ClinicalTrials.gov Protocol Registration and Results System (PRS) Receipt
Release Date: 07/05/2016

ClinicalTrials.gov ID: NCT00717405

Study Identification

Unique Protocol ID:	ML21531
Brief Title:	A Study of Avastin (Bevacizumab) Plus Herceptin (Trastuzumab) in Patients With Primary Inflammatory HER2-Positive Breast Cancer.
Official Title:	An Open Label Study to Assess the Rate of Pathological Complete Response in Patients With Primary Inflammatory HER2-positive Breast Cancer Treated With Avastin + Herceptin Based Chemotherapy
Secondary IDs:	2008-000783-16

Study Status

Record Verification:	July 2016
Overall Status:	Completed
Study Start:	October 2008
Primary Completion:	April 2010 [Actual]
Study Completion:	October 2014 [Actual]

Sponsor/Collaborators

Sponsor:	Hoffmann-La Roche
Responsible Party:	Sponsor
Collaborators:	

Oversight

FDA Regulated?:	No

IND/IDE Protocol?:	No
Review Board:	Approval Status: Approved Approval Number: 2008-000783-16 Board Name: Sud-Mediterranee I Board Affiliation: unknown Phone: +33 491223425 Email: cppsudmed1@gmail.com
Data Monitoring?:	
Plan to Share Data?:	
Oversight Authorities:	France: Agence francaise de securite sanitaire des produits de sante (AFSSAPS)

Study Description

Brief Summary:	This single arm study will assess the efficacy and safety of preoperative treatment with Avastin combined with Herceptin-based chemotherapy in patients with primary inflammatory HER2-positive breast cancer. Patients will be treated with a total of 8 cycles of pre-operative chemotherapy + Avastin + Herceptin. The anticipated time on study treatment is 3-12 months, and the target sample size is <100 individuals.
Detailed Description:	

Conditions

Conditions:	Breast Cancer
Keywords:	

Study Design

Study Type:	Interventional
Primary Purpose:	Treatment
Study Phase:	Phase 2
Intervention Model:	Single Group Assignment
Number of Arms:	1
Masking:	Open Label
Allocation:	N/A
Endpoint Classification:	Safety/Efficacy Study

Enrollment: 52 [Actual]

Arms and Interventions

Arms	Assigned Interventions
Experimental: 1	Drug: Standard chemotherapy As prescribed Drug: bevacizumab [Avastin] 15mg/kg iv 3 weekly in cycles 1-8 Drug: trastuzumab [Herceptin] 8mg/kg iv loading dose followed by 6mg/kg iv 3 weekly in cycles 5-8.

Outcome Measures

[See Results Section.]

Eligibility

Minimum Age: 18 Years

Maximum Age:

Gender: Female

Accepts Healthy Volunteers?: No

Criteria: Inclusion Criteria:

- adult females, >=18 years of age;
- inflammatory breast cancer;
- HER2-positive tumors;
- performance status 0-2.

Exclusion Criteria:

- metastases;
- previous treatment with chemotherapy, radiation therapy or hormone therapy for a breast tumor;
- clinically significant cardiovascular disease, or history of thrombotic disorders.

Contacts/Locations

Study Officials: Clinical Trials
Study Director

Hoffmann-La Roche

Locations: France

Marseille, France, 13273

Lyon, France, 69373

Saint Herblain, France, 44805

Caen, France, 14076

Nice, France, 06189

Dijon, France, 21079

Montpellier, France, 34298

St Cloud, France, 92210

Paris, France, 75231

Toulouse, France, 31059

Villejuif, France, 94805

Rouen, France, 76038

Rennes, France, 35042

Strasbourg, France, 67065

Clermont Ferrand, France, 63011

Vandoeuvre Les Nancy, France, 54511

Reims CEDEX, France, 51056

Paris, France, 75970

Paris, France, 75475

Saint Brieuc, France, 22015

Besancon, France, 25030

Brest, France, 29609

St Priest En Jarez, France, 42271

La Tronche, France, 38700

Bordeaux, France, 33000

Lille, France, 59020

Nantes, France, 44202

Strasbourg, France, 67098

References

Citations:

Links:

Study Data/Documents:

Study Results

Participant Flow

Reporting Groups

	Description
Bevacizumab + Trastuzumab Chemotherapy	Neoadjuvant treatment (Cycles 1-8, 3-week cycle): Participants received 15 milligrams per kilogram (mg/kg) intravenous (IV) bevacizumab every 3 weeks (q3w) for 8 cycles, 4 cycles of 500 milligrams per squared-meter (mg/m^2) IV 5-fluorouracil, 100 mg/m^2 IV epirubicin, and 500 mg/m^2 IV cyclophosphamide, q3w, followed by 4 cycles of 100 mg/m^2 IV docetaxel q3w plus trastuzumab (loading dose of 8 mg/kg and then 6 mg/kg q3w). Participants underwent surgery (mastectomy) after neoadjuvant treatment, maintaining trastuzumab (6 mg/kg). Adjuvant treatment: Participants received radiotherapy 2-4 weeks after surgery and lasted for 4-6 weeks, 6 mg/kg IV trastuzumab q3w and 15 mg/kg IV bevacizumab q3w administered along with/after the radiotherapy (administered up to a cumulative [neoadjuvant + adjuvant] total of 18 injections each. Hormonal therapy (at investigator discretion) after the end of radiotherapy was administered for 5 years, if participant was hormone receptor positive.

Overall Study

	Bevacizumab + Trastuzumab Chemotherapy
Started	52

	Bevacizumab + Trastuzumab Chemotherapy
Completed	52
Not Completed	0

Baseline Characteristics

Analysis Population Description

Intent to treat population (ITT): Included all enrolled participants who had at least 1 post baseline assessment.

Reporting Groups

	Description
Bevacizumab + Trastuzumab	Neoadjuvant treatment (Cycles 1-8, 3-week cycle): Participants received 15 mg/kg IV bevacizumab q3w for 8 cycles, 4 cycles of 500 mg/m^2 IV 5-fluorouracil, 100 mg/m^2 IV epirubicin, and 500 mg/m^2 IV cyclophosphamide, q3w, followed by 4 cycles of 100 mg/m^2 IV docetaxel q3w plus trastuzumab (loading dose of 8 mg/kg and then 6 mg/kg q3w). Participants underwent surgery (mastectomy) after neoadjuvant treatment, maintaining trastuzumab (6 mg/kg). Adjuvant treatment: Participants received radiotherapy 2-4 weeks after surgery and lasted for 4-6 weeks, 6 mg/kg IV trastuzumab q3w and 15 mg/kg IV bevacizumab q3w administered along with/after the radiotherapy (administered up to a cumulative [neoadjuvant + adjuvant] total of 18 injections each. Hormonal therapy (at investigator discretion) after the end of radiotherapy was administered for 5 years, if participant was hormone receptor positive.

Baseline Measures

	Bevacizumab + Trastuzumab
Number of Participants	52
Age, Continuous [units: years] Mean (Standard Deviation)	51.48 (9.78)
Gender, Male/Female [units: participants]	
Female	52
Male	0

Outcome Measures

1. Primary Outcome Measure:

Measure Title	Percentage of Participants With a Pathological Complete Response (PCR) According to the Sataloff Classification

Measure Description	PCR was assessed at the time of definitive surgery according to Sataloff classification and centrally reviewed by an independent committee under blinded conditions. Pathological response was defined based on the therapeutic response at the primary tumor site and axillary lymph nodes. Primary tumor response criteria were as follows: T-A (Total / near total therapeutic effect), T-B (Subjectively greater than [>] 50 percent [%] therapeutic effect but less than [<] T-A), T-C (<50% therapeutic effect, but effect evident), T-D (No therapeutic effect). Axillary lymph node response: N-A (Evidence of therapeutic effect, no metastases), N-B (No therapeutic effect, no nodal metastases), N-C (Nodal metastasis but evident therapeutic effect), N-D (Nodal metastasis with no therapeutic effect). T-A and N-A or T-A and N-B responses were defined as PCR and all other tumor responses as non-responders. Participants with missing values were considered as non-responders.
Time Frame	From baseline through Week 25 (Up to 6 months)
Safety Issue?	No

Analysis Population Description

ITT population.

Reporting Groups

	Description
Bevacizumab + Trastuzumab	Neoadjuvant treatment (Cycles 1-8, 3-week cycle): Participants received 15 mg/kg IV bevacizumab q3w for 8 cycles, 4 cycles of 500 mg/m^2 IV 5-fluorouracil, 100 mg/m^2 IV epirubicin, and 500 mg/m^2 IV cyclophosphamide, q3w, followed by 4 cycles of 100 mg/m^2 IV docetaxel q3w plus trastuzumab (loading dose of 8 mg/kg and then 6 mg/kg q3w). Participants underwent surgery (mastectomy) after neoadjuvant treatment, maintaining trastuzumab (6 mg/kg). Adjuvant treatment: Participants received radiotherapy 2-4 weeks after surgery and lasted for 4-6 weeks, 6 mg/kg IV trastuzumab q3w and 15 mg/kg IV bevacizumab q3w administered along with/after the radiotherapy (administered up to a cumulative [neoadjuvant + adjuvant] total of 18 injections each. Hormonal therapy (at investigator discretion) after the end of radiotherapy was administered for 5 years, if participant was hormone receptor positive.

Measured Values

	Bevacizumab + Trastuzumab
Number of Participants Analyzed	52
Percentage of Participants With a Pathological Complete Response (PCR) According to the Sataloff Classification [units: percentage of participants] Number (95% Confidence Interval)	63.46 (49.41 to 77.51)

2. Secondary Outcome Measure:

Measure Title	Percentage of Participants With a PCR According to the Chevallier Classification

Measure Description	PCR was assessed at the time of definitive surgery according to Chevallier classification and centrally reviewed by an independent committee under blinded conditions. The Chevallier classification for grading of therapeutic effect related to the primary tumor site and axillary lymph nodes was defined by microscopic changes as follows - Grade 1: Disappearance of all tumors either in the breast or in the nodes, Grade 2: Persistence of carcinoma in situ in the breast only and no nodal invasion, Grade 3: Presence of invasive carcinoma with stromal alteration, Grade 4: Presence of invasive carcinoma without modification. Grade 1 response was considered as PCR. Participants with missing values were considered as non-responders.
Time Frame	From baseline through Week 25 (Up to 6 months)
Safety Issue?	No

Analysis Population Description
ITT population.

Reporting Groups

	Description
Bevacizumab + Trastuzumab	Neoadjuvant treatment (Cycles 1-8, 3-week cycle): Participants received 15 mg/kg IV bevacizumab q3w for 8 cycles, 4 cycles of 500 mg/m^2 IV 5-fluorouracil, 100 mg/m^2 IV epirubicin, and 500 mg/m^2 IV cyclophosphamide, q3w, followed by 4 cycles of 100 mg/m^2 IV docetaxel q3w plus trastuzumab (loading dose of 8 mg/kg and then 6 mg/kg q3w). Participants underwent surgery (mastectomy) after neoadjuvant treatment, maintaining trastuzumab (6 mg/kg). Adjuvant treatment: Participants received radiotherapy 2-4 weeks after surgery and lasted for 4-6 weeks, 6 mg/kg IV trastuzumab q3w and 15 mg/kg IV bevacizumab q3w administered along with/after the radiotherapy (administered up to a cumulative [neoadjuvant + adjuvant] total of 18 injections each. Hormonal therapy (at investigator discretion) after the end of radiotherapy was administered for 5 years, if participant was hormone receptor positive.

Measured Values

	Bevacizumab + Trastuzumab
Number of Participants Analyzed	52
Percentage of Participants With a PCR According to the Chevallier Classification [units: percentage of participants] Number (95% Confidence Interval)	53.85 (39.34 to 68.36)

3. Secondary Outcome Measure:

Measure Title	Percentage of Participants Who Were Responders Based on Inflammatory Signs From Baseline at Cycle 5 and Final Treatment Visit

Measure Description	Breast tumor was physically evaluated during the study which included assessment for inflammatory signs and for overall clinical response. Participant with response from baseline based on inflammatory signs at Cycle 5 and final treatment visit were presented.
Time Frame	Baseline, Cycle 5 (Week 15), Neo-adjuvant treatment final visit (Week 25)
Safety Issue?	No

Analysis Population Description

ITT population. Number of participants analyzed included participants for whom tumor physical examination was performed and were evaluated for response from baseline assessment of inflammatory signs. n included number of participants who were evaluable at a particular time point.

Reporting Groups

	Description
Bevacizumab + Trastuzumab	Neoadjuvant treatment (Cycles 1-8, 3-week cycle): Participants received 15 mg/kg IV bevacizumab q3w for 8 cycles, 4 cycles of 500 mg/m^2 IV 5-fluorouracil, 100 mg/m^2 IV epirubicin, and 500 mg/m^2 IV cyclophosphamide, q3w, followed by 4 cycles of 100 mg/m^2 IV docetaxel q3w plus trastuzumab (loading dose of 8 mg/kg and then 6 mg/kg q3w). Participants underwent surgery (mastectomy) after neoadjuvant treatment, maintaining trastuzumab (6 mg/kg). Adjuvant treatment: Participants received radiotherapy 2-4 weeks after surgery and lasted for 4-6 weeks, 6 mg/kg IV trastuzumab q3w and 15 mg/kg IV bevacizumab q3w administered along with/after the radiotherapy (administered up to a cumulative [neoadjuvant + adjuvant] total of 18 injections each. Hormonal therapy (at investigator discretion) after the end of radiotherapy was administered for 5 years, if participant was hormone receptor positive.

Measured Values

	Bevacizumab + Trastuzumab
Number of Participants Analyzed	43
Percentage of Participants Who Were Responders Based on Inflammatory Signs From Baseline at Cycle 5 and Final Treatment Visit [units: percentage of participants]	
Response from baseline at Week 15 (n=43)	88.4
Response from baseline at Week 25 (n=42)	100.0

4. Secondary Outcome Measure:

Measure Title	Percentage of Participants Who Were Responders Based on Overall Clinical Response From Baseline at Cycle 5 and Final Treatment Visit

Measure Description	Breast tumor was physically evaluated during the study which included assessment for inflammatory signs and for overall clinical response. Participant with response from baseline based on overall clinical response at Cycle 5 and final treatment visit were presented.
Time Frame	Baseline, Cycle 5 (Week 15), Neo-adjuvant treatment final visit (Week 25)
Safety Issue?	No

Analysis Population Description

ITT population. Number of participants analyzed included participants for whom tumor physical examination was performed. n included number of participants who were evaluable at a particular time point.

Reporting Groups

	Description
Bevacizumab + Trastuzumab	Neoadjuvant treatment (Cycles 1-8, 3-week cycle): Participants received 15 mg/kg IV bevacizumab q3w for 8 cycles, 4 cycles of 500 mg/m^2 IV 5-fluorouracil, 100 mg/m^2 IV epirubicin, and 500 mg/m^2 IV cyclophosphamide, q3w, followed by 4 cycles of 100 mg/m^2 IV docetaxel q3w plus trastuzumab (loading dose of 8 mg/kg and then 6 mg/kg q3w). Participants underwent surgery (mastectomy) after neoadjuvant treatment, maintaining trastuzumab (6 mg/kg). Adjuvant treatment: Participants received radiotherapy 2-4 weeks after surgery and lasted for 4-6 weeks, 6 mg/kg IV trastuzumab q3w and 15 mg/kg IV bevacizumab q3w administered along with/after the radiotherapy (administered up to a cumulative [neoadjuvant + adjuvant] total of 18 injections each. Hormonal therapy (at investigator discretion) after the end of radiotherapy was administered for 5 years, if participant was hormone receptor positive.

Measured Values

	Bevacizumab + Trastuzumab
Number of Participants Analyzed	45
Percentage of Participants Who Were Responders Based on Overall Clinical Response From Baseline at Cycle 5 and Final Treatment Visit [units: percentage of participants]	
Response from baseline at Week 15 (n=44)	90.9
Response from baseline at Week 25 (n=45)	97.8

5. Secondary Outcome Measure:

Measure Title	Number of Participants Who Underwent Mastectomy
Measure Description	Surgery included a mastectomy with axillary node dissection and had to be performed at least 4 weeks after the last infusion of neoadjuvant bevacizumab treatment.

Time Frame	Anytime between Week 26 and Week 29
Safety Issue?	No

Analysis Population Description
ITT population.

Reporting Groups

	Description
Bevacizumab + Trastuzumab	Neoadjuvant treatment (Cycles 1-8, 3-week cycle): Participants received 15 mg/kg IV bevacizumab q3w for 8 cycles, 4 cycles of 500 mg/m^2 IV 5-fluorouracil, 100 mg/m^2 IV epirubicin, and 500 mg/m^2 IV cyclophosphamide, q3w, followed by 4 cycles of 100 mg/m^2 IV docetaxel q3w plus trastuzumab (loading dose of 8 mg/kg and then 6 mg/kg q3w). Participants underwent surgery (mastectomy) after neoadjuvant treatment, maintaining trastuzumab (6 mg/kg). Adjuvant treatment: Participants received radiotherapy 2-4 weeks after surgery and lasted for 4-6 weeks, 6 mg/kg IV trastuzumab q3w and 15 mg/kg IV bevacizumab q3w administered along with/after the radiotherapy (administered up to a cumulative [neoadjuvant + adjuvant] total of 18 injections each. Hormonal therapy (at investigator discretion) after the end of radiotherapy was administered for 5 years, if participant was hormone receptor positive.

Measured Values

	Bevacizumab + Trastuzumab
Number of Participants Analyzed	52
Number of Participants Who Underwent Mastectomy [units: participants]	49

6. Secondary Outcome Measure:

Measure Title	Percentage of Participants With Macroscopically Visible Tumor
Measure Description	Local pathologists assessed the tumor whether it was macroscopically visible or not and percentage of participants for whom the tumor was macroscopically visible was reported.
Time Frame	Anytime between Week 26 and Week 29
Safety Issue?	No

Analysis Population Description
ITT population. Included participants who underwent mastectomy.

Reporting Groups

	Description
Bevacizumab + Trastuzumab	Neoadjuvant treatment (Cycles 1-8, 3-week cycle): Participants received 15 mg/kg IV bevacizumab q3w for 8 cycles, 4 cycles of 500 mg/m^2 IV 5-fluorouracil, 100 mg/m^2 IV epirubicin, and 500 mg/m^2 IV cyclophosphamide, q3w, followed by 4 cycles of 100 mg/m^2 IV docetaxel q3w plus trastuzumab (loading dose of 8 mg/kg and then 6 mg/kg q3w). Participants underwent surgery (mastectomy) after neoadjuvant treatment, maintaining trastuzumab (6 mg/kg). Adjuvant treatment: Participants received radiotherapy 2-4 weeks after surgery and lasted for 4-6 weeks, 6 mg/kg IV trastuzumab q3w and 15 mg/kg IV bevacizumab q3w administered along with/after the radiotherapy (administered up to a cumulative [neoadjuvant + adjuvant] total of 18 injections each. Hormonal therapy (at investigator discretion) after the end of radiotherapy was administered for 5 years, if participant was hormone receptor positive.

Measured Values

	Bevacizumab + Trastuzumab
Number of Participants Analyzed	49
Percentage of Participants With Macroscopically Visible Tumor [units: percentage of participants]	26.5

7. Secondary Outcome Measure:

Measure Title	Percentage of Participants Who Underwent Lymph Node Resection
Measure Description	Among the participants who were planned to undergo mastectomy, lymph node resection was also performed by the physician depending up on the participant's breast cancer grades.
Time Frame	Anytime between Week 26 and Week 29
Safety Issue?	No

Analysis Population Description

ITT population. Included participants who underwent mastectomy.

Reporting Groups

	Description
Bevacizumab + Trastuzumab	Neoadjuvant treatment (Cycles 1-8, 3-week cycle): Participants received 15 mg/kg IV bevacizumab q3w for 8 cycles, 4 cycles of 500 mg/m^2 IV 5-fluorouracil, 100 mg/m^2 IV epirubicin, and 500 mg/m^2 IV cyclophosphamide, q3w, followed by 4 cycles of 100 mg/m^2 IV docetaxel q3w plus trastuzumab (loading dose of 8 mg/kg and then 6 mg/kg q3w). Participants underwent surgery (mastectomy) after neoadjuvant treatment, maintaining trastuzumab (6 mg/kg). Adjuvant treatment: Participants received radiotherapy 2-4 weeks after surgery and lasted for 4-6 weeks, 6 mg/kg IV trastuzumab q3w and 15 mg/kg IV bevacizumab q3w administered along with/after the radiotherapy (administered up to a cumulative [neoadjuvant + adjuvant] total of 18 injections each. Hormonal therapy (at investigator discretion) after the end of radiotherapy was administered for 5 years, if participant was hormone receptor positive.

Measured Values

	Bevacizumab + Trastuzumab
Number of Participants Analyzed	49
Percentage of Participants Who Underwent Lymph Node Resection [units: percentage of participants]	98.0

8. Secondary Outcome Measure:

Measure Title	Breast Cancer Marker CA15.3 at Baseline, Neoadjuvant Final Visit and Change From Baseline at Neoadjuvant Final Visit
Measure Description	
Time Frame	Baseline, Neoadjuvant Final Visit (Week 25)
Safety Issue?	No

Analysis Population Description

Safety population: Number of participants included all the participants who received at least one infusion of bevacizumab. n included participants who were evaluable at that time point.

Reporting Groups

	Description
Bevacizumab + Trastuzumab	Neoadjuvant treatment (Cycles 1-8, 3-week cycle): Participants received 15 mg/kg IV bevacizumab q3w for 8 cycles, 4 cycles of 500 mg/m^2 IV 5-fluorouracil, 100 mg/m^2 IV epirubicin, and 500 mg/m^2 IV cyclophosphamide, q3w, followed by 4 cycles of 100 mg/m^2 IV docetaxel q3w plus trastuzumab (loading dose of 8 mg/kg and then 6 mg/kg q3w). Participants underwent surgery (mastectomy) after neoadjuvant treatment, maintaining trastuzumab (6 mg/kg). Adjuvant treatment: Participants received radiotherapy 2-4 weeks after surgery and lasted for 4-6 weeks, 6 mg/kg IV trastuzumab q3w and 15 mg/kg IV bevacizumab q3w administered along with/after the radiotherapy (administered up to a cumulative [neoadjuvant + adjuvant] total of 18 injections each. Hormonal therapy (at investigator discretion) after the end of radiotherapy was administered for 5 years, if participant was hormone receptor positive.

Measured Values

	Bevacizumab + Trastuzumab
Number of Participants Analyzed	52
Breast Cancer Marker CA15.3 at Baseline, Neoadjuvant Final Visit and Change From Baseline at Neoadjuvant Final Visit [units: Units per milliliter (U/mL)] Mean (Standard Deviation)	
Baseline (n=52)	39.66 (79.49)
Neoadjuvant final visit (n=37)	29.39 (10.06)
Change in CA15.3 at neoadjuvant final visit (n=37)	-3.39 (33.05)

9. Secondary Outcome Measure:

Measure Title	Percentage of Participants Who Were Disease Free at 3 and 5 Years
Measure Description	A participant was considered disease free if the participant did not experience any of the following events: local recurrence in the ipsilateral breast following lumpectomy, regional recurrence, distant recurrence, contralateral breast cancer, second primary cancer (other than squamous or basal cell carcinoma of the skin, melanoma in situ, carcinoma in situ of the cervix, colon carcinoma in situ, or lobular carcinoma in situ of the breast), or death from any cause.
Time Frame	3, 5 years
Safety Issue?	No

Analysis Population Description

ITT population.

Reporting Groups

	Description
Bevacizumab + Trastuzumab	Neoadjuvant treatment (Cycles 1-8, 3-week cycle): Participants received 15 mg/kg IV bevacizumab q3w for 8 cycles, 4 cycles of 500 mg/m^2 IV 5-fluorouracil, 100 mg/m^2 IV epirubicin, and 500 mg/m^2 IV cyclophosphamide, q3w, followed by 4 cycles of 100 mg/m^2 IV docetaxel q3w plus trastuzumab (loading dose of 8 mg/kg and then 6 mg/kg q3w). Participants underwent surgery (mastectomy) after neoadjuvant treatment, maintaining trastuzumab (6 mg/kg). Adjuvant treatment: Participants received radiotherapy 2-4 weeks after surgery and lasted for 4-6 weeks, 6 mg/kg IV trastuzumab q3w and 15 mg/kg IV bevacizumab q3w administered along with/after the radiotherapy (administered up to a cumulative [neoadjuvant + adjuvant] total of 18 injections each. Hormonal therapy (at investigator discretion) after the end of radiotherapy was administered for 5 years, if participant was hormone receptor positive.

Measured Values

	Bevacizumab + Trastuzumab
Number of Participants Analyzed	52
Percentage of Participants Who Were Disease Free at 3 and 5 Years [units: percentage of participants] Number (95% Confidence Interval)	
3 years	66.7 (52.0 to 77.8)
5 years	60.8 (46.1 to 72.7)

10. Secondary Outcome Measure:

Measure Title	Disease Free Survival (DFS) Duration
Measure Description	DFS was estimated using Kaplan-Meier method.
Time Frame	Up to 5 Years
Safety Issue?	No

Analysis Population Description

ITT population.

Reporting Groups

	Description
Bevacizumab + Trastuzumab	Neoadjuvant treatment (Cycles 1-8, 3-week cycle): Participants received 15 mg/kg IV bevacizumab q3w for 8 cycles, 4 cycles of 500 mg/m^2 IV 5-fluorouracil, 100 mg/m^2 IV epirubicin, and 500 mg/m^2 IV cyclophosphamide, q3w, followed by 4 cycles of 100 mg/m^2 IV docetaxel q3w plus trastuzumab (loading dose of 8 mg/kg and then 6 mg/kg q3w). Participants underwent surgery (mastectomy) after neoadjuvant treatment, maintaining trastuzumab (6 mg/kg). Adjuvant treatment: Participants received radiotherapy 2-4 weeks after surgery and lasted for 4-6 weeks, 6 mg/kg IV trastuzumab q3w and 15 mg/kg IV bevacizumab q3w administered along with/after the radiotherapy (administered up to a cumulative [neoadjuvant + adjuvant] total of 18 injections each. Hormonal therapy (at investigator discretion) after the end of radiotherapy was administered for 5 years, if participant was hormone receptor positive.

Measured Values

	Bevacizumab + Trastuzumab
Number of Participants Analyzed	52
Disease Free Survival (DFS) Duration [units: months] Median (95% Confidence Interval)	NA (NA to NA) [1]

[1] Using Kaplan-Meier method, median DFS was not reached due to higher (>50%) number of censored participants.

11. Secondary Outcome Measure:

Measure Title	Percentage of Participants Who Were Recurrence Free at 3 and 5 Years
Measure Description	A participant was considered recurrence free if the participant did not experience local or regional recurrence (wall or axillaries nodes), or occurrence of distant metastases (including soft tissue and distal lymph nodes).
Time Frame	3, 5 years
Safety Issue?	No

Analysis Population Description

ITT population.

Reporting Groups

	Description
Bevacizumab + Trastuzumab	Neoadjuvant treatment (Cycles 1-8, 3-week cycle): Participants received 15 mg/kg IV bevacizumab q3w for 8 cycles, 4 cycles of 500 mg/m^2 IV 5-fluorouracil, 100 mg/m^2 IV epirubicin, and 500 mg/m^2 IV cyclophosphamide, q3w, followed by 4 cycles of 100 mg/m^2 IV docetaxel q3w plus trastuzumab (loading dose of 8 mg/kg and then 6 mg/kg q3w). Participants underwent surgery (mastectomy) after neoadjuvant treatment, maintaining trastuzumab (6 mg/kg). Adjuvant treatment: Participants received radiotherapy 2-4 weeks after surgery and lasted for 4-6 weeks, 6 mg/kg IV trastuzumab q3w and 15 mg/kg IV bevacizumab q3w administered along with/after the radiotherapy (administered up to a cumulative [neoadjuvant + adjuvant] total of 18 injections each. Hormonal therapy (at investigator discretion) after the end of radiotherapy was administered for 5 years, if participant was hormone receptor positive.

Measured Values

	Bevacizumab + Trastuzumab
Number of Participants Analyzed	52
Percentage of Participants Who Were Recurrence Free at 3 and 5 Years [units: percentage of participants] Number (95% Confidence Interval)	
3 years	69.7 (54.8 to 80.5)
5 years	65.4 (50.4 to 76.9)

12. Secondary Outcome Measure:

Measure Title	Recurrence Free Survival (RFS) Duration
Measure Description	RFS was estimated using Kaplan-Meier method.
Time Frame	Up to 5 Years
Safety Issue?	No

Analysis Population Description

ITT population.

Reporting Groups

	Description
Bevacizumab + Trastuzumab	Neoadjuvant treatment (Cycles 1-8, 3-week cycle): Participants received 15 mg/kg IV bevacizumab q3w for 8 cycles, 4 cycles of 500 mg/m^2 IV 5-fluorouracil, 100 mg/m^2 IV epirubicin, and 500 mg/m^2 IV cyclophosphamide, q3w, followed by 4 cycles of 100 mg/m^2 IV docetaxel q3w plus trastuzumab (loading dose of 8 mg/kg and then 6 mg/kg q3w). Participants underwent surgery (mastectomy) after neoadjuvant treatment, maintaining trastuzumab (6 mg/kg). Adjuvant treatment: Participants received radiotherapy 2-4 weeks after surgery and lasted for 4-6 weeks, 6 mg/kg IV trastuzumab q3w and 15 mg/kg IV bevacizumab q3w administered along with/after the radiotherapy (administered up to a cumulative [neoadjuvant + adjuvant] total of 18 injections each. Hormonal therapy (at investigator discretion) after the end of radiotherapy was administered for 5 years, if participant was hormone receptor positive.

Measured Values

	Bevacizumab + Trastuzumab
Number of Participants Analyzed	52
Recurrence Free Survival (RFS) Duration [units: months] Median (95% Confidence Interval)	NA (NA to NA) [1]

[1] Using Kaplan-Meier method, median RFS was not reached due to higher (>50%) number of censored participants.

13. Secondary Outcome Measure:

Measure Title	Percentage of Participants Who Were Alive at 3 and 5 Years
Measure Description	
Time Frame	3, 5 years
Safety Issue?	No

Analysis Population Description

ITT population.

Reporting Groups

	Description
Bevacizumab + Trastuzumab	Neoadjuvant treatment (Cycles 1-8, 3-week cycle): Participants received 15 mg/kg IV bevacizumab q3w for 8 cycles, 4 cycles of 500 mg/m^2 IV 5-fluorouracil, 100 mg/m^2 IV epirubicin, and 500 mg/m^2 IV cyclophosphamide, q3w, followed by 4 cycles of 100 mg/m^2 IV docetaxel q3w plus trastuzumab (loading dose of 8 mg/kg and then 6 mg/kg q3w). Participants underwent surgery (mastectomy) after neoadjuvant treatment, maintaining trastuzumab (6 mg/kg). Adjuvant treatment: Participants received radiotherapy 2-4 weeks after surgery and lasted for 4-6 weeks, 6 mg/kg IV trastuzumab q3w and 15 mg/kg IV bevacizumab q3w administered along with/after the radiotherapy (administered up to a cumulative [neoadjuvant + adjuvant] total of 18 injections each. Hormonal therapy (at investigator discretion) after the end of radiotherapy was administered for 5 years, if participant was hormone receptor positive.

Measured Values

	Bevacizumab + Trastuzumab
Number of Participants Analyzed	52
Percentage of Participants Who Were Alive at 3 and 5 Years [units: percentage of participants] Number (95% Confidence Interval)	
Alive at 3 years	90.0 (77.6 to 95.7)
Alive at 5 years	81.8 (67.9 to 90.1)

14. Secondary Outcome Measure:

Measure Title	Overall Survival (OS) Duration
Measure Description	OS was defined as the time from the first administration of neoadjuvant treatment to death of any cause. OS was estimated using Kaplan-Meier method.
Time Frame	Up to 5 years
Safety Issue?	No

Analysis Population Description

ITT population.

Reporting Groups

	Description
Bevacizumab + Trastuzumab	Neoadjuvant treatment (Cycles 1-8, 3-week cycle): Participants received 15 mg/kg IV bevacizumab q3w for 8 cycles, 4 cycles of 500 mg/m^2 IV 5-fluorouracil, 100 mg/m^2 IV epirubicin, and 500 mg/m^2 IV cyclophosphamide, q3w, followed by 4 cycles of 100 mg/m^2 IV docetaxel q3w plus trastuzumab (loading dose of 8 mg/kg and then 6 mg/kg q3w). Participants underwent surgery (mastectomy) after neoadjuvant treatment, maintaining trastuzumab (6 mg/kg). Adjuvant treatment: Participants received radiotherapy 2-4 weeks after surgery and lasted for 4-6 weeks, 6 mg/kg IV trastuzumab q3w and 15 mg/kg IV bevacizumab q3w administered along with/after the radiotherapy (administered up to a cumulative [neoadjuvant + adjuvant] total of 18 injections each. Hormonal therapy (at investigator discretion) after the end of radiotherapy was administered for 5 years, if participant was hormone receptor positive.

Measured Values

	Bevacizumab + Trastuzumab
Number of Participants Analyzed	52
Overall Survival (OS) Duration [units: months] Median (95% Confidence Interval)	NA (NA to NA) [1]

[1] Using Kaplan-Meier method, Median OS was not reached due to higher (>50%) number of censored participants

Reported Adverse Events

Time Frame	From Baseline until end of study (Up to approximately 6 years)
Additional Description	[Not specified]

Reporting Groups

	Description
Bevacizumab + Trastuzumab	Neoadjuvant treatment (Cycles 1-8, 3-week cycle): Participants received 15 mg/kg IV bevacizumab q3w for 8 cycles, 4 cycles of 500 mg/m^2 IV 5-fluorouracil, 100 mg/m^2 IV epirubicin, and 500 mg/m^2 IV cyclophosphamide, q3w, followed by 4 cycles of 100 mg/m^2 IV docetaxel q3w plus trastuzumab (loading dose of 8 mg/kg and then 6 mg/kg q3w). Participants underwent surgery (mastectomy) after neoadjuvant treatment, maintaining trastuzumab (6 mg/kg). Adjuvant treatment: Participants received radiotherapy 2-4 weeks after surgery and lasted for 4-6 weeks, 6 mg/kg IV trastuzumab q3w and 15 mg/kg IV bevacizumab q3w administered along with/after the radiotherapy (administered up to a cumulative [neoadjuvant + adjuvant] total of 18 injections each. Hormonal therapy (at investigator discretion) after the end of radiotherapy was administered for 5 years, if participant was hormone receptor positive.

Serious Adverse Events

	Bevacizumab + Trastuzumab
	Affected/At Risk (%)
Total	20/52 (38.46%)
Blood and lymphatic system disorders	
Febrile bone marrow aplasia [A] *	5/52 (9.62%)
Febrile neutropenia [A] *	6/52 (11.54%)
Leukopenia [A] *	6/52 (11.54%)
Cardiac disorders	
Atrial tachycardia [A] *	1/52 (1.92%)
Gastrointestinal disorders	
Tooth loss [A] *	1/52 (1.92%)
Vomiting [A] *	1/52 (1.92%)
General disorders	
Hyperthermia [A] *	1/52 (1.92%)
Impaired healing [A] *	3/52 (5.77%)
Inflammation [A] *	1/52 (1.92%)
Malaise [A] *	1/52 (1.92%)
Pyrexia [A] *	1/52 (1.92%)
Infections and infestations	
Anal abscess [A] *	2/52 (3.85%)
Appendicitis [A] *	1/52 (1.92%)
Incision site abscess [A] *	1/52 (1.92%)
Pyelonephritis [A] *	1/52 (1.92%)
Septic shock [A] *	1/52 (1.92%)

	Bevacizumab + Trastuzumab
	Affected/At Risk (%)
Injury, poisoning and procedural complications	
Spinal fracture [A] *	1/52 (1.92%)
Investigations	
Ejection fraction decreased [A] *	2/52 (3.85%)
Musculoskeletal and connective tissue disorders	
Back pain [A] *	1/52 (1.92%)
Reproductive system and breast disorders	
Metrorrhagia [A] *	1/52 (1.92%)
Respiratory, thoracic and mediastinal disorders	
Nasal septum perforation [A] *	1/52 (1.92%)
Skin and subcutaneous tissue disorders	
Palmar-plantar erythrodysaesthesia syndrome [A] *	1/52 (1.92%)
Vascular disorders	
Hypertension [A] *	1/52 (1.92%)
Jugular vein thrombosis [A] *	1/52 (1.92%)
Lymphocele [A] *	1/52 (1.92%)

* Indicates events were collected by non-systematic methods.
A Term from vocabulary, MedDRA (16.1)

Other Adverse Events

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

	Bevacizumab + Trastuzumab
	Affected/At Risk (%)
Total	52/52 (100%)
Blood and lymphatic system disorders	

	Bevacizumab + Trastuzumab
	Affected/At Risk (%)
Anaemia [A] *	8/52 (15.38%)
Febrile neutropenia [A] *	11/52 (21.15%)
Leukopenia [A] *	7/52 (13.46%)
Neutropenia [A] *	24/52 (46.15%)
Cardiac disorders	
Cardiac failure congestive [A] *	10/52 (19.23%)
Ear and labyrinth disorders	
Vertigo [A] *	6/52 (11.54%)
Eye disorders	
Conjunctivitis [A] *	12/52 (23.08%)
Lacrimation increased [A] *	13/52 (25%)
Gastrointestinal disorders	
Abdominal pain [A] *	3/52 (5.77%)
Abdominal pain upper [A] *	11/52 (21.15%)
Constipation [A] *	14/52 (26.92%)
Diarrhoea [A] *	9/52 (17.31%)
Dyspepsia [A] *	6/52 (11.54%)
Dysphagia [A] *	6/52 (11.54%)
Gastrooesophageal reflux disease [A] *	8/52 (15.38%)
Gingival bleeding [A] *	8/52 (15.38%)
Gingivitis [A] *	5/52 (9.62%)
Haemorrhoids [A] *	7/52 (13.46%)
Nausea [A] *	36/52 (69.23%)

	Bevacizumab + Trastuzumab
	Affected/At Risk (%)
Oesophagitis [A] *	4/52 (7.69%)
Rectal hemorrhage [A] *	3/52 (5.77%)
Vomiting [A] *	18/52 (34.62%)
General disorders	
Asthenia [A] *	41/52 (78.85%)
Chest pain [A] *	4/52 (7.69%)
Fatigue [A] *	4/52 (7.69%)
Mucosal inflammation [A] *	34/52 (65.38%)
Oedema peripheral [A] *	6/52 (11.54%)
Pain [A] *	3/52 (5.77%)
Pyrexia [A] *	10/52 (19.23%)
Infections and infestations	
Bronchitis [A] *	8/52 (15.38%)
Cystitis [A] *	4/52 (7.69%)
Nasopharyngitis [A] *	8/52 (15.38%)
Oral fungal infection [A] *	4/52 (7.69%)
Pharyngitis [A] *	5/52 (9.62%)
Rhinitis [A] *	9/52 (17.31%)
Sinusitis [A] *	4/52 (7.69%)
Skin infection [A] *	5/52 (9.62%)
Tonsillitis [A] *	6/52 (11.54%)
Tooth abscess [A] *	3/52 (5.77%)

	Bevacizumab + Trastuzumab
	Affected/At Risk (%)
Tooth infection [A] *	4/52 (7.69%)
Urinary tract infection [A] *	6/52 (11.54%)
Injury, poisoning and procedural complications	
Radiation skin injury [A] *	19/52 (36.54%)
Wound dehiscence [A] *	4/52 (7.69%)
Investigations	
Ejection fraction decreased [A] *	5/52 (9.62%)
Gamma-glutamyltransferase increased [A] *	5/52 (9.62%)
Weight decreased [A] *	6/52 (11.54%)
Metabolism and nutrition disorders	
Anorexia [A] *	12/52 (23.08%)
Musculoskeletal and connective tissue disorders	
Arthralgia [A] *	15/52 (28.85%)
Back pain [A] *	8/52 (15.38%)
Bone pain [A] *	3/52 (5.77%)
Musculoskeletal pain [A] *	4/52 (7.69%)
Myalgia [A] *	13/52 (25%)
Neck pain [A] *	5/52 (9.62%)
Osteoarthritis [A] *	3/52 (5.77%)
Pain in extremity [A] *	5/52 (9.62%)
Nervous system disorders	
Ageusia [A] *	5/52 (9.62%)
Dysgeusia [A] *	8/52 (15.38%)

	Bevacizumab + Trastuzumab
	Affected/At Risk (%)
Headache [A] *	17/52 (32.69%)
Neuralgia [A] *	4/52 (7.69%)
Neuropathy peripheral [A] *	10/52 (19.23%)
Paraesthesia [A] *	5/52 (9.62%)
Psychiatric disorders	
Anxiety [A] *	4/52 (7.69%)
Insomnia [A] *	4/52 (7.69%)
Renal and urinary disorders	
Proteinuria [A] *	32/52 (61.54%)
Reproductive system and breast disorders	
Breast pain [A] *	4/52 (7.69%)
Respiratory, thoracic and mediastinal disorders	
Cough [A] *	8/52 (15.38%)
Dyspnoea [A] *	3/52 (5.77%)
Epistaxis [A] *	33/52 (63.46%)
Rhinorrhoea [A] *	7/52 (13.46%)
Skin and subcutaneous tissue disorders	
Alopecia [A] *	36/52 (69.23%)
Dermatitis [A] *	5/52 (9.62%)
Dry skin [A] *	9/52 (17.31%)
Erythema [A] *	16/52 (30.77%)
Nail toxicity [A] *	7/52 (13.46%)
Onycholysis [A] *	10/52 (19.23%)

	Bevacizumab + Trastuzumab
	Affected/At Risk (%)
Palmar-plantar erythrodysaesthesia syndrome [A] *	9/52 (17.31%)
Rash [A] *	4/52 (7.69%)
Skin exfoliation [A] *	5/52 (9.62%)
Skin hyperpigmentation [A] *	4/52 (7.69%)
Skin toxicity [A] *	4/52 (7.69%)
Vascular disorders	
Hot flush [A] *	7/52 (13.46%)
Hypertension [A] *	21/52 (40.38%)
Lymphocele [A] *	15/52 (28.85%)
Lymphoedema [A] *	10/52 (19.23%)

* Indicates events were collected by non-systematic methods.
A Term from vocabulary, MedDRA (16.1)

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.

Study being conducted under this Agreement is part of the Overall Study. Investigator is free to publish in reputable journals or to present at professional conferences the results of the Study, but only after the first publication or presentation that involves the Overall Study. The Sponsor may request that Confidential Information be deleted and/or the publication be postponed in order to protect the Sponsor's intellectual property rights.

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