, OS was censored at the time of last contact.
Time Frame	Baseline to death or 30 days after last dose for the last participant (up to 216 weeks)
Safety Issue?	No

Analysis Population Description

ITT Population. Only participants with progesterone receptor status were considered for evaluation.

Reporting Groups

	Description
Trastuzumab + Lapatinib	Participants received Lapatinib 1000 milligram (mg) tablets orally daily 1 hour before or after breakfast along with Trastuzumab infusion at a loading dose of 4 milligrams/kilogram (mg/kg) body weight intravenously (IV) over 90 minutes on Day 1, followed by 2 mg/kg IV over 30 minutes weekly, in a 4 week cycle.

	Description
Lapatinib	Participants received Lapatinib 1500 mg tablets orally daily 1 hour before or after breakfast.

Measured Values

	Trastuzumab + Lapatinib	Lapatinib
Number of Participants Analyzed	146	145
Overall Survival (OS) [units: weeks] Median (95% Confidence Interval)	51.6 (42.9 to 57.3)	39.0 (32.9 to 52.1)

Statistical Analysis 1 for Overall Survival (OS)

Groups	Trastuzumab + Lapatinib, Lapatinib
Method	Log Rank
P-Value	0.106
Hazard Ratio (HR)	0.75
95% Confidence Interval	0.53 to 1.07

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

[Not specified.]

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

[Not specified.]

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

[Not specified.]

Other relevant estimation information:

The Pike estimator of the treatment hazard ratio based on the log-rank test was provided, together with a 95% confidence

interval.

3. Secondary Outcome Measure:

Measure Title	Overall Tumor Response (OR)
Measure Description	OR was defined as the percentage of participants experiencing either a confirmed complete response (CR) or a confirmed partial response (PR) according to Response Evaluation Criteria in Solid Tumors (RECIST) criteria 1.0. CR was defined as the disappearance of all lesions (target and/or non-target). PR was defined as at least a 30% decrease in the sum of the longest dimensions (LD) of target lesions taking as a reference the baseline sum LD, with non-target lesions not increased or absent.
Time Frame	Baseline to disease progression or death or discontinuation from study or 30 days after last dose (up to 216 weeks)
Safety Issue?	No

Analysis Population Description

ITT Population. Only participants with progesterone receptor status were considered for evaluation.

Reporting Groups

	Description
Trastuzumab + Lapatinib	Participants received Lapatinib 1000 milligram (mg) tablets orally daily 1 hour before or after breakfast along with Trastuzumab infusion at a loading dose of 4 milligrams/kilogram (mg/kg) body weight intravenously (IV) over 90 minutes on Day 1, followed by 2 mg/kg IV over 30 minutes weekly, in a 4 week cycle.
Lapatinib	Participants received Lapatinib 1500 mg tablets orally daily 1 hour before or after breakfast.

Measured Values

	Trastuzumab + Lapatinib	Lapatinib
Number of Participants Analyzed	146	145
Overall Tumor Response (OR) [units: percentage of participants]	10.3	6.9

Statistical Analysis 1 for Overall Tumor Response (OR)

Groups	Trastuzumab + Lapatinib, Lapatinib
Method	Fisher Exact
P-Value	0.460
Odds Ratio (OR)	1.5
95% Confidence Interval	0.6 to 3.9

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

[Not specified.]

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

[Not specified.]

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

[Not specified.]

Other relevant estimation information:

Responses were compared between treatment arms using stratified Fisher's exact tests.

4. Secondary Outcome Measure:

Measure Title	Clinical Benefit Response (CBR)
Measure Description	CBR: percentage of participants with confirmed CR or PR or stable

	disease (SD) for at least 24 weeks according to RECIST criteria. CR: disappearance of all lesions (target and/or non-target). PR: at least a 30% decrease in the sum of the LD of target lesions taking as reference baseline sum LD, with non-target lesions not increased or absent. SD: neither had sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease (PD) in target lesions, taking as reference the smallest sum LD since treatment started; persistence of 1 or more non-target lesions.
Time Frame	Baseline to disease progression or death or discontinuation from study or 30 days after last dose (up to 216 weeks)
Safety Issue?	No

Analysis Population Description

ITT Population

Reporting Groups

	Description
Trastuzumab + Lapatinib	Participants received Lapatinib 1000 milligram (mg) tablets orally daily 1 hour before or after breakfast along with Trastuzumab infusion at a loading dose of 4 milligrams/kilogram (mg/kg) body weight intravenously (IV) over 90 minutes on Day 1, followed by 2 mg/kg IV over 30 minutes weekly, in a 4 week cycle.
Lapatinib	Participants received Lapatinib 1500 mg tablets orally daily 1 hour before or after breakfast.

Measured Values

	Trastuzumab + Lapatinib	Lapatinib
Number of Participants Analyzed	148	148

	Trastuzumab + Lapatinib	Lapatinib
Clinical Benefit Response (CBR) [units: percentage of participants]	24.7	12.4

Statistical Analysis 1 for Clinical Benefit Response (CBR)

Groups	Trastuzumab + Lapatinib, Lapatinib
Method	Fisher Exact
P-Value	0.010
Odds Ratio (OR)	2.2
95% Confidence Interval	1.2 to 4.5

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

[Not specified.]

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

[Not specified.]

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

[Not specified.]

Other relevant estimation information:

Clinical Benefit was compared between treatment arms using stratified Fisher's exact tests.

5. Secondary Outcome Measure:

Measure Title	Time to Response (TTR)
Measure Description	TTR was defined as the time from randomization until the first documented evidence of CR or PR (whichever status was recorded first). TTR could not be analyzed because too few participants experienced a confirmed CR or PR.

Time Frame	Baseline until first documented evidence of CR or PR or 30 days after last dose (up to 216 weeks)
Safety Issue?	No

Analysis Population Description

ITT Population

Reporting Groups

	Description
Trastuzumab + Lapatinib	Participants received Lapatinib 1000 milligram (mg) tablets orally daily 1 hour before or after breakfast along with Trastuzumab infusion at a loading dose of 4 milligrams/kilogram (mg/kg) body weight intravenously (IV) over 90 minutes on Day 1, followed by 2 mg/kg IV over 30 minutes weekly, in a 4 week cycle.
Lapatinib	Participants received Lapatinib 1500 mg tablets orally daily 1 hour before or after breakfast.

Measured Values

	Trastuzumab + Lapatinib	Lapatinib
Number of Participants Analyzed	0	0

No data displayed because Outcome Measure has zero total participants analyzed.

6. Secondary Outcome Measure:

Measure Title	Duration of Response (DR)
Measure Description	DR was defined for the subset of participants who showed a confirmed CR or PR, as the time from the first documented evidence of CR or PR until the first documented sign of disease progression or death.

	Because of the low number of participants experiencing a confirmed response in both treatment arms, analysis for this outcome measure was not performed.
Time Frame	Time from first documented evidence of CR or PR until the first documented sign of disease progression or death or 30 days after last dose (up to 216 weeks)
Safety Issue?	No

Analysis Population Description

ITT Population

Reporting Groups

	Description
Trastuzumab + Lapatinib	Participants received Lapatinib 1000 milligram (mg) tablets orally daily 1 hour before or after breakfast along with Trastuzumab infusion at a loading dose of 4 milligrams/kilogram (mg/kg) body weight intravenously (IV) over 90 minutes on Day 1, followed by 2 mg/kg IV over 30 minutes weekly, in a 4 week cycle.
Lapatinib	Participants received Lapatinib 1500 mg tablets orally daily 1 hour before or after breakfast.

Measured Values

	Trastuzumab + Lapatinib	Lapatinib
Number of Participants Analyzed	0	0

No data displayed because Outcome Measure has zero total participants analyzed.

7. Secondary Outcome Measure:

Measure Title	Time to Progression (TTP)
Measure Description	TTP was defined as the interval between the date of randomization and the earlier of the date of disease progression or death due to breast cancer. Because this outcome measure was confounded by death due to other causes and was similar to PFS, it was not analyzed.
Time Frame	Baseline to disease progression or death or 30 days after last dose (up to 216 weeks)
Safety Issue?	No

Analysis Population Description

ITT Population

Reporting Groups

	Description
Trastuzumab + Lapatinib	Participants received Lapatinib 1000 milligram (mg) tablets orally daily 1 hour before or after breakfast along with Trastuzumab infusion at a loading dose of 4 milligrams/kilogram (mg/kg) body weight intravenously (IV) over 90 minutes on Day 1, followed by 2 mg/kg IV over 30 minutes weekly, in a 4 week cycle.
Lapatinib	Participants received Lapatinib 1500 mg tablets orally daily 1 hour before or after breakfast.

Measured Values

	Trastuzumab + Lapatinib	Lapatinib
Number of Participants Analyzed	0	0

No data displayed because Outcome Measure has zero total participants analyzed.

8. Secondary Outcome Measure:

Measure Title	Change From Baseline in Functional Assessment of Cancer Therapy-Breast (FACT-B) Scores at Week 4, Week 12, Week 16, Week 24, and Conclusion or Withdrawal From Study
Measure Description	Quality of Life (QOL) was assessed using the FACT-B questionnaire, which was a 37-item (27 general and 10 breast cancer-specific questions) self-reporting instrument consisting of 5 dimensions: physical-, social/family-, emotional-, functional-well being, and a breast cancer subscale. Higher scores on the FACT-B scales indicate a higher QOL; each ranging from 0 (not at all) to 4 (very much). The score is transformed for FACT-B and results in a total score ranging from 0 to 144.
Time Frame	Baseline, Week 4, Week 12, Week 16, Week 24, and conclusion or withdrawal from study (up to Week 108)
Safety Issue?	No

Analysis Population Description

Safety Population: all randomized participants who received >=1 dose of investigational product. The Safety Population was based on the actual treatment received, if this differed from that to which the participant was randomized. Only participants whose overall item response rate was greater than 80% for the FACT-B total score were considered (n).

Reporting Groups

	Description
Trastuzumab + Lapatinib	Participants received Lapatinib 1000 milligram (mg) tablets orally daily 1 hour before or after breakfast along with Trastuzumab infusion at a loading dose of 4 milligrams/kilogram (mg/kg) body weight intravenously (IV) over 90 minutes on Day 1, followed by 2 mg/kg IV over 30 minutes weekly, in a 4 week cycle.

	Description
Lapatinib	Participants received Lapatinib 1500 mg tablets orally daily 1 hour before or after breakfast.

Measured Values

	Trastuzumab + Lapatinib	Lapatinib
Number of Participants Analyzed	137	137
Change From Baseline in Functional Assessment of Cancer Therapy-Breast (FACT-B) Scores at Week 4, Week 12, Week 16, Week 24, and Conclusion or Withdrawal From Study [units: scores on a scale] Mean (Standard Deviation)		
Baseline, n=137, 137	98.7 (21.17)	97.2 (21.85)
Change at Week 4, n=101, 109	-0.4 (11.52)	-0.6 (13.00)
Change at Week 12, n=57, 51	1.5 (10.87)	-3.0 (12.54)
Change at Week 16, n=42, 38	-0.1 (13.34)	0.4 (17.65)
Change at Week 24, n=28, 28	1.3 (12.60)	-1.3 (15.67)
Change at Conclusion/Withdrawal, n=63, 67	-7.3 (15.48)	-8.0 (15.54)

Reported Adverse Events

Reporting Groups

	Description
Trastuzumab + Lapatinib	Participants received Lapatinib 1000 milligram (mg) tablets orally daily 1 hour before or after breakfast along with Trastuzumab infusion at a loading dose of 4 milligrams/kilogram (mg/kg) body weight intravenously (IV) over 90 minutes on Day 1, followed by 2 mg/kg IV over 30 minutes weekly, in a 4 week cycle.
Lapatinib	Participants received Lapatinib 1500 mg tablets orally daily 1 hour before or after breakfast.

Time Frame

Serious adverse events (SAEs) and non-serious AEs were collected from Baseline to conclusion or withdrawal from study; time from the first dose of treatment until 30 days after the last dose of study treatment (up to 216 weeks).

Additional Description

SAEs and AEs were collected in the Safety Population, which consisted of all randomized participants who received at least one dose of investigational product, and was based on the actual treatment received, if this differed from that to which the participant was randomized.

Serious Adverse Events

	Trastuzumab + Lapatinib	Lapatinib
Total # participants affected/at risk	40/149 (26.85%)	24/146 (16.44%)
Blood and lymphatic system disorders		
Anaemia * [A]		
# participants affected/at risk	1/149 (0.67%)	0/146 (0%)
# events		

	Trastuzumab + Lapatinib	Lapatinib
Febrile neutropenia * [A]		
# participants affected/at risk	2/149 (1.34%)	0/146 (0%)
# events		
Thrombocytopenia * [A]		
# participants affected/at risk	1/149 (0.67%)	0/146 (0%)
# events		
Cardiac disorders		
Cardiac failure * [A]		
# participants affected/at risk	1/149 (0.67%)	0/146 (0%)
# events		
Left ventricular dysfunction * [A]		
# participants affected/at risk	1/149 (0.67%)	2/146 (1.37%)
# events		
Myocardial infarction * [A]		
# participants affected/at risk	1/149 (0.67%)	0/146 (0%)
# events		
Pericardial effusion * [A]		

	Trastuzumab + Lapatinib	Lapatinib
# participants affected/at risk	0/149 (0%)	1/146 (0.68%)
# events		
Ear and labyrinth disorders		
Vertigo * [A]		
# participants affected/at risk	1/149 (0.67%)	0/146 (0%)
# events		
Gastrointestinal disorders		
Abdominal pain * [A]		
# participants affected/at risk	0/149 (0%)	1/146 (0.68%)
# events		
Ascites * [A]		
# participants affected/at risk	1/149 (0.67%)	0/146 (0%)
# events		
Diarrhoea * [A]		
# participants affected/at risk	2/149 (1.34%)	3/146 (2.05%)
# events		

	Trastuzumab + Lapatinib	Lapatinib
Dysphagia * [A]		
# participants affected/at risk	1/149 (0.67%)	0/146 (0%)
# events		
Flatulence * [A]		
# participants affected/at risk	1/149 (0.67%)	0/146 (0%)
# events		
Impaired gastric emptying * [A]		
# participants affected/at risk	1/149 (0.67%)	0/146 (0%)
# events		
Nausea * [A]		
# participants affected/at risk	2/149 (1.34%)	2/146 (1.37%)
# events		
Pancreatitis * [A]		
# participants affected/at risk	1/149 (0.67%)	0/146 (0%)
# events		
Vomiting * [A]		
# participants affected/at	3/149 (2.01%)	2/146 (1.37%)

	Trastuzumab + Lapatinib	Lapatinib
risk		
# events		
General disorders		
Asthenia * [A]		
# participants affected/at risk	1/149 (0.67%)	0/146 (0%)
# events		
Hepatobiliary disorders		
Bile duct obstruction * [A]		
# participants affected/at risk	1/149 (0.67%)	0/146 (0%)
# events		
Hepatic failure * [A]		
# participants affected/at risk	0/149 (0%)	1/146 (0.68%)
# events		
Jaundice * [A]		
# participants affected/at risk	1/149 (0.67%)	1/146 (0.68%)
# events		
Jaundice cholestatic * [A]		
# participants affected/at	0/149 (0%)	1/146 (0.68%)

	Trastuzumab + Lapatinib	Lapatinib
risk		
# events		
Infections and infestations		
Cellulitis * [A]		
# participants affected/at risk	1/149 (0.67%)	0/146 (0%)
# events		
Device related infection * [A]		
# participants affected/at risk	1/149 (0.67%)	0/146 (0%)
# events		
Diverticulitis * [A]		
# participants affected/at risk	1/149 (0.67%)	0/146 (0%)
# events		
Erysipelas * [A]		
# participants affected/at risk	0/149 (0%)	1/146 (0.68%)
# events		
Gastroenteritis * [A]		
# participants affected/at risk	1/149 (0.67%)	0/146 (0%)

	Trastuzumab + Lapatinib	Lapatinib
# events		
Infection * [A]		
# participants affected/at risk	1/149 (0.67%)	0/146 (0%)
# events		
Pneumonia * [A]		
# participants affected/at risk	1/149 (0.67%)	1/146 (0.68%)
# events		
Sepsis * [A]		
# participants affected/at risk	1/149 (0.67%)	0/146 (0%)
# events		
Injury, poisoning and procedural complications		
Fall * [A]		
# participants affected/at risk	0/149 (0%)	1/146 (0.68%)
# events		
Femoral neck fracture * [A]		
# participants affected/at risk	0/149 (0%)	1/146 (0.68%)
# events		

	Trastuzumab + Lapatinib	Lapatinib
Femur fracture * [A]		
# participants affected/at risk	1/149 (0.67%)	0/146 (0%)
# events		
Hip fracture * [A]		
# participants affected/at risk	1/149 (0.67%)	0/146 (0%)
# events		
Internal injury * [A]		
# participants affected/at risk	0/149 (0%)	1/146 (0.68%)
# events		
Investigations		
Ejection fraction decreased * [A]		
# participants affected/at risk	7/149 (4.7%)	1/146 (0.68%)
# events		
Weight decreased * [A]		
# participants affected/at risk	0/149 (0%)	1/146 (0.68%)
# events		
Metabolism and nutrition		

	Trastuzumab + Lapatinib	Lapatinib
disorders		
Dehydration * [A]		
# participants affected/at risk	4/149 (2.68%)	0/146 (0%)
# events		
Failure to thrive * [A]		
# participants affected/at risk	1/149 (0.67%)	0/146 (0%)
# events		
Hypocalcaemia * [A]		
# participants affected/at risk	0/149 (0%)	1/146 (0.68%)
# events		
Malnutrition * [A]		
# participants affected/at risk	1/149 (0.67%)	0/146 (0%)
# events		
Musculoskeletal and connective tissue disorders		
Arthralgia * [A]		
# participants affected/at risk	1/149 (0.67%)	0/146 (0%)

	Trastuzumab + Lapatinib	Lapatinib
# events		
Back pain * [A]		
# participants affected/at risk	0/149 (0%)	1/146 (0.68%)
# events		
Muscular weakness * [A]		
# participants affected/at risk	0/149 (0%)	1/146 (0.68%)
# events		
Osteoarthritis * [A]		
# participants affected/at risk	1/149 (0.67%)	0/146 (0%)
# events		
Osteonecrosis * [A]		
# participants affected/at risk	1/149 (0.67%)	0/146 (0%)
# events		
Pain in extremity * [A]		
# participants affected/at risk	0/149 (0%)	1/146 (0.68%)
# events		
Neoplasms benign, malignant and		

	Trastuzumab + Lapatinib	Lapatinib
unspecified (incl cysts and polyps)		
Cancer pain * [A]		
# participants affected/at risk	1/149 (0.67%)	0/146 (0%)
# events		
Metastases to liver * [A]		
# participants affected/at risk	0/149 (0%)	1/146 (0.68%)
# events		
Nervous system disorders		
Brain oedema * [A]		
# participants affected/at risk	1/149 (0.67%)	0/146 (0%)
# events		
Convulsion * [A]		
# participants affected/at risk	2/149 (1.34%)	0/146 (0%)
# events		
Headache * [A]		
# participants affected/at risk	2/149 (1.34%)	0/146 (0%)

	Trastuzumab + Lapatinib	Lapatinib
# events		
Hepatic encephalopathy * [A]		
# participants affected/at risk	1/149 (0.67%)	0/146 (0%)
# events		
Hypoaesthesia * [A]		
# participants affected/at risk	0/149 (0%)	1/146 (0.68%)
# events		
Radiculopathy * [A]		
# participants affected/at risk	0/149 (0%)	1/146 (0.68%)
# events		
Psychiatric disorders		
Confusional state * [A]		
# participants affected/at risk	0/149 (0%)	1/146 (0.68%)
# events		
Psychotic disorder * [A]		
# participants affected/at risk	0/149 (0%)	1/146 (0.68%)
# events		

	Trastuzumab + Lapatinib	Lapatinib
Renal and urinary disorders		
Renal failure * [A]		
# participants affected/at risk	0/149 (0%)	1/146 (0.68%)
# events		
Urinary retention * [A]		
# participants affected/at risk	1/149 (0.67%)	0/146 (0%)
# events		
Respiratory, thoracic and mediastinal disorders		
Cough * [A]		
# participants affected/at risk	0/149 (0%)	1/146 (0.68%)
# events		
Dyspnoea * [A]		
# participants affected/at risk	1/149 (0.67%)	1/146 (0.68%)
# events		
Hydrothorax * [A]		
# participants affected/at risk	0/149 (0%)	1/146 (0.68%)

	Trastuzumab + Lapatinib	Lapatinib
# events		
Pleural effusion * [A]		
# participants affected/at risk	1/149 (0.67%)	1/146 (0.68%)
# events		
Pneumothorax * [A]		
# participants affected/at risk	1/149 (0.67%)	0/146 (0%)
# events		
Pulmonary embolism * [A]		
# participants affected/at risk	2/149 (1.34%)	0/146 (0%)
# events		
Respiratory failure * [A]		
# participants affected/at risk	1/149 (0.67%)	0/146 (0%)
# events		
Vascular disorders		
Lymphoedema * [A]		
# participants affected/at risk	1/149 (0.67%)	1/146 (0.68%)
# events		

* Indicates events were collected by non-systematic methods.

A Term from vocabulary, MedDRA Version 11.0

Other Adverse Events

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

	Trastuzumab + Lapatinib	Lapatinib
Total # participants affected/at risk	140/149 (93.96%)	132/146 (90.41%)
Blood and lymphatic system disorders		
Anaemia * [A]		
# participants affected/at risk	7/149 (4.7%)	3/146 (2.05%)
# events		
Gastrointestinal disorders		
Abdominal pain * [A]		
# participants affected/at risk	8/149 (5.37%)	7/146 (4.79%)
# events		
Abdominal pain upper * [A]		
# participants affected/at risk	8/149 (5.37%)	3/146 (2.05%)
# events		
Constipation * [A]		

	Trastuzumab + Lapatinib	Lapatinib
# participants affected/at risk	9/149 (6.04%)	11/146 (7.53%)
# events		
Diarrhea * [A]		
# participants affected/at risk	92/149 (61.74%)	70/146 (47.95%)
# events		
Dry mouth * [A]		
# participants affected/at risk	2/149 (1.34%)	7/146 (4.79%)
# events		
Dyspepsia * [A]		
# participants affected/at risk	10/149 (6.71%)	11/146 (7.53%)
# events		
Nausea * [A]		
# participants affected/at risk	42/149 (28.19%)	41/146 (28.08%)
# events		
Vomiting * [A]		
# participants affected/at risk	22/149 (14.77%)	26/146 (17.81%)
# events		

	Trastuzumab + Lapatinib	Lapatinib
General disorders		
Asthenia * [A]		
# participants affected/at risk	11/149 (7.38%)	10/146 (6.85%)
# events		
Fatigue * [A]		
# participants affected/at risk	33/149 (22.15%)	29/146 (19.86%)
# events		
Oedema peripheral * [A]		
# participants affected/at risk	5/149 (3.36%)	8/146 (5.48%)
# events		
Pyrexia * [A]		
# participants affected/at risk	10/149 (6.71%)	7/146 (4.79%)
# events		
Investigations		
Aspartate aminotransferase increased * [A]		
# participants affected/at risk	9/149 (6.04%)	3/146 (2.05%)
# events		

	Trastuzumab + Lapatinib	Lapatinib
Blood alkaline phosphatase increased * [A]		
# participants affected/at risk	11/149 (7.38%)	5/146 (3.42%)
# events		
Ejection fraction decreased * [A]		
# participants affected/at risk	9/149 (6.04%)	1/146 (0.68%)
# events		
Weight decreased * [A]		
# participants affected/at risk	8/149 (5.37%)	9/146 (6.16%)
# events		
Metabolism and nutrition disorders		
Decreased appetite * [A]		
# participants affected/at risk	20/149 (13.42%)	21/146 (14.38%)
# events		
Musculoskeletal and connective tissue disorders		

	Trastuzumab + Lapatinib	Lapatinib
Arthralgia * [A]		
# participants affected/at risk	4/149 (2.68%)	8/146 (5.48%)
# events		
Back pain * [A]		
# participants affected/at risk	12/149 (8.05%)	8/146 (5.48%)
# events		
Pain in extremity * [A]		
# participants affected/at risk	12/149 (8.05%)	8/146 (5.48%)
# events		
Nervous system disorders		
Dizziness * [A]		
# participants affected/at risk	7/149 (4.7%)	2/146 (1.37%)
# events		
Headache * [A]		
# participants affected/at risk	16/149 (10.74%)	13/146 (8.9%)
# events		
Psychiatric disorders		

	Trastuzumab + Lapatinib	Lapatinib
Insomnia * [A]		
# participants affected/at risk	8/149 (5.37%)	1/146 (0.68%)
# events		
Respiratory, thoracic and mediastinal disorders		
Cough * [A]		
# participants affected/at risk	9/149 (6.04%)	14/146 (9.59%)
# events		
Dyspnoea * [A]		
# participants affected/at risk	19/149 (12.75%)	14/146 (9.59%)
# events		
Skin and subcutaneous tissue disorders		
Dermatitis acneiform * [A]		
# participants affected/at risk	8/149 (5.37%)	14/146 (9.59%)
# events		
Dry skin * [A]		
# participants affected/at risk	7/149 (4.7%)	4/146 (2.74%)

	Trastuzumab + Lapatinib	Lapatinib
# events		
Pruritus * A		
# participants affected/at risk	7/149 (4.7%)	10/146 (6.85%)
# events		
Rash * A		
# participants affected/at risk	35/149 (23.49%)	43/146 (29.45%)
# events		

* Indicates events were collected by non-systematic methods.

A Term from vocabulary, MedDRA Version 11.0

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.

Limitations and Caveats:

Results Point of Contact:

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