ClinicalTrials.gov Protocol Registration and Results System (PRS) Receipt
Release Date: 02/22/2016

ClinicalTrials.gov ID: NCT00429299

## Study Identification

| | |
|---|---|
| Unique Protocol ID: | EGF106988 |
| Brief Title: | Neoadjuvant Study With Chemotherapy, Lapatinib And Trastuzumab In Breast Cancer ( CHERLOB ) |
| Official Title: | Chemotherapy Plus Lapatinib or Trastuzumab or Both in Her2+ Primary Breast Cancer. A Randomized Phase IIb Study With Biomarker Evaluation. |
| Secondary IDs: | |

## Study Status

| | |
|---|---|
| Record Verification: | January 2016 |
| Overall Status: | Completed |
| Study Start: | August 2006 |
| Primary Completion: | June 2012 [Actual] |
| Study Completion: | June 2012 [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?: | No |
| Review Board: | Approval Status: Approved<br>Approval Number: Prot.4746/CE; Approv.152/05<br>Board Name: Comitato Etico Provinciale<br>Board Affiliation: Azienda Ospedaliero-Universitaria di Modena,Azienda Unità Sanitaria Locale di Modena, Italy<br>Phone: +39 059 422.2990<br>Email: comitatoetico@policlinico.mo.it |
| Data Monitoring?: | No |
| Plan to Share Data?: | |
| Oversight Authorities: | Italy: Ministry of Health<br>Germany: Ministry of Health<br>United States: Food and Drug Administration |

## Study Description

| | |
|---|---|
| Brief Summary: | Evaluate the activity of Trastuzumab, Lapatinib, and a combination of both agents with chemotherapy in the preoperative (neoadjuvant) treatment of early breast cancer. |
| Detailed Description: | |

## Conditions

| | |
|---|---|
| Conditions: | Neoplasms, Breast |
| Keywords: | neo-adjuvant trastuzumab early breast cancer lapatinib |

## 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: 121 [Actual]

## Arms and Interventions

| Arms | Assigned Interventions |
|---|---|
| Active Comparator: Arm A<br>Chemotherapy plus trastuzumab | Biological/Vaccine: trastuzumab<br>First dose 4mg/kg in 60mins, then weekly 2mg/kg in 30 mins<br>Other Names:<br>• Herceptin<br>Drug: paclitaxel<br>80mg/sqm 1 hour infusion for 12 weeks<br>Other Names:<br>• Taxol<br>Drug: fluorouracil<br>600mg/sqm iv day 1 q21 days for four coursess<br>Drug: epidoxorubicin<br>75mg/sqm iv day 1 q21 days for four courses<br>Drug: cyclophosphamide<br>600mg/sqm day 1 q21 days for four courses |
| Experimental: Arm B<br>Chemotherapy plus lapatinib | Drug: lapatinib<br>Arm B 1250mg/d PO Arm C 750mg/d PO<br>Other Names:<br>• Tyverb/Tykerb<br>Drug: paclitaxel<br>80mg/sqm 1 hour infusion for 12 weeks<br>Other Names:<br>• Taxol<br>Drug: fluorouracil<br>600mg/sqm iv day 1 q21 days for four coursess<br>Drug: epidoxorubicin<br>75mg/sqm iv day 1 q21 days for four courses<br>Drug: cyclophosphamide<br>600mg/sqm day 1 q21 days for four courses |
| Active Comparator: Arm C<br>Chemotherapy plus trastuzumab plus lapatinib | Drug: lapatinib<br>Arm B 1250mg/d PO Arm C 750mg/d PO<br>Other Names:<br>• Tyverb/Tykerb<br>Biological/Vaccine: trastuzumab<br>First dose 4mg/kg in 60mins, then weekly 2mg/kg in 30 mins |

| Arms | Assigned Interventions |
|---|---|
| | Other Names:<br>• Herceptin<br>Drug: paclitaxel<br>80mg/sqm 1 hour infusion for 12 weeks<br>Other Names:<br>• Taxol<br>Drug: fluorouracil<br>600mg/sqm iv day 1 q21 days for four coursess<br>Drug: epidoxorubicin<br>75mg/sqm iv day 1 q21 days for four courses<br>Drug: cyclophosphamide<br>600mg/sqm day 1 q21 days for four courses |

## Outcome Measures

[See Results Section.]

## Eligibility

Minimum Age: 18 Years

Maximum Age: 65 Years

Gender: Female

Accepts Healthy Volunteers?: No

Criteria: Inclusion criteria:

- Histologically confirmed infiltrating primary breast cancer of > 2.0 cm in largest clinical diameter

HER2 positive tumor (either IHC 3+ or FISH+)

- Availability of tumor tissue suitable for biological and molecular examination before starting primary treatment
- Age >18, < 65 years
- ECOG PS 0-1
- Normal organ and marrow function as defined below:

leukocytes ³ 3000/microL

absolute neutrophil count ³ 1,500/microL

platelets ³ 100,000/microL

total bilirubin <= 1.5x ULN. In case of Gilbert's syndrome, <2 x ULN is allowed

AST (SGOT)/ALT(SGPT)<= 2.5 X institutional upper limit of normal

Alkaline phosphatase <= 2.5 x ULN

Creatinine within normal institutional limits

- Cardiac ejection fraction within the institutional range of normal as measured by echocardiogram or MUGA scan
- Eligibility of patients receiving medications or substances known to affect, or with the potential to affect the activity or pharmacokinetics of lapatinib will be determined following review of their use by the Principal Investigator. A list of medications and substances known or with the potential to interact with CYP450 isoenzymes is provided
- The effects of lapatinib on the developing human fetus at the recommended therapeutic dose are unknown; women of child-bearing potential must agree to use adequate contraception (hormonal or barrier method of birth control or abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately, the patient should be apprised of the potential hazard to the fetus and potential risk for loss of the pregnancy
- Ability to understand and the willingness to sign a written informed consent document
- Ability to swallow and retain oral medication

Exclusion criteria:

- Stage IIIB, IIIC, and inflammatory breast cancer
- Stage IV breast cancer
- Contraindication to the treatment with anthracycline, paclitaxel and/or trastuzumab
- Prior treatment with chemotherapy, endocrine therapy or radiotherapy. Prior treatment with EGFR targeting therapies
- Treatment with any other investigational agents, or with all herbal (alternative) medicines
- History of allergic reactions attributed to compounds of similar chemical or biologic composition to lapatinib
- Uncontrolled inter-current illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements
- Pregnancy or breastfeeding; (breast feeding should be discontinued to be enrolled in the study)
- Women of childbearing potential that refusal to adopt adequate contraceptive measures
- HIV-positive patients receiving combination anti-retroviral therapy
- GI tract disease resulting in an inability to take oral medication, malabsorption syndrome, a requirement for IV alimentation, prior surgical procedures affecting absorption, uncontrolled inflammatory GI disease (e.g., Crohn's, ulcerative colitis)
- Concomitant requirement for medication classified as CYP3A4 inducers or inhibitors

## Contacts/Locations

Study Officials: GSK Clinical Trials
Study Director
GlaxoSmithKline

Locations: Italy
GSK Investigational Site
Candiolo (TO), Piemonte, Italy, 10060

Poland
GSK Investigational Site
Warszawa, Poland, 00-909

Italy
GSK Investigational Site
Modena, Emilia-Romagna, Italy, 41100

GSK Investigational Site
Cremona, Italy, 26100

Germany
GSK Investigational Site
Berlin, Berlin, Germany, 13125

Italy
GSK Investigational Site
Carpi (MO), Emilia-Romagna, Italy, 41012

GSK Investigational Site
Reggio Emilia, Italy, 42100

GSK Investigational Site
Piacenza, Emilia-Romagna, Italy, 29100

GSK Investigational Site
Parma, Emilia-Romagna, Italy, 43100

GSK Investigational Site
Brindisi, Puglia, Italy, 72100

GSK Investigational Site
Pavia, Italy, 27100

GSK Investigational Site
Treviglio (BG), Lombardia, Italy, 24047

GSK Investigational Site
Pisa, Toscana, Italy, 56126

GSK Investigational Site
Forlì, Emilia-Romagna, Italy, 47100

GSK Investigational Site
Rimini, Emilia-Romagna, Italy, 47900

GSK Investigational Site
Perugia, Italy, 06156

GSK Investigational Site
Varese, Italy, 21100

## References

Citations: Conte et al. Preoperative chemotherapy plus trastuzumab, lapatinib or both in HER2 positive operable breast cancer: results of the randomized phase II CHER-LOB study.. [J Clin Oncol]. 2012;

Links:

Study Data/Documents:

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# Study Results

## Participant Flow

| | |
|---|---|
| Pre-Assignment Details | Participants underwent core biopsy of the primary tumor, for the histological diagnosis and the biological characterization of the tumor. Radiological investigations were performed to rule out the metastatic disease. After diagnostic confirmation of the infiltrating carcinoma, participants were randomized to one of the three treatment arms. |

Reporting Groups

| | Description |
|---|---|
| Chemotherapy (CT) Plus Trastuzumab | Participants received chemotherapy (CT), which included paclitaxel 80 milligrams per meters squared (mg/m^2) weekly for 12 weeks, followed by intravenous (IV) fluorouracil 600 mg/m^2, IV epidoxorubicin 75 mg/m^2, and IV cyclophosphamide 600 mg/m^2, once every 21 days for four treatment courses. Trastuzumab was administered throughout the course of the CT and for two weeks after the last CT administration. The first dose of trastuzumab was administered at 4 milligrams per kilogram (mg/kg) IV for 60 minutes on the day of the first paclitaxel course. Subsequent administrations were given weekly at 2 mg/kg IV for 30 minutes. Treatments were administered for 26 weeks prior to surgery. |
| CT Plus Lapatinib 1500 mg | Participants received CT, which included paclitaxel 80 mg/m^2 weekly for 12 weeks, followed by IV fluorouracil 600 mg/m^2, IV epidoxorubicin 75 mg/m^2, and IV cyclophosphamide 600 mg/m^2, once every 21 days for four treatment courses. Participants received lapatinib 1500 mg/day orally on an empty stomach throughout the course of the CT and for three weeks after the last CT administration. Treatments were administered for 26 weeks prior to surgery. Following Independent Data Monitoring Committee (IDMC) recommendations, lapatinib doses were reduced to 1250 mg/day orally on an empty stomach. |

| | Description |
|---|---|
| CT Plus Trastuzumab and Lapatinib 1000 mg | Participants received CT, which included paclitaxel 80 mg/m^2 weekly for 12 weeks, followed by IV fluorouracil 600 mg/m^2, IV epidoxorubicin 75 mg/m^2, and IV cyclophosphamide 600 mg/m^2, once every 21 days for four treatment courses. Trastuzumab was administered throughout the course of the CT and for two weeks after the last CT administration. The first dose of trastuzumab was administered at 4 mg/kg IV for 60 minutes on the day of the first paclitaxel course. Subsequent administrations were given weekly at 2 mg/kg IV for 30 minutes. Participants received lapatinib 1000 mg/day orally on an empty stomach throughout the course of the CT and for three weeks after the last CT administration. Treatments were administered for 26 weeks prior to surgery. Following IDMC recommendations, lapatinib doses were reduced to 750 mg/day orally on an empty stomach. |

Overall Study

| | Chemotherapy (CT) Plus Trastuzumab | CT Plus Lapatinib 1500 mg | CT Plus Trastuzumab and Lapatinib 1000 mg |
|---|---|---|---|
| Started | 36 | 39 | 46 |
| Completed | 32 | 32 | 42 |
| Not Completed | 4 | 7 | 4 |
| Disease Progression | 1 | 1 | 0 |
| Adverse Event | 2 | 5 | 1 |
| Protocol Violation | 1 | 0 | 0 |
| Withdrawal by Subject | 0 | 1 | 3 |

## Baseline Characteristics

Reporting Groups

| | Description |
|---|---|
| CT Plus Trastuzumab | Participants received chemotherapy (CT), which included paclitaxel 80 milligrams per meters squared (mg/m^2) weekly for 12 weeks, followed by intravenous (IV) fluorouracil 600 mg/m^2, IV epidoxorubicin 75 mg/m^2, and IV cyclophosphamide 600 mg/m^2, once every 21 days for four treatment courses. Trastuzumab was administered throughout the course of the CT and for two weeks after the last CT administration. The first dose of trastuzumab was administered at 4 milligrams per kilogram (mg/kg) IV for 60 minutes on the day of the first paclitaxel course. Subsequent administrations were given weekly at 2 mg/kg IV for 30 minutes. Treatments were administered for 26 weeks prior to surgery. |

| | Description |
|---|---|
| CT Plus Lapatinib 1500 mg | Participants received CT, which included paclitaxel 80 mg/m^2 weekly for 12 weeks, followed by IV fluorouracil 600 mg/m^2, IV epidoxorubicin 75 mg/m^2, and IV cyclophosphamide 600 mg/m^2, once every 21 days for four treatment courses. Participants received lapatinib 1500 mg/day orally on an empty stomach throughout the course of the CT and for three weeks after the last CT administration. Treatments were administered for 26 weeks prior to surgery. Following Independent Data Monitoring Committee (IDMC) recommendations, lapatinib doses were reduced to 1250 mg/day orally on an empty stomach. |
| CT Plus Trastuzumab and Lapatinib 1000 mg | Participants received CT, which included paclitaxel 80 mg/m^2 weekly for 12 weeks, followed by IV fluorouracil 600 mg/m^2, IV epidoxorubicin 75 mg/m^2, and IV cyclophosphamide 600 mg/m^2, once every 21 days for four treatment courses. Trastuzumab was administered throughout the course of the CT and for two weeks after the last CT administration. The first dose of trastuzumab was administered at 4 mg/kg IV for 60 minutes on the day of the first paclitaxel course. Subsequent administrations were given weekly at 2 mg/kg IV for 30 minutes. Participants received lapatinib 1000 mg/day orally on an empty stomach throughout the course of the CT and for three weeks after the last CT administration. Treatments were administered for 26 weeks prior to surgery. Following IDMC recommendations, lapatinib doses were reduced to 750 mg/day orally on an empty stomach. |

Baseline Measures

| | CT Plus Trastuzumab | CT Plus Lapatinib 1500 mg | CT Plus Trastuzumab and Lapatinib 1000 mg | Total |
|---|---|---|---|---|
| Number of Participants | 36 | 39 | 46 | 121 |
| Age, Continuous<br>[units: Years]<br>Mean (Full Range) | 50 (34 to 65) | 49 (34 to 68) | 49 (26 to 65) | 49.3 (26 to 68) |
| Gender, Male/Female<br>[units: Participants] | | | | |
| Female | 36 | 39 | 46 | 121 |
| Male | 0 | 0 | 0 | 0 |
| Race/Ethnicity, Customized<br>[units: Participants] | | | | |
| Caucasian | 34 | 37 | 44 | 115 |
| Asian | 1 | 2 | 2 | 5 |
| Unknown | 1 | 0 | 0 | 1 |

## Outcome Measures

1. Primary Outcome Measure:

| | |
|---|---|
| Measure Title | Percentage of Participants With Pathological Complete Response (pCR) in the Breast and in the Lymph Nodes |

| | |
|---|---|
| Measure Description | Pathological Complete Response (pCR) is defined by the complete absence of infiltrating tumor cells in the breast and in the lymph nodes. The pathological response in the breast was evaluated according to the criteria of Miller and Payne as follows: Grade 1, no change or some alteration to individual malignant cells, but no reduction in overall cellularity; Grade 2, a minor loss in tumor cells (up to 30%); Grade 3, between an estimated 30% and 90% reduction in tumor cells; Grade 4, marked disappearance of tumor cells, with only a small cluster or a dispersed cell remaining (more than 90% loss); Grade 5, no identifiable malignant cells. Ductal carcinoma in situ (DCIS) may be present. Grades were interpreted as follows: Grade 1-2=no response; Grade 3-4=partial response; Grade 5=complete response. pCR was defined by comparing specimens obtained at Baseline (biopsy) to those obtained upon surgery. |
| Time Frame | At Baseline and surgery (within 5 weeks after the last chemotherapy administration) (assessed up to Study Week 29) |
| Safety Issue? | No |

Analysis Population Description

Efficacy Analysis Population: all participants in the Intent-to-Treat Population (all participants who were randomized), except for the 2 participants who were excluded because of withdraw of consent and major protocol deviation

Reporting Groups

| | Description |
|---|---|
| CT Plus Trastuzumab | Participants received chemotherapy (CT), which included paclitaxel 80 milligrams per meters squared (mg/m^2) weekly for 12 weeks, followed by intravenous (IV) fluorouracil 600 mg/m^2, IV epidoxorubicin 75 mg/m^2, and IV cyclophosphamide 600 mg/m^2, once every 21 days for four treatment courses. Trastuzumab was administered throughout the course of the CT and for two weeks after the last CT administration. The first dose of trastuzumab was administered at 4 milligrams per kilogram (mg/kg) IV for 60 minutes on the day of the first paclitaxel course. Subsequent administrations were given weekly at 2 mg/kg IV for 30 minutes. Treatments were administered for 26 weeks prior to surgery. |
| CT Plus Lapatinib 1500 mg | Participants received CT, which included paclitaxel 80 mg/m^2 weekly for 12 weeks, followed by IV fluorouracil 600 mg/m^2, IV epidoxorubicin 75 mg/m^2, and IV cyclophosphamide 600 mg/m^2, once every 21 days for four treatment courses. Participants received lapatinib 1500 mg/day orally on an empty stomach throughout the course of the CT and for three weeks after the last CT administration. Treatments were administered for 26 weeks prior to surgery.<br><br>Following Independent Data Monitoring Committee (IDMC) recommendations, lapatinib doses were reduced to 1250 mg/day orally on an empty stomach. |
| CT Plus Trastuzumab and Lapatinib 1000 mg | Participants received CT, which included paclitaxel 80 mg/m^2 weekly for 12 weeks, followed by IV fluorouracil 600 mg/m^2, IV epidoxorubicin 75 mg/m^2, and IV cyclophosphamide 600 mg/m^2, once every 21 days for four treatment courses. Trastuzumab was administered throughout the course of the CT and for two weeks after the last CT administration. The first dose of trastuzumab was administered at 4 mg/kg IV for 60 minutes on the day of the first paclitaxel course. Subsequent administrations were given weekly at 2 mg/kg IV for 30 minutes. Participants received lapatinib 1000 mg/day orally on an empty stomach throughout the course of the CT and for three weeks after the last CT administration. Treatments were administered for 26 weeks prior to surgery.<br><br>Following IDMC recommendations, lapatinib doses were reduced to 750 mg/day orally on an empty stomach. |

Measured Values

| | CT Plus Trastuzumab | CT Plus Lapatinib 1500 mg | CT Plus Trastuzumab and Lapatinib 1000 mg |
|---|---|---|---|
| Number of Participants Analyzed | 36 | 38 | 45 |
| Percentage of Participants With Pathological Complete Response (pCR) in the Breast and in the Lymph Nodes<br>[units: Percentage of participants] | 25 | 26.3 | 46.7 |

Statistical Analysis 1 for Percentage of Participants With Pathological Complete Response (pCR) in the Breast and in the Lymph Nodes

| | | |
|---|---|---|
| Statistical Analysis Overview | Comparison Groups | CT Plus Trastuzumab, CT Plus Lapatinib 1500 mg, CT Plus Trastuzumab and Lapatinib 1000 mg |
| | Comments | [Not specified] |
| | Non-Inferiority or Equivalence Analysis? | Yes |
| | Comments | An exploratory comparison between the combined two single anti-HER2 arms and the dual anti-HER2 arm was performed (Arm 3 versus Arms 1 and 2). |

| | | |
|---|---|---|
| Statistical Test of Hypothesis | P-Value | 0.019 |
| | Comments | Exploratory analysis |
| | Method | Chi-squared |
| | Comments | [Not specified] |

| | | |
|---|---|---|
| Method of Estimation | Estimation Parameter | Other [percentage of participants] |
| | Estimated Value | 25.0 |
| | Confidence Interval | (2-Sided) 90%<br>13.1 to 36.9 |
| | Estimation Comments | The estimated value represents the percentage of particpants in the CT plus trastuzumab treatment group with pathological complete response. |

Statistical Analysis 2 for Percentage of Participants With Pathological Complete Response (pCR) in the Breast and in the Lymph Nodes

| | | |
|---|---|---|
| Statistical Analysis Overview | Comparison Groups | CT Plus Lapatinib 1500 mg |
| | Comments | [Not specified] |

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

| | | |
|---|---|---|
| Method of Estimation | Estimation Parameter | Other [percentage of participants] |
| | Estimated Value | 26.3 |
| | Confidence Interval | (2-Sided) 90%<br>14.5 to 38.1 |
| | Estimation Comments | The estimated value represents the percentage of particpants in the CT plus lapatinib 1500 mg treatment group with pathological complete response. |

Statistical Analysis 3 for Percentage of Participants With Pathological Complete Response (pCR) in the Breast and in the Lymph Nodes

| | | |
|---|---|---|
| Statistical Analysis Overview | Comparison Groups | CT Plus Trastuzumab and Lapatinib 1000 mg |
| | Comments | [Not specified] |
| | Non-Inferiority or Equivalence Analysis? | No |
| | Comments | [Not specified] |

| | | |
|---|---|---|
| Method of Estimation | Estimation Parameter | Other [percentage of participants] |
| | Estimated Value | 46.7 |
| | Confidence Interval | (2-Sided) 90%<br>34.4 to 58.9 |
| | Estimation Comments | The estimated value represents the percentage of particpants in the CT plus traztuzumab plus lapatinib 1000 mg treatment group with pathological complete response. |

2. Secondary Outcome Measure:

| | |
|---|---|
| Measure Title | Percentage of Participants With the Indicated Clinical Objective Response (Complete Response and Partial Response), Stable Disease, and Progressive Disease, as Assessed by Ultrasonography |

| | |
|---|---|
| Measure Description | The clinical response was evaluated by comparing the tumor size (largest tumor diameter) before (at Baseline [biopsy]) and after treatment (before surgery), as assessed by ultrasonography examination. The clinical response was scored by Response Evaluation Criteria in Solid Tumors (RECIST) as follows: complete clinical response: the nodule is not detectable and all the ultrasound abnormality detected at diagnosis disappeared (margins circumscribed, round oval shape, parallel orientation, isoechoic echo pattern, no posterior acoustic features, echogenic lesion boundary, and tumor vascularity not present); partial clinical response: the longest diameter of the tumor has been reduced by >50%, and the ultrasound characteristics of the tumor persist; no response (stable disease): the longest diameter of the tumor has been reduced by <50% or has increased by no more than 20% from the starting value; progressive disease: tumor longest diameter has increased >20% from the starting value. |
| Time Frame | At Baseline and after primary treatment (within 2 weeks before surgery; up to Study Week 27) |
| Safety Issue? | No |

Analysis Population Description

Efficacy Analysis Population

Reporting Groups

| | Description |
|---|---|
| CT Plus Trastuzumab | Participants received chemotherapy (CT), which included paclitaxel 80 milligrams per meters squared (mg/m^2) weekly for 12 weeks, followed by intravenous (IV) fluorouracil 600 mg/m^2, IV epidoxorubicin 75 mg/m^2, and IV cyclophosphamide 600 mg/m^2, once every 21 days for four treatment courses. Trastuzumab was administered throughout the course of the CT and for two weeks after the last CT administration. The first dose of trastuzumab was administered at 4 milligrams per kilogram (mg/kg) IV for 60 minutes on the day of the first paclitaxel course. Subsequent administrations were given weekly at 2 mg/kg IV for 30 minutes. Treatments were administered for 26 weeks prior to surgery. |
| CT Plus Lapatinib 1500 mg | Participants received CT, which included paclitaxel 80 mg/m^2 weekly for 12 weeks, followed by IV fluorouracil 600 mg/m^2, IV epidoxorubicin 75 mg/m^2, and IV cyclophosphamide 600 mg/m^2, once every 21 days for four treatment courses. Participants received lapatinib 1500 mg/day orally on an empty stomach throughout the course of the CT and for three weeks after the last CT administration. Treatments were administered for 26 weeks prior to surgery.<br><br>Following Independent Data Monitoring Committee (IDMC) recommendations, lapatinib doses were reduced to 1250 mg/day orally on an empty stomach. |
| CT Plus Trastuzumab and Lapatinib 1000 mg | Participants received CT, which included paclitaxel 80 mg/m^2 weekly for 12 weeks, followed by IV fluorouracil 600 mg/m^2, IV epidoxorubicin 75 mg/m^2, and IV cyclophosphamide 600 mg/m^2, once every 21 days for four treatment courses. Trastuzumab was administered throughout the course of the CT and for two weeks after the last CT administration. The first dose of trastuzumab was administered at 4 mg/kg IV for 60 minutes on the day of the first paclitaxel course. Subsequent administrations were given weekly at 2 mg/kg IV for 30 minutes. Participants received lapatinib 1000 mg/day orally on an empty stomach throughout the course of the CT and for three weeks after the last CT administration. Treatments were administered for 26 weeks prior to surgery.<br><br>Following IDMC recommendations, lapatinib doses were reduced to 750 mg/day orally on an empty stomach. |

Measured Values

| | CT Plus Trastuzumab | CT Plus Lapatinib 1500 mg | CT Plus Trastuzumab and Lapatinib 1000 mg |
|---|---|---|---|
| Number of Participants Analyzed | 36 | 38 | 45 |
| Percentage of Participants With the Indicated Clinical Objective Response (Complete Response and Partial Response), Stable Disease, and Progressive Disease, as Assessed by Ultrasonography [units: Percentage of participants] | | | |
| Complete Response (CR) | 30.5 | 15.8 | 42.2 |
| Partial Response (PR) | 41.7 | 44.7 | 28.9 |
| Stable Disease | 5.5 | 13.1 | 0 |
| Progressive Disease | 2.8 | 2.6 | 0 |
| Not Evaluable | 19.4 | 23.7 | 28.9 |

3. Secondary Outcome Measure:

| | |
|---|---|
| Measure Title | Percentage of Participants Who Had Breast-conserving Surgery (BCS), Mastectomy, and Conversion From Mastectomy to BCS |
| Measure Description | The percentage of participants who had BCS and mastectomy and who were initiallycandidates for mastectomy and who actually had BCS was measured. At Baseline, the surgeon stated, within 4 weeks before starting the primary treatment, which type of surgical treatment he would perform in the absence of primary therapy and in the case of primary therapy (if the tumor size was reduced by the primary treatment to less than 3 centimeters), and the reasons for these choices. The rules for choosing the type of surgical treatment are reported in the Consensus Conference on Primary Treatment of Early Breast Cancer. The surgeon was to have re-evaluated the participant after primary treatment. In cases in which the type of surgical procedure was different from that originally programmed, the reason for this chance was to have been reported. |
| Time Frame | At Baseline and at surgery (up to Study Week 29) |
| Safety Issue? | No |

Analysis Population Description

Efficacy Analysis Population

Reporting Groups

| | Description |
|---|---|
| CT Plus Trastuzumab | Participants received chemotherapy (CT), which included paclitaxel 80 milligrams per meters squared (mg/m^2) weekly for 12 weeks, followed by intravenous (IV) fluorouracil 600 mg/m^2, IV epidoxorubicin 75 mg/m^2, and IV cyclophosphamide 600 mg/m^2, once every 21 days for four treatment courses. Trastuzumab was administered throughout the course of the CT and for two weeks after the last CT administration. The first dose of trastuzumab was administered at 4 milligrams per kilogram (mg/kg) IV for 60 minutes on the day of the first paclitaxel course. Subsequent administrations were given weekly at 2 mg/kg IV for 30 minutes. Treatments were administered for 26 weeks prior to surgery. |
| CT Plus Lapatinib 1500 mg | Participants received CT, which included paclitaxel 80 mg/m^2 weekly for 12 weeks, followed by IV fluorouracil 600 mg/m^2, IV epidoxorubicin 75 mg/m^2, and IV cyclophosphamide 600 mg/m^2, once every 21 days for four treatment courses. Participants received lapatinib 1500 mg/day orally on an empty stomach throughout the course of the CT and for three weeks after the last CT administration. Treatments were administered for 26 weeks prior to surgery.<br><br>Following Independent Data Monitoring Committee (IDMC) recommendations, lapatinib doses were reduced to 1250 mg/day orally on an empty stomach. |
| CT Plus Trastuzumab and Lapatinib 1000 mg | Participants received CT, which included paclitaxel 80 mg/m^2 weekly for 12 weeks, followed by IV fluorouracil 600 mg/m^2, IV epidoxorubicin 75 mg/m^2, and IV cyclophosphamide 600 mg/m^2, once every 21 days for four treatment courses. Trastuzumab was administered throughout the course of the CT and for two weeks after the last CT administration. The first dose of trastuzumab was administered at 4 mg/kg IV for 60 minutes on the day of the first paclitaxel course. Subsequent administrations were given weekly at 2 mg/kg IV for 30 minutes. Participants received lapatinib 1000 mg/day orally on an empty stomach throughout the course of the CT and for three weeks after the last CT administration. Treatments were administered for 26 weeks prior to surgery.<br><br>Following IDMC recommendations, lapatinib doses were reduced to 750 mg/day orally on an empty stomach. |

Measured Values

| | CT Plus Trastuzumab | CT Plus Lapatinib 1500 mg | CT Plus Trastuzumab and Lapatinib 1000 mg |
|---|---|---|---|
| Number of Participants Analyzed | 36 | 38 | 45 |
| Percentage of Participants Who Had Breast-conserving Surgery (BCS), Mastectomy, and Conversion From Mastectomy to BCS<br>[units: Percentage of participants] | | | |
| BCS | 66.7 | 57.9 | 68.9 |
| Mastectomy | 33.3 | 39.5 | 31.1 |
| Conversion from mastectomy to BCS | 61.9 | 42.8 | 60 |

4. Secondary Outcome Measure:

| | |
|---|---|
| Measure Title | Time to Treatment Failure From the Start of Primary Therapy |
| Measure Description | Time to treatment failure (TTF) is defined as the interval of time between the date of randomization and the earliest date of disease progression, premature treatment discontinuation and death due to any cause. The overall disease progression date is the earlier of the two disease progression dates from ultrasonography and mammography assessments. For ultrasonography, disease progression is defined as at least 20% increase in the longest diameter of the primary lesion at pre-surgery comparing to Baseline. For mammography, disease progression is defined as at least 20% increase in the larger nodule dimension at pre-surgery comparing to Baseline. For participants who has neither progressed, pre-maturely withdrawn or died, time to treatment failure will be censored at the latest date of ultrasonography and mammography tumor assessments. |
| Time Frame | From randomization up to Study Week 307 |
| Safety Issue? | No |

Analysis Population Description

ITT Population: all participants who were randomized

Reporting Groups

| | Description |
|---|---|
| CT Plus Trastuzumab | Participants received chemotherapy (CT), which included paclitaxel 80 milligrams per meters squared (mg/m^2) weekly for 12 weeks, followed by intravenous (IV) fluorouracil 600 mg/m^2, IV epidoxorubicin 75 mg/m^2, and IV cyclophosphamide 600 mg/m^2, once every 21 days for four treatment courses. Trastuzumab was administered throughout the course of the CT and for two weeks after the last CT administration. The first dose of trastuzumab was administered at 4 milligrams per kilogram (mg/kg) IV for 60 minutes on the day of the first paclitaxel course. Subsequent administrations were given weekly at 2 mg/kg IV for 30 minutes. Treatments were administered for 26 weeks prior to surgery. |
| CT Plus Lapatinib 1500 mg | Participants received CT, which included paclitaxel 80 mg/m^2 weekly for 12 weeks, followed by IV fluorouracil 600 mg/m^2, IV epidoxorubicin 75 mg/m^2, and IV cyclophosphamide 600 mg/m^2, once every 21 days for four treatment courses. Participants received lapatinib 1500 mg/day orally on an empty stomach throughout the course of the CT and for three weeks after the last CT administration. Treatments were administered for 26 weeks prior to surgery.<br><br>Following Independent Data Monitoring Committee (IDMC) recommendations, lapatinib doses were reduced to 1250 mg/day orally on an empty stomach. |

| | Description |
|---|---|
| CT Plus Trastuzumab and Lapatinib 1000 mg | Participants received CT, which included paclitaxel 80 mg/m^2 weekly for 12 weeks, followed by IV fluorouracil 600 mg/m^2, IV epidoxorubicin 75 mg/m^2, and IV cyclophosphamide 600 mg/m^2, once every 21 days for four treatment courses. Trastuzumab was administered throughout the course of the CT and for two weeks after the last CT administration. The first dose of trastuzumab was administered at 4 mg/kg IV for 60 minutes on the day of the first paclitaxel course. Subsequent administrations were given weekly at 2 mg/kg IV for 30 minutes. Participants received lapatinib 1000 mg/day orally on an empty stomach throughout the course of the CT and for three weeks after the last CT administration. Treatments were administered for 26 weeks prior to surgery.<br><br>Following IDMC recommendations, lapatinib doses were reduced to 750 mg/day orally on an empty stomach. |

Measured Values

| | CT Plus Trastuzumab | CT Plus Lapatinib 1500 mg | CT Plus Trastuzumab and Lapatinib 1000 mg |
|---|---|---|---|
| Number of Participants Analyzed | 36 | 39 | 46 |
| Time to Treatment Failure From the Start of Primary Therapy<br>[units: Months]<br>Median (95% Confidence Interval) | 28.2 (28.2 to 59.8) | 39.6 (NA to NA) [1] | 39.6 (6.3 to 39.6) |

[1] The confidence limits for the median value are not estimable because there are no time points that satisfy the condition using the method of Klein and Moeschberger (1997).

5. Secondary Outcome Measure:

| | |
|---|---|
| Measure Title | Number of Participants With Treatment Failure |
| Measure Description | Treatment failure is defined as the occurrence of local tumor progression (including ipsilateral and controlateral breast), distant tumor progression, permanent treatment discontinuation (either for the experimental or conventional arm), or death due to any cause. |
| Time Frame | From randomization up to 29 weeks |
| Safety Issue? | No |

Analysis Population Description

ITT Population

Reporting Groups

| | Description |
|---|---|
| CT Plus Trastuzumab | Participants received chemotherapy (CT), which included paclitaxel 80 milligrams per meters squared (mg/m^2) weekly for 12 weeks, followed by intravenous (IV) fluorouracil 600 mg/m^2, IV epidoxorubicin 75 mg/m^2, and IV cyclophosphamide 600 mg/m^2, once every 21 days for four treatment courses. Trastuzumab was administered throughout the course of the CT and for two weeks after the last CT administration. The first dose of trastuzumab was administered at 4 milligrams per kilogram (mg/kg) IV for 60 minutes on the day of the first paclitaxel course. Subsequent administrations were given weekly at 2 mg/kg IV for 30 minutes. Treatments were administered for 26 weeks prior to surgery. |
| CT Plus Lapatinib 1500 mg | Participants received CT, which included paclitaxel 80 mg/m^2 weekly for 12 weeks, followed by IV fluorouracil 600 mg/m^2, IV epidoxorubicin 75 mg/m^2, and IV cyclophosphamide 600 mg/m^2, once every 21 days for four treatment courses. Participants received lapatinib 1500 mg/day orally on an empty stomach throughout the course of the CT and for three weeks after the last CT administration. Treatments were administered for 26 weeks prior to surgery.<br><br>Following Independent Data Monitoring Committee (IDMC) recommendations, lapatinib doses were reduced to 1250 mg/day orally on an empty stomach. |
| CT Plus Trastuzumab and Lapatinib 1000 mg | Participants received CT, which included paclitaxel 80 mg/m^2 weekly for 12 weeks, followed by IV fluorouracil 600 mg/m^2, IV epidoxorubicin 75 mg/m^2, and IV cyclophosphamide 600 mg/m^2, once every 21 days for four treatment courses. Trastuzumab was administered throughout the course of the CT and for two weeks after the last CT administration. The first dose of trastuzumab was administered at 4 mg/kg IV for 60 minutes on the day of the first paclitaxel course. Subsequent administrations were given weekly at 2 mg/kg IV for 30 minutes. Participants received lapatinib 1000 mg/day orally on an empty stomach throughout the course of the CT and for three weeks after the last CT administration. Treatments were administered for 26 weeks prior to surgery.<br><br>Following IDMC recommendations, lapatinib doses were reduced to 750 mg/day orally on an empty stomach. |

Measured Values

| | CT Plus Trastuzumab | CT Plus Lapatinib 1500 mg | CT Plus Trastuzumab and Lapatinib 1000 mg |
|---|---|---|---|
| Number of Participants Analyzed | 36 | 39 | 46 |
| Number of Participants With Treatment Failure<br>[units: Participants] | 7 | 9 | 7 |

6. Secondary Outcome Measure:

| | |
|---|---|
| Measure Title | Percentage of Inhibition of Biomarkers Ki67, pAKT, pMAPK, Tunel Test, PTEN, and pEGFR After Treatment |

| | |
|---|---|
| Measure Description | The percentage of inhibition of intermediate (EGFR, HER2, pMAPK, pAKT, PTEN, and PI3KCA) and final (TUNEL and Ki67) biomarkers of the proliferation and apoptosis pathways was calculated as the difference between the staining scores before (Baseline [biopsy]) and after treatment (withdrawal). |
| Time Frame | At Baseline and Withdrawal (assessed up to Study Week 29) |
| Safety Issue? | No |

Analysis Population Description

ITT Population. Only those participants contributing data to the indicated time points were analyzed.

Reporting Groups

| | Description |
|---|---|
| CT Plus Trastuzumab | Participants received chemotherapy (CT), which included paclitaxel 80 milligrams per meters squared (mg/m^2) weekly for 12 weeks, followed by intravenous (IV) fluorouracil 600 mg/m^2, IV epidoxorubicin 75 mg/m^2, and IV cyclophosphamide 600 mg/m^2, once every 21 days for four treatment courses. Trastuzumab was administered throughout the course of the CT and for two weeks after the last CT administration. The first dose of trastuzumab was administered at 4 milligrams per kilogram (mg/kg) IV for 60 minutes on the day of the first paclitaxel course. Subsequent administrations were given weekly at 2 mg/kg IV for 30 minutes. Treatments were administered for 26 weeks prior to surgery. |
| CT Plus Lapatinib 1500 mg | Participants received CT, which included paclitaxel 80 mg/m^2 weekly for 12 weeks, followed by IV fluorouracil 600 mg/m^2, IV epidoxorubicin 75 mg/m^2, and IV cyclophosphamide 600 mg/m^2, once every 21 days for four treatment courses. Participants received lapatinib 1500 mg/day orally on an empty stomach throughout the course of the CT and for three weeks after the last CT administration. Treatments were administered for 26 weeks prior to surgery.<br><br>Following Independent Data Monitoring Committee (IDMC) recommendations, lapatinib doses were reduced to 1250 mg/day orally on an empty stomach. |
| CT Plus Trastuzumab and Lapatinib 1000 mg | Participants received CT, which included paclitaxel 80 mg/m^2 weekly for 12 weeks, followed by IV fluorouracil 600 mg/m^2, IV epidoxorubicin 75 mg/m^2, and IV cyclophosphamide 600 mg/m^2, once every 21 days for four treatment courses. Trastuzumab was administered throughout the course of the CT and for two weeks after the last CT administration. The first dose of trastuzumab was administered at 4 mg/kg IV for 60 minutes on the day of the first paclitaxel course. Subsequent administrations were given weekly at 2 mg/kg IV for 30 minutes. Participants received lapatinib 1000 mg/day orally on an empty stomach throughout the course of the CT and for three weeks after the last CT administration. Treatments were administered for 26 weeks prior to surgery.<br><br>Following IDMC recommendations, lapatinib doses were reduced to 750 mg/day orally on an empty stomach. |

Measured Values

| | CT Plus Trastuzumab | CT Plus Lapatinib 1500 mg | CT Plus Trastuzumab and Lapatinib 1000 mg |
|---|---|---|---|
| Number of Participants Analyzed | 34 | 37 | 42 |

| | CT Plus Trastuzumab | CT Plus Lapatinib 1500 mg | CT Plus Trastuzumab and Lapatinib 1000 mg |
|---|---|---|---|
| Percentage of Inhibition of Biomarkers Ki67, pAKT, pMAPK, Tunel Test, PTEN, and pEGFR After Treatment<br>[units: Percentage of inhibition]<br>Median (Full Range) | | | |
| Ki67, Baseline, n=34, 37, 42 | 25 (10 to 60) | 25 (4 to 70) | 30 (4 to 90) |
| Ki67, Post-treatment, n=22, 21, 18 | 19 (1 to 50) | 15 (3 to 40) | 10 (1 to 30) |
| pAKT, Baseline, n=34, 37, 42 | 2.5 (1 to 100) | 10 (0 to 90) | 0 (0 to 90) |
| pAKT, Post-treatment, 18, 20, 17 | 0 (0 to 10) | 0 (0 to 90) | 0 (0 to 90) |
| pMAPK, Baseline, n=9, 5, 7 | 0 (0 to 10) | 10 (0 to 80) | 0 (0 to 20) |
| pMAPK, Post-treatment, n=0, 1, 2 | NA (NA to NA) [1] | 70 (70 to 70) | 5 (0 to 10) |
| Tunel test, Baseline, n=25, 27, 31 | 0.4 (0.05 to 2.6) | 0.58 (0.05 to 1.5) | 0.8 (0.05 to 2.5) |
| Tunel test, Post-treatment, n=7, 12, 11 | 0.1 (0.05 to 1.1) | 0.1 (0.05 to 0.55) | 0.05 (0.05 to 0.4) |
| PTEN, Baseline, n=27, 35, 37 | 80 (0 to 100) | 80 (0 to 100) | 90 (0 to 100) |
| PTEN, Post-treatment, n=14, 17, 15 | 100 (10 to 100) | 80 (0 to 100) | 80 (0 to 100) |
| pEGFR, Baseline, n=21, 24, 28 | 0 (0 to 80) | 0 (0 to 60) | 0 (0 to 70) |
| pEGFR, Post-treatment, n=5, 10, 11 | 0 (0 to 90) | 0 (0 to 0) | 0 (0 to 5) |

[1] No participants were analyzed for pMAPK at this time point.

7. Secondary Outcome Measure:

| | |
|---|---|
| Measure Title | Number of Participants With Any Adverse Event (AE), Including Serious Adverse Events (SAEs), Occurring in >=5% of Participants |
| Measure Description | An AE is defined as any untoward medical occurrence in a participant, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. An SAE is defined as any untoward medical occurrence that, at any dose, results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in disability/incapacity, or is a congenital anomaly/birth defect. Medical or scientific judgment had been exercised in deciding whether reporting was appropriate in other situations. |
| Time Frame | From the first dose of randomized therapy to 30 days after the last dose of randomized therapy (assessed up to Study Week 29) |
| Safety Issue? | No |

Analysis Population Description

Safety Population: all randomized participants

Reporting Groups

| | Description |
|---|---|
| CT Plus Trastuzumab | Participants received chemotherapy (CT), which included paclitaxel 80 milligrams per meters squared (mg/m^2) weekly for 12 weeks, followed by intravenous (IV) fluorouracil 600 mg/m^2, IV epidoxorubicin 75 mg/m^2, and IV cyclophosphamide 600 mg/m^2, once every 21 days for four treatment courses. Trastuzumab was administered throughout the course of the CT and for two weeks after the last CT administration. The first dose of trastuzumab was administered at 4 milligrams per kilogram (mg/kg) IV for 60 minutes on the day of the first paclitaxel course. Subsequent administrations were given weekly at 2 mg/kg IV for 30 minutes. Treatments were administered for 26 weeks prior to surgery. |
| CT Plus Lapatinib 1500 mg | Participants received CT, which included paclitaxel 80 mg/m^2 weekly for 12 weeks, followed by IV fluorouracil 600 mg/m^2, IV epidoxorubicin 75 mg/m^2, and IV cyclophosphamide 600 mg/m^2, once every 21 days for four treatment courses. Participants received lapatinib 1500 mg/day orally on an empty stomach throughout the course of the CT and for three weeks after the last CT administration. Treatments were administered for 26 weeks prior to surgery.<br><br>Following Independent Data Monitoring Committee (IDMC) recommendations, lapatinib doses were reduced to 1250 mg/day orally on an empty stomach. |
| CT Plus Trastuzumab and Lapatinib 1000 mg | Participants received CT, which included paclitaxel 80 mg/m^2 weekly for 12 weeks, followed by IV fluorouracil 600 mg/m^2, IV epidoxorubicin 75 mg/m^2, and IV cyclophosphamide 600 mg/m^2, once every 21 days for four treatment courses. Trastuzumab was administered throughout the course of the CT and for two weeks after the last CT administration. The first dose of trastuzumab was administered at 4 mg/kg IV for 60 minutes on the day of the first paclitaxel course. Subsequent administrations were given weekly at 2 mg/kg IV for 30 minutes. Participants received lapatinib 1000 mg/day orally on an empty stomach throughout the course of the CT and for three weeks after the last CT administration. Treatments were administered for 26 weeks prior to surgery.<br><br>Following IDMC recommendations, lapatinib doses were reduced to 750 mg/day orally on an empty stomach. |

Measured Values

| | CT Plus Trastuzumab | CT Plus Lapatinib 1500 mg | CT Plus Trastuzumab and Lapatinib 1000 mg |
|---|---|---|---|
| Number of Participants Analyzed | 36 | 39 | 46 |
| Number of Participants With Any Adverse Event (AE), Including Serious Adverse Events (SAEs), Occurring in >=5% of Participants<br>[units: Participants] | 35 | 38 | 46 |

8. Secondary Outcome Measure:

| | |
|---|---|
| Measure Title | Number of Variations/Somatic Mutation in PI3KCA at Baseline |
| Measure Description | Analysis of mutations in the PI3KCA gene was performed from RNA extracted from frozen tumor tissue samples (sections). A gene is either a wild-type (no mutation) or mutated (presence of a mutation). Exons 9 and 20 of the PI3KCA gene were accessed (high frequency mutation at these two spots). |
| Time Frame | Baseline |
| Safety Issue? | No |

Analysis Population Description

ITT Population. Only those participants for which high-quality tumor tissue samples were available were analyzed.

Reporting Groups

| | Description |
|---|---|
| CT Plus Trastuzumab | Participants received chemotherapy (CT), which included paclitaxel 80 milligrams per meters squared (mg/m^2) weekly for 12 weeks, followed by intravenous (IV) fluorouracil 600 mg/m^2, IV epidoxorubicin 75 mg/m^2, and IV cyclophosphamide 600 mg/m^2, once every 21 days for four treatment courses. Trastuzumab was administered throughout the course of the CT and for two weeks after the last CT administration. The first dose of trastuzumab was administered at 4 milligrams per kilogram (mg/kg) IV for 60 minutes on the day of the first paclitaxel course. Subsequent administrations were given weekly at 2 mg/kg IV for 30 minutes. Treatments were administered for 26 weeks prior to surgery. |
| CT Plus Lapatinib 1500 mg | Participants received CT, which included paclitaxel 80 mg/m^2 weekly for 12 weeks, followed by IV fluorouracil 600 mg/m^2, IV epidoxorubicin 75 mg/m^2, and IV cyclophosphamide 600 mg/m^2, once every 21 days for four treatment courses. Participants received lapatinib 1500 mg/day orally on an empty stomach throughout the course of the CT and for three weeks after the last CT administration. Treatments were administered for 26 weeks prior to surgery.<br><br>Following Independent Data Monitoring Committee (IDMC) recommendations, lapatinib doses were reduced to 1250 mg/day orally on an empty stomach. |
| CT Plus Trastuzumab and Lapatinib 1000 mg | Participants received CT, which included paclitaxel 80 mg/m^2 weekly for 12 weeks, followed by IV fluorouracil 600 mg/m^2, IV epidoxorubicin 75 mg/m^2, and IV cyclophosphamide 600 mg/m^2, once every 21 days for four treatment courses. Trastuzumab was administered throughout the course of the CT and for two weeks after the last CT administration. The first dose of trastuzumab was administered at 4 mg/kg IV for 60 minutes on the day of the first paclitaxel course. Subsequent administrations were given weekly at 2 mg/kg IV for 30 minutes. Participants received lapatinib 1000 mg/day orally on an empty stomach throughout the course of the CT and for three weeks after the last CT administration. Treatments were administered for 26 weeks prior to surgery.<br><br>Following IDMC recommendations, lapatinib doses were reduced to 750 mg/day orally on an empty stomach. |

Measured Values

| | CT Plus Trastuzumab | CT Plus Lapatinib 1500 mg | CT Plus Trastuzumab and Lapatinib 1000 mg |
|---|---|---|---|
| Number of Participants Analyzed | 30 | 37 | 42 |
| Number of Variations/Somatic Mutation in PI3KCA at Baseline<br>[units: Variations/Somatic mutations] | | | |
| PIK3CA Exon 9 Wild-Type | 29 | 35 | 39 |
| PIK3CA Exon 9 Mutation | 1 | 2 | 3 |
| PIK3CA Exon 20 Wild-type | 25 | 31 | 37 |
| PIK3CA Exon 20 Mutation | 5 | 6 | 5 |

## Reported Adverse Events

| | |
|---|---|
| Time Frame | Serious adverse events (SAEs) and non-serious AEs were collected from the first dose of randomized therapy to 30 days after the last dose of randomized therapy (up to Study Week 29). |
| Additional Description | SAEs and non-serious AEs were collected for all participants who received at least one dose of study medication. |

Reporting Groups

| | Description |
|---|---|
| CT Plus Trastuzumab | Participants received chemotherapy (CT), which included paclitaxel 80 milligrams per meters squared (mg/m^2) weekly for 12 weeks, followed by intravenous (IV) fluorouracil 600 mg/m^2, IV epidoxorubicin 75 mg/m^2, and IV cyclophosphamide 600 mg/m^2, once every 21 days for four treatment courses. Trastuzumab was administered throughout the course of the CT and for two weeks after the last CT administration. The first dose of trastuzumab was administered at 4 milligrams per kilogram (mg/kg) IV for 60 minutes on the day of the first paclitaxel course. Subsequent administrations were given weekly at 2 mg/kg IV for 30 minutes. Treatments were administered for 26 weeks prior to surgery. |
| CT Plus Lapatinib 1500 mg | Participants received CT, which included paclitaxel 80 mg/m^2 weekly for 12 weeks, followed by IV fluorouracil 600 mg/m^2, IV epidoxorubicin 75 mg/m^2, and IV cyclophosphamide 600 mg/m^2, once every 21 days for four treatment courses. Participants received lapatinib 1500 mg/day orally on an empty stomach throughout the course of the CT and for three weeks after the last CT administration. Treatments were administered for 26 weeks prior to surgery. Following Independent Data Monitoring Committee (IDMC) recommendations, lapatinib doses were reduced to 1250 mg/day orally on an empty stomach. |

| | Description |
|---|---|
| CT Plus Trastuzumab and Lapatinib 1000 mg | Participants received CT, which included paclitaxel 80 mg/m^2 weekly for 12 weeks, followed by IV fluorouracil 600 mg/m^2, IV epidoxorubicin 75 mg/m^2, and IV cyclophosphamide 600 mg/m^2, once every 21 days for four treatment courses. Trastuzumab was administered throughout the course of the CT and for two weeks after the last CT administration. The first dose of trastuzumab was administered at 4 mg/kg IV for 60 minutes on the day of the first paclitaxel course. Subsequent administrations were given weekly at 2 mg/kg IV for 30 minutes. Participants received lapatinib 1000 mg/day orally on an empty stomach throughout the course of the CT and for three weeks after the last CT administration. Treatments were administered for 26 weeks prior to surgery. Following IDMC recommendations, lapatinib doses were reduced to 750 mg/day orally on an empty stomach. |

Serious Adverse Events

| | CT Plus Trastuzumab | CT Plus Lapatinib 1500 mg | CT Plus Trastuzumab and Lapatinib 1000 mg |
|---|---|---|---|
| | Affected/At Risk (%) | Affected/At Risk (%) | Affected/At Risk (%) |
| Total | 14/36 (38.89%) | 13/39 (33.33%) | 21/46 (45.65%) |
| Blood and lymphatic system disorders | | | |
| Febrile neutropenia [A] † | 1/36 (2.78%) | 2/39 (5.13%) | 1/46 (2.17%) |
| Neutropenia [A] † | 10/36 (27.78%) | 7/39 (17.95%) | 16/46 (34.78%) |
| Gastrointestinal disorders | | | |
| Abdominal pain [A] † | 0/36 (0%) | 1/39 (2.56%) | 0/46 (0%) |
| Diarrhoea [A] † | 0/36 (0%) | 3/39 (7.69%) | 1/46 (2.17%) |
| Rectal haemorrhage [A] † | 1/36 (2.78%) | 0/39 (0%) | 0/46 (0%) |
| Stomatitis [A] † | 1/36 (2.78%) | 0/39 (0%) | 0/46 (0%) |
| Vomiting [A] † | 1/36 (2.78%) | 3/39 (7.69%) | 0/46 (0%) |
| General disorders | | | |
| Hyperpyrexia [A] † | 0/36 (0%) | 1/39 (2.56%) | 0/46 (0%) |
| Pyrexia [A] † | 1/36 (2.78%) | 1/39 (2.56%) | 0/46 (0%) |
| Immune system disorders | | | |
| Drug hypersensitivity [A] † | 0/36 (0%) | 0/39 (0%) | 1/46 (2.17%) |
| Infections and infestations | | | |

| | CT Plus Trastuzumab | CT Plus Lapatinib 1500 mg | CT Plus Trastuzumab and Lapatinib 1000 mg |
|---|---|---|---|
| | Affected/At Risk (%) | Affected/At Risk (%) | Affected/At Risk (%) |
| Device related infection [A] † | 0/36 (0%) | 0/39 (0%) | 1/46 (2.17%) |
| Fungal skin infection [A] † | 1/36 (2.78%) | 0/39 (0%) | 0/46 (0%) |
| Investigations | | | |
| Alanine aminotransferase increased [A] † | 1/36 (2.78%) | 0/39 (0%) | 3/46 (6.52%) |
| Aspartate aminotransferase increased [A] † | 0/36 (0%) | 0/39 (0%) | 1/46 (2.17%) |
| Blood bilirubin increased [A] † | 0/36 (0%) | 1/39 (2.56%) | 1/46 (2.17%) |
| Neutrophil count [A] † | 0/36 (0%) | 1/39 (2.56%) | 0/46 (0%) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Clear cell renal cell carcinoma [A] † | 0/36 (0%) | 0/39 (0%) | 1/46 (2.17%) |
| Nervous system disorders | | | |
| Syncope [A] † | 0/36 (0%) | 0/39 (0%) | 1/46 (2.17%) |
| Skin and subcutaneous tissue disorders | | | |
| Nail disorder [A] † | 0/36 (0%) | 0/39 (0%) | 1/46 (2.17%) |
| Rash [A] † | 0/36 (0%) | 1/39 (2.56%) | 0/46 (0%) |

† Indicates events were collected by systematic assessment.
A Term from vocabulary, CTCAE version 3.0

Other Adverse Events

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

| | CT Plus Trastuzumab | CT Plus Lapatinib 1500 mg | CT Plus Trastuzumab and Lapatinib 1000 mg |
|---|---|---|---|
| | Affected/At Risk (%) | Affected/At Risk (%) | Affected/At Risk (%) |
| Total | 35/36 (97.22%) | 38/39 (97.44%) | 46/46 (100%) |
| Blood and lymphatic system disorders | | | |
| Anaemia [A] † | 4/36 (11.11%) | 4/39 (10.26%) | 3/46 (6.52%) |

| | CT Plus Trastuzumab | CT Plus Lapatinib 1500 mg | CT Plus Trastuzumab and Lapatinib 1000 mg |
|---|---|---|---|
| | Affected/At Risk (%) | Affected/At Risk (%) | Affected/At Risk (%) |
| Febrile neutropenia [A] † | 0/36 (0%) | 1/39 (2.56%) | 3/46 (6.52%) |
| Leukopenia [A] † | 4/36 (11.11%) | 2/39 (5.13%) | 9/46 (19.57%) |
| Lymphadenopathy [A] † | 0/36 (0%) | 2/39 (5.13%) | 0/46 (0%) |
| Neutropenia [A] † | 22/36 (61.11%) | 19/39 (48.72%) | 31/46 (67.39%) |
| Thrombocytopenia [A] † | 3/36 (8.33%) | 1/39 (2.56%) | 0/46 (0%) |
| Gastrointestinal disorders | | | |
| Abdominal pain [A] † | 4/36 (11.11%) | 5/39 (12.82%) | 6/46 (13.04%) |
| Abdominal pain upper [A] † | 4/36 (11.11%) | 10/39 (25.64%) | 12/46 (26.09%) |
| Cheilitis [A] † | 0/36 (0%) | 2/39 (5.13%) | 1/46 (2.17%) |
| Constipation [A] † | 7/36 (19.44%) | 4/39 (10.26%) | 5/46 (10.87%) |
| Diarrhoea [A] † | 12/36 (33.33%) | 27/39 (69.23%) | 38/46 (82.61%) |
| Dyspepsia [A] † | 5/36 (13.89%) | 8/39 (20.51%) | 10/46 (21.74%) |
| Haemorrhoids [B] † | 1/36 (2.78%) | 2/39 (5.13%) | 9/46 (19.57%) |
| Lip dry [A] † | 0/36 (0%) | 2/39 (5.13%) | 0/46 (0%) |
| Nausea [A] † | 22/36 (61.11%) | 18/39 (46.15%) | 26/46 (56.52%) |
| Stomatitis [A] † | 2/36 (5.56%) | 4/39 (10.26%) | 7/46 (15.22%) |
| Vomiting [A] † | 13/36 (36.11%) | 16/39 (41.03%) | 22/46 (47.83%) |
| General disorders | | | |
| Asthenia [A] † | 17/36 (47.22%) | 10/39 (25.64%) | 12/46 (26.09%) |
| Fatigue [A] † | 7/36 (19.44%) | 6/39 (15.38%) | 6/46 (13.04%) |
| Influenza like illness [A] † | 2/36 (5.56%) | 1/39 (2.56%) | 0/46 (0%) |
| Mucosal inflammation [A] † | 2/36 (5.56%) | 6/39 (15.38%) | 7/46 (15.22%) |

| | CT Plus Trastuzumab | CT Plus Lapatinib 1500 mg | CT Plus Trastuzumab and Lapatinib 1000 mg |
|---|---|---|---|
| | Affected/At Risk (%) | Affected/At Risk (%) | Affected/At Risk (%) |
| Oedema peripheral [A] † | 2/36 (5.56%) | 2/39 (5.13%) | 1/46 (2.17%) |
| Pyrexia [A] † | 2/36 (5.56%) | 10/39 (25.64%) | 14/46 (30.43%) |
| Hepatobiliary disorders | | | |
| Hyperbilirubinaemia [B] † | 2/36 (5.56%) | 3/39 (7.69%) | 1/46 (2.17%) |
| Infections and infestations | | | |
| Conjunctivitis [A] † | 1/36 (2.78%) | 2/39 (5.13%) | 2/46 (4.35%) |
| Cystitis [A] † | 3/36 (8.33%) | 2/39 (5.13%) | 6/46 (13.04%) |
| Folliculitis [A] † | 0/36 (0%) | 2/39 (5.13%) | 5/46 (10.87%) |
| Influenza [A] † | 1/36 (2.78%) | 0/39 (0%) | 3/46 (6.52%) |
| Nasopharyngitis [A] † | 0/36 (0%) | 2/39 (5.13%) | 3/46 (6.52%) |
| Pharyngitis [A] † | 3/36 (8.33%) | 1/39 (2.56%) | 2/46 (4.35%) |
| Rhinitis [A] † | 2/36 (5.56%) | 0/39 (0%) | 1/46 (2.17%) |
| Investigations | | | |
| Alanine aminotransferase increased [A] † | 4/36 (11.11%) | 6/39 (15.38%) | 8/46 (17.39%) |
| Aspartate aminotransferase increased [A] † | 1/36 (2.78%) | 5/39 (12.82%) | 4/46 (8.7%) |
| Blood bilirubin increased [A] † | 0/36 (0%) | 2/39 (5.13%) | 3/46 (6.52%) |
| Ejection fraction decreased [A] † | 1/36 (2.78%) | 2/39 (5.13%) | 1/46 (2.17%) |
| Haemoglobin decreased [A] † | 0/36 (0%) | 2/39 (5.13%) | 1/46 (2.17%) |
| Neutrophil count decreased [A] † | 0/36 (0%) | 2/39 (5.13%) | 1/46 (2.17%) |
| White blood cell count decreased [A] † | 2/36 (5.56%) | 3/39 (7.69%) | 0/46 (0%) |
| Metabolism and nutrition disorders | | | |
| Decreased appetite [A] † | 0/36 (0%) | 2/39 (5.13%) | 4/46 (8.7%) |

| | CT Plus Trastuzumab | CT Plus Lapatinib 1500 mg | CT Plus Trastuzumab and Lapatinib 1000 mg |
|---|---|---|---|
| | Affected/At Risk (%) | Affected/At Risk (%) | Affected/At Risk (%) |
| Hypokalaemia [A] † | 1/36 (2.78%) | 1/39 (2.56%) | 4/46 (8.7%) |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia [A] † | 1/36 (2.78%) | 1/39 (2.56%) | 4/46 (8.7%) |
| Back pain [A] † | 2/36 (5.56%) | 2/39 (5.13%) | 1/46 (2.17%) |
| Bone pain [A] † | 2/36 (5.56%) | 4/39 (10.26%) | 2/46 (4.35%) |
| Drug hypersensitivity [A] † | 0/36 (0%) | 3/39 (7.69%) | 4/46 (8.7%) |
| Myalgia [A] † | 1/36 (2.78%) | 5/39 (12.82%) | 2/46 (4.35%) |
| Pain in extremity [A] † | 1/36 (2.78%) | 3/39 (7.69%) | 1/46 (2.17%) |
| Nervous system disorders | | | |
| Dizziness [A] † | 2/36 (5.56%) | 0/39 (0%) | 1/46 (2.17%) |
| Dysgeusia [A] † | 0/36 (0%) | 2/39 (5.13%) | 1/46 (2.17%) |
| Headache [A] † | 6/36 (16.67%) | 5/39 (12.82%) | 7/46 (15.22%) |
| Paraesthesia [A] † | 2/36 (5.56%) | 5/39 (12.82%) | 4/46 (8.7%) |
| Peripheral sensory neuropathy [A] † | 4/36 (11.11%) | 5/39 (12.82%) | 8/46 (17.39%) |
| Syncope [A] † | 0/36 (0%) | 1/39 (2.56%) | 6/46 (13.04%) |
| Psychiatric disorders | | | |
| Anxiety [A] † | 1/36 (2.78%) | 1/39 (2.56%) | 3/46 (6.52%) |
| Insomnia [A] † | 4/36 (11.11%) | 1/39 (2.56%) | 2/46 (4.35%) |
| Renal and urinary disorders | | | |
| Dysuria [A] † | 0/36 (0%) | 2/39 (5.13%) | 4/46 (8.7%) |
| Reproductive system and breast disorders | | | |
| Breast pain [A] † | 3/36 (8.33%) | 1/39 (2.56%) | 0/46 (0%) |

| | CT Plus Trastuzumab | CT Plus Lapatinib 1500 mg | CT Plus Trastuzumab and Lapatinib 1000 mg |
|---|---|---|---|
| | Affected/At Risk (%) | Affected/At Risk (%) | Affected/At Risk (%) |
| Vaginal haemorrhage [A] † | 0/36 (0%) | 0/39 (0%) | 3/46 (6.52%) |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough [A] † | 6/36 (16.67%) | 6/39 (15.38%) | 5/46 (10.87%) |
| Dysphonia [A] † | 0/36 (0%) | 2/39 (5.13%) | 0/46 (0%) |
| Dyspnoea [A] † | 2/36 (5.56%) | 2/39 (5.13%) | 1/46 (2.17%) |
| Epistaxis [A] † | 7/36 (19.44%) | 8/39 (20.51%) | 6/46 (13.04%) |
| Nasal inflammation [A] † | 1/36 (2.78%) | 1/39 (2.56%) | 3/46 (6.52%) |
| Oropharyngeal pain [A] † | 2/36 (5.56%) | 2/39 (5.13%) | 1/46 (2.17%) |
| Skin and subcutaneous tissue disorders | | | |
| Acne [A] † | 1/36 (2.78%) | 2/39 (5.13%) | 2/46 (4.35%) |
| Alopecia [A] † | 7/36 (19.44%) | 7/39 (17.95%) | 16/46 (34.78%) |
| Dermatitis [A] † | 0/36 (0%) | 3/39 (7.69%) | 0/46 (0%) |
| Erythema [A] † | 2/36 (5.56%) | 5/39 (12.82%) | 5/46 (10.87%) |
| Nail disorder [A] † | 4/36 (11.11%) | 6/39 (15.38%) | 8/46 (17.39%) |
| Nail dystrophy [A] † | 0/36 (0%) | 2/39 (5.13%) | 1/46 (2.17%) |
| Palmar-plantar erythrodysaesthesia syndrome [A] † | 2/36 (5.56%) | 2/39 (5.13%) | 6/46 (13.04%) |
| Pruritus [A] † | 3/36 (8.33%) | 1/39 (2.56%) | 6/46 (13.04%) |
| Rash [A] † | 3/36 (8.33%) | 20/39 (51.28%) | 17/46 (36.96%) |
| Skin toxicity [A] † | 0/36 (0%) | 1/39 (2.56%) | 6/46 (13.04%) |
| Urticaria [A] † | 0/36 (0%) | 2/39 (5.13%) | 1/46 (2.17%) |
| Vascular disorders | | | |

| | CT Plus Trastuzumab | CT Plus Lapatinib 1500 mg | CT Plus Trastuzumab and Lapatinib 1000 mg |
|---|---|---|---|
| | Affected/At Risk (%) | Affected/At Risk (%) | Affected/At Risk (%) |
| Hot flush [A] † | 1/36 (2.78%) | 2/39 (5.13%) | 2/46 (4.35%) |
| Hypertension [A] † | 5/36 (13.89%) | 2/39 (5.13%) | 4/46 (8.7%) |
| Hypotension [A] † | 0/36 (0%) | 2/39 (5.13%) | 0/46 (0%) |

† Indicates events were collected by systematic assessment.
A Term from vocabulary, CTCAE version 3.0
B Term from vocabulary, CTCAE version 3.0s

## Limitations and Caveats

[Not specified]

## More Information

Certain Agreements:

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

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

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

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