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Clinical Trial Results Website

Sponsor

Novartis Pharmaceuticals

Generic Drug Name

Lapatinib/LAP016 (GW572016)

Trial Indication(s)

ErbB2 amplified metastatic breast cancer

Protocol Number

EGF104535 / CLAP016A2302

Protocol Title

A Randomized, Multicenter, Double-Blind, Placebo-Controlled, Phase III Study of Lapatinib (GW572016) in Combination with Paclitaxel versus Paclitaxel plus Placebo in Subjects with ErbB2 Amplified Metastatic Breast Cancer

Clinical Trial Phase

Phase 3

Phase of Drug Development

Phase III

Study Start/End Dates

Study Start Date: January 2006 (Actual)
Primary Completion Date: June 2010 (Actual)
Study Completion Date: November 2021 (Actual)

Reason for Termination (If applicable)

Not applicable

Study Design/Methodology

This was a randomized, double-blind, placebo-controlled, multicenter, Phase III study to evaluate and compare the efficacy and safety of lapatinib+paclitaxel versus placebo+paclitaxel in men and women with ErbB2 amplified metastatic (Stage IV) breast cancer who had not received prior therapy for metastatic disease.
Approximately 430 subjects (215 in each treatment arm) were planned to be enrolled in order to observe 255 deaths. Subjects were randomized to receive either lapatinib (1500 mg once daily)+paclitaxel (80 mg/m2 IV weekly for 3 weeks every 4 weeks) or placebo (once daily)+paclitaxel (80 mg/m2 IV weekly for 3 weeks every 4 weeks). Following the primary OS analysis and subsequent implementation of Protocol Amendment 03, subjects who were still receiving active treatment entered the LTFU phase of the study. At the point of disease progression in the randomization phase of the study, only subjects randomized to the placebo+paclitaxel arm could move to an extension phase to receive open label lapatinib monotherapy or combination therapy until further disease progression or an unacceptable toxicity. Subjects randomized to the lapatinib+paclitaxel arm were not eligible to enter the open label extension phase. Reporting requirements in the LTFU phase were limited to AESIs, SAEs and pregnancy, and the subjects continued to receive treatment until the occurrence of unacceptable toxicity or disease progression (as determined by the investigator) or permanent withdrawal from treatment for any reason. Subjects who were no longer receiving active treatment were withdrawn from the study.

Centers

43 centers in 8 participating countries enrolled subjects into this study (Brazil 7; China 20; Hong Kong 3; Pakistan 3; Peru 1; Russian Federation 6; Thailand 2; Ukraine 1)

Objectives:

Primary objective

- To evaluate and compare overall survival (OS) for subjects with ErbB2 amplified metastatic breast cancer when treated with lapatinib+paclitaxel versus placebo+paclitaxel.

Secondary objectives

- To evaluate and compare the two treatment arms with respect to:
  - Progression Free Survival (PFS);
  - Overall Response Rate (ORR) (complete and partial responses);
  - Clinical Benefit Rate (CBR) (complete response [CR] or partial response [PR] or stable disease [SD] ≥24 weeks);
  - Duration of Response (DOR);
  - Time to Response (TTR)
- To determine the qualitative and quantitative toxicities associated with the combination of paclitaxel and oral lapatinib.
- To compare and correlate tumor response rates with relevant biomarkers and genetic changes in serum, plasma, and intra-tumoral samples*.

*The analyses for tumor tissue were performed by GSK and the results were published in 2014, prior to transfer to Novartis

Test Product (s), Dose(s), and Mode(s) of Administration

Subjects were randomized to receive either lapatinib (1500 mg once daily)+paclitaxel (80 mg/m^2 IV weekly for 3 weeks every 4 weeks) or placebo (once daily)+paclitaxel (80 mg/m^2 IV weekly for 3 weeks every 4 weeks).

Subjects received study treatment until disease progression or unacceptable toxicity. Based on the positive results in the primary analysis, Protocol Amendment 02 (dated 09-May-2011) discontinued further entry into the lapatinib monotherapy extension phase, and ongoing subjects taking placebo were permitted to replace it with open label lapatinib therapy (with or without continued paclitaxel therapy).

Statistical Methods

Analysis of the primary efficacy variable:

Overall Survival (OS) is defined as the interval of time (in months) between the date of randomization and the date of death due to any cause. The OS was summarized using Kaplan-Meier estimates. For each treatment group, the Kaplan-Meier estimates for the median overall survival time, the first and third quartiles were presented, along with approximate 95% CIs. The Cox proportional hazards model was used to calculate adjusted HR estimate of the treatment effect and 95% CI.

Analysis of secondary variables:

All efficacy analyses were performed on ITT population and were only done in the randomized period of the study. No efficacy analyses were performed in the open label treatment period (monotherapy or combination therapy.

Progression-free survival (PFS):

Progression-free survival (PFS) during the randomized phase is defined as the interval of time (in months) between the date of randomization and the earlier date of disease progression, or date of death due to any cause. PFS was summarized using Kaplan-Meier estimates.

Overall Response Rate (ORR):

Overall response rate (ORR) during the randomized phase is defined as the percentage of subjects achieving either a CR or PR. Exact 95% CI for the tumor response rates in each arm was calculated. Odds ratios was compared between treatment arms using stratified Fisher's exact tests. Zelen’s test for homogeneity of the odds ratios across all strata was performed as a measure of validation.

Clinical Benefit Rate (CBR):

Clinical benefit rate (CBR) is defined as the percentage of subjects with evidence of CR, PR, or SD for at least 24 weeks. An estimate of the proportion of subjects who experienced clinical benefit during the randomized phase was calculated for each treatment arm and analyzed similar to ORR.

Time to Response (TTR):

Time to response (TTR) during the randomized phase is defined as the time from randomization until first documented evidence of PR or CR (whichever status is recorded first). A summary of crude cumulative response rates was produced

by nominal visit time and the number of subjects in each treatment group responding by Week 8, Week 16, Week 24, etc were presented.

Duration of Response (DOR):

For subjects who show CR or PR, duration of response (DOR) is defined to be the time from first documented evidence of PR or CR until the first documented sign of disease progression or death due to any cause, if sooner during the randomized phase. The median DOR was calculated from the Kaplan-Meier estimates. First and third quartiles were also to be calculated if there were a sufficient number of responders who subsequently progress or died due to any cause.

Biomarkers:

Tumor tissue

Immunohistochemistry and mutation analyses were used to assess correlation between tumor response rates with relevant biomarkers and genetic changes in intra-tumoral samples. In this process, levels of tensin homolog (PTEN) and phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (PIK3CA) were evaluated at Baseline. Association between PTEN low, PTEN any expression, PIK3CA mutation, PI3K pathway activation, and ORR and CBR was assessed using logistic regression models for each separately. For ORR, subjects were divided into responder (CR and PR), and non-responder groups (progressive disease (PD) or SD). For CBR, subjects were divided into clinical benefit (CR, PR, or SD ≥24 weeks) and nonclinical benefit (SD <24 weeks, PD) groups. Unknown responses were excluded as these were exploratory analyses. HER2 results were summarized in the primary CSR, and thus not included in this report.

Serum and Plasma

At the time of final CSR, serum and plasma samples were no longer available and no analysis was performed.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion criteria:

- Signed informed consent;
- Male or female ≥18 years;
- Histologically confirmed invasive breast cancer with stage IV disease;

If the disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology or histology.

- Documented amplification of ErbB2 by fluorescence in situ hybridization (FISH) in primary or metastatic tumor tissue by the central laboratory for randomization into the study;
- If a taxane was administered in the neoadjuvant or adjuvant setting, progression must have occurred >12 months after completion of this treatment and the patient recovered from all associated toxicities;
- Measurable lesion(s) according to RECIST (Response Evaluation Criteria in Solid Tumors);
- Radiotherapy as palliative treatment for painful metastatic disease is permitted but must have been stopped within 2 weeks prior to initiation of any investigational treatment. All subjects must have recovered from all radiotherapy related toxicities prior to initiation of any investigational treatment. The site of radiotherapy must not be used as a site of measurable disease;
- Bisphosphonate therapy for bone metastases and is allowed; however, treatment must be initiated prior to the first dose of investigational treatment. Prophylactic use of bisphosphonates in subjects without bone disease is not permitted, except for the treatment of osteoporosis;
- For those patients whose disease is ER+ and/or PR+ the following criteria should be met:

Patients with visceral disease that requires chemotherapy (eg., patients with liver or lung metastases)
Rapidly progressing or life threatening disease, as determined by the investigator
Patients who received hormonal therapy and are no longer benefiting from this therapy and the hormonal treatment must have been stopped before the first dose of investigational treatment;

- 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;
- ECOG Performance Status of 0 to 1;
- Life expectancy of ≥ 12 weeks;
- Able to swallow and retain oral medication;
- Archived tumor tissue available for testing;
- Women and men with potential to have children must be willing to practice acceptable methods of birth control during the study;
- Willing to complete all screening assessments as outlined in the protocol;
- Adequate organ function as defined in Table 1 Baseline Laboratory Values;

Exclusion Criteria:

- Pregnant or lactating females at anytime during the study
- Subjects with only non-measurable metastatic sites of disease per RECIST, (e.g. bone metastases, pleural effusion, or ascites, etc. (Refer to Section 5.3 Efficacy for list sites considered to be non-measurable disease.);
- Received prior chemotherapy, immunotherapy, biologic therapy, or anti-ErbB1/ErbB2 therapy for metastatic disease.
- Prior therapy with an ErbB1 and/or ErbB2 inhibitor, other than trastuzumab in the adjuvant setting. If trastuzumab was administered in the adjuvant setting, then > 12 months must have elapsed since completion of trastuzumab therapy;
- Planned concurrent anti-cancer therapy (chemotherapy, radiation therapy, immunotherapy, biologic therapy, hormonal therapy) while taking investigational treatment;
- Unresolved or unstable, serious toxicity from prior administration of another investigational drug and/or of prior cancer treatment;
- Peripheral neuropathy of Grade 2 or greater;
- 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;
- 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 central nervous system (CNS) metastases or leptomeningeal carcinomatosis;
- Concurrent treatment with prohibited medications, including herbal remedies and Chinese traditional medicines;
- Concurrent treatment with an investigational agent or participation in another clinical trial involving investigational agents;
- Used an investigational drug within 30 days or 5 half-lives, whichever is longer, preceding the first dose of investigational treatment;
- Known immediate or delayed hypersensitivity reaction or idiosyncrasy to drugs chemically related to paclitaxel or lapatinib or their excipients.

Participant Flow Table

Randomized Phase

	Lapatinib 1500 mg + Paclitaxel	Placebo + Paclitaxel	Open Label - Monotherapy	Open Label - Combination Therapy	Total
Arm/Group Description	Lapatinib 1500 milligrams (mg) administered once daily plus paclitaxel 80 mg/meters squared (m^2) administered intravenously (IV) weekly for 3 weeks every 4 weeks	Matching placebo administered once daily plus paclitaxel 80 mg/m^2 administered IV weekly for 3 weeks every 4 weeks	Open Label - Monotherapy (Lapatinib)	Open Label - Combination Therapy (Lapatinib and Paclitaxel)	
Started	222	222	0	0	444
Safety Population	222	221	0	0	443
Completed	133	149	0	0	282
Not Completed	89	73	0	0	162
Adverse Event	0	2	0	0	2
Lost to Follow-up	34	27	0	0	61
Withdrawal by Subject	8	7	0	0	15
Study closed/terminated	1	1	0	0	2
Disease progression	36	27	0	0	63
Physician Decision	1	1	0	0	2
Other reasons as defined per protocol	4	3	0	0	7
Reason for withdrawal unspecified	4	5	0	0	9
Treatment ongoing	1	0	0	0	1

Open Label Phase

	Lapatinib 1500 mg + Paclitaxel	Placebo + Paclitaxel	Open Label - Monotherapy	Open Label - Combination Therapy	Total
Arm/Group Description	Lapatinib 1500 milligrams (mg) administered once daily plus paclitaxel 80 mg/meters squared (m^2) administered intravenously (IV) weekly for 3 weeks every 4 weeks	Matching placebo administered once daily plus paclitaxel 80 mg/m^2 administered IV weekly for 3 weeks every 4 weeks	Open Label - Monotherapy (Lapatinib)	Open Label - Combination Therapy (Lapatinib and Paclitaxel)	
Started	0	0	149	4	153
Completed	0	0	104	0	104
Not Completed	0	0	45	4	49
Adverse Event	0	0	1	0	1
Lost to Follow-up	0	0	16	2	18
Withdrawal by Subject	0	0	3	2	5
Disease progression	0	0	18	0	18
Physician Decision	0	0	1	0	1
Relocation of patient	0	0	1	0	1
Reason for withdrawal unspecified	0	0	5	0	5

Baseline Characteristics

	Lapatinib 1500 mg + Paclitaxel	Placebo + Paclitaxel	Total
Arm/Group Description	Lapatinib 1500 milligrams (mg) administered once daily plus paclitaxel 80 mg/meters squared (m^2) administered intravenously (IV) weekly for 3 weeks every 4 weeks	Matching placebo administered once daily plus paclitaxel 80 mg/m^2 administered IV weekly for 3 weeks every 4 weeks	
Number of Participants [units: participants]	222	222	444
AgeContinuous (units: Years) Mean ± Standard Deviation			
	49.1±10.74	49.3±9.75	49.2±10.25
Sex: Female, Male (units: Participants) Count of Participants (Not Applicable)			
Female	222	217	439
Male	0	5	5
Race/Ethnicity, Customized (units: Participants)			
White	9	13	22
Asian	192	192	384
Hispanic	21	16	37
Other	0	1	1
Number of participants with any visceral metastatic disease and with only non-visceral disease[1] (units: Participants) Count of Participants (Not Applicable)			
Visceral	187	186	373
Non-visceral	35	36	71

Number of Participants with the Indicated Hormone Receptor Status[2] (units: Participants) Count of Participants (Not Applicable)			
ER+ and/or PgR+ or Unknown	111	113	224
ER- and PgR-	111	109	220
Number of Participants with the Indicated Stage of Disease at Initial Diagnosis[3] (units: Participants) Count of Participants (Not Applicable)			
Stage I to II	107	119	226
Stage III	75	68	143
Stage IV	30	24	54
Unknown	10	11	21
Number of Participants with the Indicated Eastern Cooperative Oncology Group Performance Status[4] (units: Participants) Count of Participants (Not Applicable)			
0, Fully Active	103	113	216
1, Ambulatory, Restricted Strenuous Activity	119	109	228
Number of Participants with the Indicated Number of Metastatic Sites[5] (units: Participants) Count of Participants (Not Applicable)			
Greater than or equal to 3	131	115	246
Less than 3	91	107	198
Mean Time of Disease-Free Interval[6] (units: months) Mean ± Standard Deviation			
	27.51±27.481	29.04±34.522	28.27±31.174

[1] Metastasis is defined as the spread of a tumor or cancerous cells from the primary site to one or more sites elsewhere in the body. Visceral metastasis is defined as the spread of cancer to viscera, the internal organs of the body, specifically those within the chest (as the heart or lungs) or abdomen (as the liver, pancreas, or intestines). Non-visceral organs are defined as any organ not considered visceral.
[2] Cancer cells have hormone receptor expression of Estrogen Receptor (ER) and/or Progesterone Receptor (PR) and are thus considered to be ER+ and/or

PgR+ cells, respectively.
[3] The stage of cancer is a description of the extent to which the cancer has spread. Stage I cancer is localized; Stage II cancer has not started to spread into the surrounding tissue, but the tumor is larger than in Stage I; Stage III cancer is locally advanced and/or involves local lymph nodes; Stage IV cancer has spread to other organs.
[4] Eastern Cooperative Oncology Group (ECOG) Performance Status classifies participants according to their functional impairment, and scores indicate: 0, fully active; 1, ambulatory, restricted strenuous activity; 2, ambulatory, no work activity; 3, partially confined to bed; 4, totally confined in bed; 5, death. Participants were required to have a baseline ECOG performance status of 0 or 1 for study participation.
[5] Tumor cells move from the primary site to other sites in the body, where they continue to multiply and eventually form another clinically detectable tumor; thus, the site becomes metastatic. The table indicates number of metastatic sites.
[6] The disease-free interval was defined as the time from initial diagnosis to metastases

Primary Outcome Result(s)

Overall Survival (OS) at 53 months

(Time Frame: From date of randomization until date of death from any cause, assessed up to 53 months (Primary OS analysis cut-off date = 18-Jun-2010))

	Lapatinib 1500 mg + Paclitaxel	Placebo + Paclitaxel
Arm/Group Description	Lapatinib 1500 milligrams (mg) administered once daily plus paclitaxel 80 mg/meters squared (m^2) administered intravenously (IV) weekly for 3 weeks every 4 weeks	Matching placebo administered once daily plus paclitaxel 80 mg/m^2 administered IV weekly for 3 weeks every 4 weeks
Number of Participants Analyzed [units: participants]	222	222
Overall Survival (OS) at 53 months (units: months) Median (95% Confidence Interval)		
	27.8 (23.2 to 32.2)	20.5 (17.9 to 24.3)

Statistical Analysis

Groups	Lapatinib 1500 mg + Paclitaxel, Placebo + Paclitaxel	Primary OS analysis cut-off date = 18-Jun-2010
P Value	0.0062	Stratified Log-Rank (one-sided)
Method	Log Rank	
Hazard Ratio (HR)	0.74	The treatment hazard ratio based on the proportional hazard model stratifying for metastatic disease sites and hormonal status. A hazard ratio <1 indicates a lower risk with Lapatinib 1500mg + Paclitaxel compared with Placebo + Paclitaxel.
95 % Confidence Interval 2-Sided	0.58 to 0.94	

Secondary Outcome Result(s)

Overall Survival (OS) at 190 months

(Time Frame: From date of randomization until date of death from any cause, assessed up to 190 months (Final OS analysis cut-off date = 23-Nov-2021))

	Lapatinib 1500 mg + Paclitaxel	Placebo + Paclitaxel
Arm/Group Description	Lapatinib 1500 milligrams (mg) administered once daily plus paclitaxel 80 mg/meters squared (m^2) administered intravenously (IV) weekly for 3 weeks every 4 weeks	Matching placebo administered once daily plus paclitaxel 80 mg/m^2 administered IV weekly for 3 weeks every 4 weeks
Number of Participants Analyzed [units: participants]	222	222
Overall Survival (OS) at 190 months (units: months) Median (95% Confidence Interval)	27.6 (23.7 to 31.5)	20.3 (17.9 to 24.3)

Statistical Analysis

Groups	Lapatinib 1500 mg + Paclitaxel, Placebo + Paclitaxel	Final OS analysis cut-0ff date = 23-Nov-2021
Hazard Ratio (HR)	0.80	The treatment hazard ratio based on the proportional hazard model stratifying for metastatic disease sites and hormonal status. A hazard ratio <1 indicates a lower risk with Lapatinib 1500mg + Paclitaxel compared with Placebo + Paclitaxel.
95 % Confidence Interval 2-Sided	0.64 to 0.98	

Progression-free survival (PFS) by Investigator assessment

(Time Frame: From date of randomization until date of progression or date of death from any cause, whichever comes first, assessed up to 190 months (Final analysis cut-off date = 23-Nov-2021))

	Lapatinib 1500 mg + Paclitaxel	Placebo + Paclitaxel

Arm/Group Description	Lapatinib 1500 milligrams (mg) administered once daily plus paclitaxel 80 mg/meters squared (m^2) administered intravenously (IV) weekly for 3 weeks every 4 weeks	Matching placebo administered once daily plus paclitaxel 80 mg/m^2 administered IV weekly for 3 weeks every 4 weeks
Number of Participants Analyzed [units: participants]	222	222
Progression-free survival (PFS) by Investigator assessment (units: months) Median (95% Confidence Interval)		
	9.7 (9.2 to 11.1)	6.5 (5.5 to 7.3)

Statistical Analysis

Groups	Lapatinib 1500 mg + Paclitaxel, Placebo + Paclitaxel	
Hazard Ratio (HR)	0.54	The Pike estimator of the treatment hazard ratio based on the log rank test stratifying for metastatic disease sites and hormonal status. A hazard ratio <1 indicates a lower risk with Lapatinib 1500mg + Paclitaxel compared with Placebo + Paclitaxel.
95 % Confidence Interval 2-Sided	0.44 to 0.66	

Overall Response Rate (ORR) by Investigator assessment

(Time Frame: From date of randomization until date of radiographic progression or date of death from any cause, whichever comes first, assessed up to 190 months (Final analysis cut-off date = 23-Nov-2021))

	Lapatinib 1500 mg + Paclitaxel	Placebo + Paclitaxel
Arm/Group Description	Lapatinib 1500 milligrams (mg) administered once daily plus paclitaxel 80 mg/meters squared (m^2) administered intravenously (IV) weekly for 3 weeks every 4 weeks	Matching placebo administered once daily plus paclitaxel 80 mg/m^2 administered IV weekly for 3 weeks every 4 weeks
Number of Participants Analyzed [units: participants]	222	222

Overall Response Rate (ORR) by Investigator assessment (units: Percentage of Participants) Number (95% Confidence Interval)		
	69 (62.9 to 75.4)	50 (42.8 to 56.3)

Statistical Analysis

Groups	Lapatinib 1500 mg + Paclitaxel, Placebo + Paclitaxel
Odds Ratio (OR)	2.30
95 % Confidence Interval 2-Sided	1.54 to 3.47

Clinical Benefit Rate (CBR)

(Time Frame: From date of randomization until date of progression or date of death from any cause, whichever comes first, assessed up to 53 months (Primary analysis cut-off date = 18-Jun-2010))

	Lapatinib 1500 mg + Paclitaxel	**Placebo + Paclitaxel**
Arm/Group Description	Lapatinib 1500 milligrams (mg) administered once daily plus paclitaxel 80 mg/meters squared (m^2) administered intravenously (IV) weekly for 3 weeks every 4 weeks	Matching placebo administered once daily plus paclitaxel 80 mg/m^2 administered IV weekly for 3 weeks every 4 weeks
Number of Participants Analyzed [units: participants]	222	222
Clinical Benefit Rate (CBR) (units: Percentage of Participants) Number (95% Confidence Interval)		
	75 (68.5 to 80.3)	56 (49.1 to 62.5)

Statistical Analysis

Groups	Lapatinib 1500 mg + Paclitaxel, Placebo + Paclitaxel
Odds Ratio (OR)	2.34
95 % Confidence Interval 2-Sided	1.54 to 3.58

Duration of Response (DOR)

(Time Frame: From date of confirmed CR or PR until date of progression or date of death from any cause, whichever comes first, assessed up to 190 months
(Final analysis cut-off date = 23-Nov-2021))

	Lapatinib 1500 mg + Paclitaxel	Placebo + Paclitaxel
Arm/Group Description	Lapatinib 1500 milligrams (mg) administered once daily plus paclitaxel 80 mg/meters squared (m^2) administered intravenously (IV) weekly for 3 weeks every 4 weeks	Matching placebo administered once daily plus paclitaxel 80 mg/m^2 administered IV weekly for 3 weeks every 4 weeks
Number of Participants Analyzed [units: participants]	154	110
Duration of Response (DOR) (units: months) Median (95% Confidence Interval)		
	9.3 (7.7 to 10.7)	5.8 (5.6 to 7.4)

Number of participants with a CR or PR at Weeks 8, 12, 16, 24, 32, 40, 48, 56, 64, and 72

(Time Frame: Weeks 8, 12, 16, 24, 32, 40, 48, 56, 64, and 72)

	Lapatinib 1500 mg + Paclitaxel	Placebo + Paclitaxel
Arm/Group Description	Lapatinib 1500 milligrams (mg) administered once daily plus paclitaxel 80 mg/meters squared (m^2) administered intravenously (IV) weekly for 3 weeks every 4 weeks	Matching placebo administered once daily plus paclitaxel 80 mg/m^2 administered IV weekly for 3 weeks every 4 weeks
Number of Participants Analyzed [units: participants]	154	110

Number of participants with a CR or PR at Weeks 8, 12, 16, 24, 32, 40, 48, 56, 64, and 72
(units: Participants)

Week 8	94	61
Week 12	40	28
Week 16	6	11
Week 24	7	8
Week 32	3	2
Week 40	0	0
Week 48	1	0
Week 56	1	0
Week 64	1	0
Week 72	1	0

Number of tumors evaluable for PIK3CA mutations

(Time Frame: Baseline)

	Lapatinib 1500 mg + Paclitaxel	**Placebo + Paclitaxel**
Arm/Group Description	Lapatinib 1500 milligrams (mg) administered once daily plus paclitaxel 80 mg/meters squared (m^2) administered intravenously (IV) weekly for 3 weeks every 4 weeks	Matching placebo administered once daily plus paclitaxel 80 mg/m^2 administered IV weekly for 3 weeks every 4 weeks
Number of Participants Analyzed [units: participants]	104	106
Number of tumors evaluable for PIK3CA mutations (units: Participants) Count of Participants (Not Applicable)		
PIK3CA mutation	29 (27.88%)	36 (33.96%)

PIK3CA wild-type	58 (55.77%)	48 (45.28%)
PIK3CA indeterminate	17 (16.35%)	22 (20.75%)

Number of participants with tumors evaluable for PTEN

(Time Frame: Baseline)

	Lapatinib 1500 mg + Paclitaxel	Placebo + Paclitaxel
Arm/Group Description	Lapatinib 1500 milligrams (mg) administered once daily plus paclitaxel 80 mg/meters squared (m^2) administered intravenously (IV) weekly for 3 weeks every 4 weeks	Matching placebo administered once daily plus paclitaxel 80 mg/m^2 administered IV weekly for 3 weeks every 4 weeks
Number of Participants Analyzed [units: participants]	180	175
Number of participants with tumors evaluable for PTEN (units: Participants) Count of Participants (Not Applicable)		
PTEN IHC 0	28 (15.56%)	21 (12%)
PTEN IHC 1+	76 (42.22%)	80 (45.71%)
PTEN IHC 2+/3+	76 (42.22%)	74 (42.29%)

Predictive effect of PIK3CA mutations status on Overall Response Rate (ORR)

(Time Frame: From date of randomization until date of radiographic progression or date of death from any cause, whichever comes first, assessed up to 53 months (Primary OS analysis cut-off date = 18-Jun-2010))

	Lapatinib 1500 mg + Paclitaxel	Placebo + Paclitaxel
Arm/Group Description	Lapatinib 1500 milligrams (mg) administered once daily plus paclitaxel 80 mg/meters squared (m^2) administered intravenously (IV) weekly for 3 weeks every 4 weeks	Matching placebo administered once daily plus paclitaxel 80 mg/m^2 administered IV weekly for 3 weeks every 4 weeks

Number of Participants Analyzed [units: participants]	87	84
Predictive effect of PIK3CA mutations status on Overall Response Rate (ORR) (units: percentage of participants)		
PIK3CA mutation	62	50
PIK3CA wild-type	80	59

Statistical Analysis

Groups	Lapatinib 1500 mg + Paclitaxel, Placebo + Paclitaxel	Participants with PIK3CA wild-type
Odds Ratio (OR)	2.78	
95 % Confidence Interval 2-Sided	1.07 to 7.57	

Predictive effect of PTEN low on Overall Response Rate (ORR)

(Time Frame: From date of randomization until date of radiographic progression or date of death from any cause, whichever comes first, assessed up to 53 months (Primary OS analysis cut-off date = 18-Jun-2010))

	Lapatinib 1500 mg + Paclitaxel	**Placebo + Paclitaxel**
Arm/Group Description	Lapatinib 1500 milligrams (mg) administered once daily plus paclitaxel 80 mg/meters squared (m^2) administered intravenously (IV) weekly for 3 weeks every 4 weeks	Matching placebo administered once daily plus paclitaxel 80 mg/m^2 administered IV weekly for 3 weeks every 4 weeks
Number of Participants Analyzed [units: participants]	180	175
Predictive effect of PTEN low on Overall Response Rate (ORR) (units: percentage of participants)		
PTEN low	73	53
Without PTEN low	76	58

Statistical Analysis

Groups	Lapatinib 1500 mg + Paclitaxel, Placebo + Paclitaxel	Participants with PTEN low
Odds Ratio (OR)	2.42	
95 % Confidence Interval 2-Sided	1.28 to 4.63	

Statistical Analysis

Groups	Lapatinib 1500 mg + Paclitaxel, Placebo + Paclitaxel	Participants without PTEN low
Odds Ratio (OR)	2.21	
95 % Confidence Interval 2-Sided	1.04 to 4.82	

Predictive effect of PIK3CA mutations status on Clinical Benefit Rate (CBR)

(Time Frame: From date of randomization until date of radiographic progression or date of death from any cause, whichever comes first, assessed up to 53 months (Primary OS analysis cut-off date = 18-Jun-2010))

	Lapatinib 1500 mg + Paclitaxel	Placebo + Paclitaxel
Arm/Group Description	Lapatinib 1500 milligrams (mg) administered once daily plus paclitaxel 80 mg/meters squared (m^2) administered intravenously (IV) weekly for 3 weeks every 4 weeks	Matching placebo administered once daily plus paclitaxel 80 mg/m^2 administered IV weekly for 3 weeks every 4 weeks
Number of Participants Analyzed [units: participants]	87	84
Predictive effect of PIK3CA mutations status on Clinical Benefit Rate (CBR) (units: percentage of participants)		
PIK3CA mutation	69	56

PIK3CA wild-type	84	65

Predictive effect of PTEN low on Clinical Benefit Rate (CBR)

(Time Frame: From date of randomization until date of radiographic progression or date of death from any cause, whichever comes first, assessed up to 53 months (Primary OS analysis cut-off date = 18-Jun-2010))

	Lapatinib 1500 mg + Paclitaxel	Placebo + Paclitaxel
Arm/Group Description	Lapatinib 1500 milligrams (mg) administered once daily plus paclitaxel 80 mg/meters squared (m^2) administered intravenously (IV) weekly for 3 weeks every 4 weeks	Matching placebo administered once daily plus paclitaxel 80 mg/m^2 administered IV weekly for 3 weeks every 4 weeks
Number of Participants Analyzed [units: participants]	180	175
Predictive effect of PTEN low on Clinical Benefit Rate (CBR) (units: percentage of participants)		
PTEN low	82	59
Without PTEN low	80	61

Statistical Analysis

Groups	Lapatinib 1500 mg + Paclitaxel, Placebo + Paclitaxel	Participants with PTEN low
Odds Ratio (OR)	3.15	
95 % Confidence Interval 2-Sided	1.58 to 6.49	

Statistical Analysis

Groups	Lapatinib 1500 mg + Paclitaxel, Placebo + Paclitaxel	Participants without PTEN low

Odds Ratio (OR)	2.49
95 % Confidence Interval 2-Sided	1.13 to 5.66

Safety Results

All-Cause Mortality

	Lapatinib 1500 mg + Paclitaxel N = 222	Placebo + Paclitaxel N = 221	Open Label - Monotherapy N = 149	Open Label - Combination Therapy N = 4
Arm/Group Description	Lapatinib 1500 milligrams (mg) administered once daily plus paclitaxel 80 mg/meters squared (m^2) administered intravenously (IV) weekly for 3 weeks every 4 weeks	Matching placebo administered once daily plus paclitaxel 80 mg/m^2 administered IV weekly for 3 weeks every 4 weeks	Open Label - Monotherapy (Lapatinib)	Open Label - Combination Therapy (Lapatinib and Paclitaxel)
Total participants affected	10 (4.50%)	15 (6.79%)	2 (1.34%)	0 (0.00%)

Serious Adverse Events by System Organ Class

Time Frame	From study treatment start date till 30 days safety follow-up, assessed up to 190 months (Final OS analysis cut-off date = 23-Nov-2021)
Additional Description	Any sign or symptom that occurs during the treatment period plus 30 days post-treatment. The safety analysis were done on the safety population, which included all randomized subjects who received at least one dose of study medication.
Source Vocabulary for Table Default	MedDRA (24.1)
Assessment Type for Table Default	Systematic Assessment

	Lapatinib 1500 mg + Paclitaxel N = 222	Placebo + Paclitaxel N = 221	Open Label - Monotherapy N = 149	Open Label - Combination Therapy N = 4
Arm/Group Description	Lapatinib 1500 milligrams (mg) administered once daily plus paclitaxel 80 mg/meters	Matching placebo administered once daily plus paclitaxel 80	Open Label - Monotherapy (Lapatinib)	Open Label - Combination

	squared (m^2) administered intravenously (IV) weekly for 3 weeks every 4 weeks	mg/m^2 administered IV weekly for 3 weeks every 4 weeks		Therapy (Lapatinib and Paclitaxel)
Total participants affected	67 (30.18%)	30 (13.57%)	8 (5.37%)	0 (0.00%)
Blood and lymphatic system disorders				
Febrile neutropenia	6 (2.70%)	1 (0.45%)	0 (0.00%)	0 (0.00%)
Granulocytopenia	4 (1.80%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Leukopenia	7 (3.15%)	1 (0.45%)	0 (0.00%)	0 (0.00%)
Neutropenia	36 (16.22%)	10 (4.52%)	0 (0.00%)	0 (0.00%)
Cardiac disorders				
Cardiac failure chronic	0 (0.00%)	1 (0.45%)	0 (0.00%)	0 (0.00%)
Left ventricular dysfunction	3 (1.35%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Gastrointestinal disorders				
Abdominal pain	1 (0.45%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Diarrhoea	10 (4.50%)	0 (0.00%)	1 (0.67%)	0 (0.00%)
Pancreatitis acute	1 (0.45%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Stomatitis	0 (0.00%)	0 (0.00%)	1 (0.67%)	0 (0.00%)
Vomiting	1 (0.45%)	1 (0.45%)	0 (0.00%)	0 (0.00%)
General disorders and administration site conditions				
Fatigue	1 (0.45%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Lithiasis	1 (0.45%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Multiple organ dysfunction syndrome	0 (0.00%)	1 (0.45%)	0 (0.00%)	0 (0.00%)
Non-cardiac chest pain	0 (0.00%)	1 (0.45%)	0 (0.00%)	0 (0.00%)
Pyrexia	3 (1.35%)	0 (0.00%)	1 (0.67%)	0 (0.00%)

Hepatobiliary disorders				
Cholecystitis	0 (0.00%)	1 (0.45%)	0 (0.00%)	0 (0.00%)
Hepatic function abnormal	0 (0.00%)	1 (0.45%)	1 (0.67%)	0 (0.00%)
Hepatobiliary disease	0 (0.00%)	1 (0.45%)	0 (0.00%)	0 (0.00%)
Hepatotoxicity	0 (0.00%)	1 (0.45%)	0 (0.00%)	0 (0.00%)
Immune system disorders				
Anaphylactic reaction	0 (0.00%)	0 (0.00%)	1 (0.67%)	0 (0.00%)
Infections and infestations				
Cellulitis	2 (0.90%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Escherichia bacteraemia	1 (0.45%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Pharyngitis	1 (0.45%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Pneumonia	1 (0.45%)	1 (0.45%)	1 (0.67%)	0 (0.00%)
Pyelonephritis acute	1 (0.45%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Septic shock	0 (0.00%)	1 (0.45%)	0 (0.00%)	0 (0.00%)
Urinary tract infection	1 (0.45%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Viral infection	0 (0.00%)	1 (0.45%)	1 (0.67%)	0 (0.00%)
Injury, poisoning and procedural complications				
Femur fracture	0 (0.00%)	2 (0.90%)	0 (0.00%)	0 (0.00%)
Investigations				
Ejection fraction decreased	13 (5.86%)	3 (1.36%)	0 (0.00%)	0 (0.00%)
Haemoglobin decreased	1 (0.45%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Neutrophil count decreased	1 (0.45%)	0 (0.00%)	0 (0.00%)	0 (0.00%)

Metabolism and nutrition disorders				
Hyperglycaemia	1 (0.45%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Hypokalaemia	1 (0.45%)	1 (0.45%)	0 (0.00%)	0 (0.00%)
Musculoskeletal and connective tissue disorders				
Spinal stenosis	0 (0.00%)	0 (0.00%)	1 (0.67%)	0 (0.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)				
Breast neoplasm	1 (0.45%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Thyroid cancer	1 (0.45%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Nervous system disorders				
Intracranial pressure increased	0 (0.00%)	1 (0.45%)	0 (0.00%)	0 (0.00%)
Presyncope	0 (0.00%)	1 (0.45%)	0 (0.00%)	0 (0.00%)
Psychiatric disorders				
Completed suicide	0 (0.00%)	1 (0.45%)	0 (0.00%)	0 (0.00%)
Respiratory, thoracic and mediastinal disorders				
Dyspnoea	1 (0.45%)	2 (0.90%)	0 (0.00%)	0 (0.00%)
Interstitial lung disease	0 (0.00%)	1 (0.45%)	0 (0.00%)	0 (0.00%)
Laryngeal oedema	1 (0.45%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Pleural effusion	0 (0.00%)	1 (0.45%)	0 (0.00%)	0 (0.00%)
Pulmonary embolism	0 (0.00%)	0 (0.00%)	1 (0.67%)	0 (0.00%)
Respiratory failure	0 (0.00%)	0 (0.00%)	1 (0.67%)	0 (0.00%)

Vascular disorders				
Deep vein thrombosis	0 (0.00%)	1 (0.45%)	0 (0.00%)	0 (0.00%)

Other Adverse Events by System Organ Class

Time Frame	From study treatment start date till 30 days safety follow-up, assessed up to 190 months (Final OS analysis cut-off date = 23-Nov-2021)
Additional Description	Any sign or symptom that occurs during the treatment period plus 30 days post-treatment. The safety analysis were done on the safety population, which included all randomized subjects who received at least one dose of study medication.
Source Vocabulary for Table Default	MedDRA (24.1)
Assessment Type for Table Default	Systematic Assessment
Frequent Event Reporting Threshold	5%

	Lapatinib 1500 mg + Paclitaxel N = 222	**Placebo + Paclitaxel N = 221**	**Open Label - Monotherapy N = 149**	**Open Label - Combination Therapy N = 4**
Arm/Group Description	Lapatinib 1500 milligrams (mg) administered once daily plus paclitaxel 80 mg/meters squared (m^2) administered intravenously (IV) weekly for 3 weeks every 4 weeks	Matching placebo administered once daily plus paclitaxel 80 mg/m^2 administered IV weekly for 3 weeks every 4 weeks	Open Label - Monotherapy (Lapatinib)	Open Label - Combination Therapy (Lapatinib and Paclitaxel)
Total participants affected	219 (98.65%)	206 (93.21%)	86 (57.72%)	3 (75.00%)
Blood and lymphatic system disorders				
Anaemia	50 (22.52%)	22 (9.95%)	3 (2.01%)	0 (0.00%)
Granulocytopenia	17 (7.66%)	15 (6.79%)	0 (0.00%)	0 (0.00%)
Leukopenia	113 (50.90%)	74 (33.48%)	6 (4.03%)	0 (0.00%)

Neutropenia	168 (75.68%)	103 (46.61%)	5 (3.36%)	0 (0.00%)
Gastrointestinal disorders				
Abdominal distension	12 (5.41%)	3 (1.36%)	0 (0.00%)	0 (0.00%)
Abdominal pain	17 (7.66%)	10 (4.52%)	5 (3.36%)	0 (0.00%)
Abdominal pain upper	13 (5.86%)	3 (1.36%)	1 (0.67%)	0 (0.00%)
Constipation	8 (3.60%)	18 (8.14%)	0 (0.00%)	0 (0.00%)
Diarrhoea	172 (77.48%)	64 (28.96%)	42 (28.19%)	0 (0.00%)
Mouth ulceration	16 (7.21%)	0 (0.00%)	2 (1.34%)	0 (0.00%)
Nausea	66 (29.73%)	44 (19.91%)	4 (2.68%)	0 (0.00%)
Vomiting	48 (21.62%)	26 (11.76%)	4 (2.68%)	0 (0.00%)
General disorders and administration site conditions				
Asthenia	15 (6.76%)	7 (3.17%)	1 (0.67%)	0 (0.00%)
Fatigue	47 (21.17%)	35 (15.84%)	2 (1.34%)	0 (0.00%)
Mucosal erosion	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)
Mucosal inflammation	18 (8.11%)	3 (1.36%)	2 (1.34%)	0 (0.00%)
Oedema peripheral	9 (4.05%)	12 (5.43%)	1 (0.67%)	0 (0.00%)
Pyrexia	30 (13.51%)	34 (15.38%)	5 (3.36%)	0 (0.00%)
Hepatobiliary disorders				
Hepatic function abnormal	17 (7.66%)	9 (4.07%)	1 (0.67%)	0 (0.00%)
Hyperbilirubinaemia	12 (5.41%)	2 (0.90%)	1 (0.67%)	0 (0.00%)
Infections and infestations				
Paronychia	17 (7.66%)	1 (0.45%)	6 (4.03%)	0 (0.00%)

Upper respiratory tract infection	20 (9.01%)	12 (5.43%)	1 (0.67%)	0 (0.00%)
Investigations				
Alanine aminotransferase increased	25 (11.26%)	17 (7.69%)	3 (2.01%)	0 (0.00%)
Aspartate aminotransferase increased	20 (9.01%)	16 (7.24%)	4 (2.68%)	0 (0.00%)
Blood bilirubin increased	7 (3.15%)	5 (2.26%)	2 (1.34%)	1 (25.00%)
Haemoglobin decreased	23 (10.36%)	4 (1.81%)	0 (0.00%)	0 (0.00%)
Neutrophil count decreased	3 (1.35%)	1 (0.45%)	0 (0.00%)	1 (25.00%)
Red blood cell count decreased	6 (2.70%)	1 (0.45%)	0 (0.00%)	1 (25.00%)
White blood cell count decreased	11 (4.95%)	11 (4.98%)	0 (0.00%)	1 (25.00%)
Metabolism and nutrition disorders				
Decreased appetite	70 (31.53%)	41 (18.55%)	3 (2.01%)	0 (0.00%)
Hyperglycaemia	5 (2.25%)	6 (2.71%)	1 (0.67%)	1 (25.00%)
Musculoskeletal and connective tissue disorders				
Arthralgia	26 (11.71%)	20 (9.05%)	1 (0.67%)	0 (0.00%)
Myalgia	30 (13.51%)	26 (11.76%)	1 (0.67%)	0 (0.00%)
Nervous system disorders				
Dizziness	19 (8.56%)	11 (4.98%)	0 (0.00%)	0 (0.00%)
Headache	20 (9.01%)	20 (9.05%)	4 (2.68%)	0 (0.00%)
Hypoaesthesia	18 (8.11%)	25 (11.31%)	3 (2.01%)	0 (0.00%)
Neuropathy peripheral	31 (13.96%)	30 (13.57%)	1 (0.67%)	0 (0.00%)

Peripheral sensory neuropathy	12 (5.41%)	13 (5.88%)	0 (0.00%)	0 (0.00%)
Psychiatric disorders				
Insomnia	13 (5.86%)	18 (8.14%)	2 (1.34%)	0 (0.00%)
Respiratory, thoracic and mediastinal disorders				
Cough	22 (9.91%)	22 (9.95%)	2 (1.34%)	0 (0.00%)
Dyspnoea	13 (5.86%)	12 (5.43%)	2 (1.34%)	0 (0.00%)
Skin and subcutaneous tissue disorders				
Acne	16 (7.21%)	5 (2.26%)	4 (2.68%)	0 (0.00%)
Alopecia	104 (46.85%)	119 (53.85%)	2 (1.34%)	0 (0.00%)
Dry skin	16 (7.21%)	3 (1.36%)	8 (5.37%)	2 (50.00%)
Nail disorder	26 (11.71%)	3 (1.36%)	8 (5.37%)	0 (0.00%)
Pruritus	23 (10.36%)	9 (4.07%)	10 (6.71%)	0 (0.00%)
Rash	109 (49.10%)	47 (21.27%)	52 (34.90%)	0 (0.00%)

Other Relevant Findings

None

Conclusion:

- At the time of primary analysis lapatinib+paclitaxel offered a statistically significant and clinically meaningful benefit in OS. In the updated analyses, lapatinib+paclitaxel has continued to show clinically meaningful benefit in OS, as well as PFS, BOR, CBR, DOR and TTR as compared to placebo+paclitaxel.
- Adverse events reported in this study were consistent with the known lapatinib and paclitaxel safety profiles. No new safety signals were detected.
- The combination of lapatinib+paclitaxel continues to demonstrate a positive risk/benefit profile. Lapatinib+paclitaxel continues to offer an effective treatment option for subjects with HER2-positive metastatic breast cancer.

Date of Clinical Trial Report

23-Sep-2022	Abbreviated Close-out CSR