ClinicalTrials.gov Protocol and Results Registration System (PRS) Receipt
Release Date: 07/09/2014

ClinicalTrials.gov ID: NCT00846027

Study Identification

Unique Protocol ID:	ML21999
Brief Title:	A Study of Avastin (Bevacizumab) in Combination With Taxane-based Chemotherapy as First Line Treatment in Patients With HER-2 Negative Breast Cancer
Official Title:	An Open Label Study to Assess the Effect of First Line Treatment With Avastin in Combination With Paclitaxel and Gemcitabine in Progression-free Survival in Patients With HER-2 Negative Breast Cancer
Secondary IDs:	2008-003657-32 [EudraCT Number]

Study Status

Record Verification:	July 2014
Overall Status:	Completed
Study Start:	January 2009
Primary Completion:	December 2011 [Actual]
Study Completion:	January 2013 [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: 0219/08 Board Name: Comite Etico de Ensayo clinicos de Andalucia Board Affiliation: Unknown Phone: 95 500 65 56 Email:
Data Monitoring?:	
Plan to Share Data?:	
Oversight Authorities:	Spain: Agencia Espanola del Medicamento

Study Description

Brief Summary:	This single-arm study assessed the efficacy and safety of first-line treatment with Avastin (bevacizumab) in combination with taxane-based chemotherapy (paclitaxel and gemcitabine) in patients with HER-2 negative breast cancer. Patients received Avastin 10 mg/kg iv, paclitaxel 150 mg/m^2 iv, and gemcitabine 200 mg/m^2 iv on Day 1 and Day 15 of each 4-week treatment cycle until disease progression, death, or withdrawal of consent.
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: 90 [Actual]

Arms and Interventions

Arms	Assigned Interventions
Experimental: Bevacizumab + paclitaxel + gemcitabine Participants received bevacizumab 10 mg/kg intravenously (IV), paclitaxel 150 mg/m^2 IV, and gemcitabine 2000 mg/m^2 IV on Day 1 and Day 15 of each 4-week cycle until disease progression, unacceptable toxicity, or withdrawal of consent.	Drug: Bevacizumab Bevacizumab was supplied as a sterile liquid in glass vials. Other Names: • Avastin Drug: Paclitaxel Paclitaxel was supplied as a sterile liquid in glass vials. Other Names: • Taxol Drug: Gemcitabine Gemcitabine was supplied as a sterile liquid in glass vials. Other Names: • Gemzar

Outcome Measures

[See Results Section.]

Eligibility

Minimum Age: 18 Years

Maximum Age:

Gender: Female

Accepts Healthy Volunteers?: No

Criteria: Inclusion Criteria:

- Female patients, ≥ 18 years of age.
- Breast cancer, with measurable, locally recurrent or metastatic lesions, or patients with bone metastasis only.
- HER-2 negative disease.
- Candidates for chemotherapy.
- Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2.

Exclusion Criteria:

- Previous chemotherapy for metastatic or locally advanced breast cancer.

- Previous radiotherapy for treatment of metastatic breast cancer.
- Any prior adjuvant treatment with anthracyclines completed < 6 months prior to enrollment.
- Chronic daily treatment with corticosteroids (≥ 10 mg/day), aspirin (> 325 mg/day) or clopidogrel (> 75mg/day).

Contacts/Locations

Study Officials: Clinical Trials
Study Director
Hoffmann-La Roche

Locations: Spain

Sevilla, Sevilla, Spain, 41009

Vigo, Pontevedra, Spain, 36214

Barcelona, Barcelona, Spain, 08907

Alcorcon, Madrid, Spain, 28922

Burgos, Burgos, Spain, 09006

Marbella, Malaga, Spain, 29600

Madrid, Madrid, Spain, 28041

Lugo, Lugo, Spain, 27004

Murcia, Murcia, Spain, 30008

Las Palmas de Gran Canaria, Las Palmas, Spain, 35016

Manresa, Barcelona, Spain, 08243

Elda, Alicante, Spain, 03600

Sevilla, Sevilla, Spain, 41014

Sagunto, Valencia, Spain, 46520

Cádiz, Cadiz, Spain, 11009

Barcelona, Barcelona, Spain, 08022

Madrid, Madrid, Spain, 28222

Jaen, Jaen, Spain, 23007

Huelva, Huelva, Spain, 21005

Cordoba, Cordoba, Spain, 14004

Granada, Granada, Spain, 18014

Zaragoza, Zaragoza, Spain, 50009

Granada, Granada, Spain, 18003

References

Citations:

Links:

Study Data/Documents:

Study Results

Participant Flow

Reporting Groups

	Description
Bevacizumab + Paclitaxel + Gemcitabine	Participants received bevacizumab 10 mg/kg intravenously (IV), paclitaxel 150 mg/m^2 IV, and gemcitabine 2000 mg/m^2 IV on Day 1 and Day 15 of each 4-week cycle until disease progression, unacceptable toxicity, or withdrawal of consent.

Overall Study

	Bevacizumab + Paclitaxel + Gemcitabine
Started	90
Received Treatment	83
Completed	0
Not Completed	90
Death	3

	Bevacizumab + Paclitaxel + Gemcitabine
Disease Progression	30
Toxicity	12
Patient Decision	7
Investigator Discretion	29
Protocol Violation	2
Subject Not Treated	7

Baseline Characteristics

Analysis Population Description

Intent-to-treat population: All participants enrolled in the study.

Reporting Groups

	Description
Bevacizumab + Paclitaxel + Gemcitabine	Participants received bevacizumab 10 mg/kg intravenously (IV), paclitaxel 150 mg/m^2 IV, and gemcitabine 2000 mg/m^2 IV on Day 1 and Day 15 of each 4-week cycle until disease progression, unacceptable toxicity, or withdrawal of consent.

Baseline Measures

	Bevacizumab + Paclitaxel + Gemcitabine
Number of Participants	90
Age, Continuous [units: years] Mean (Standard Deviation)	52.20 (12.48)
Gender, Male/Female [units: participants]	
Female	89
Male	1

Outcome Measures

1. Primary Outcome Measure:

Measure Title	Progression-free Survival

Measure Description	Progression-free survival was defined as the time from enrollment in the study to the first documented disease progression using Response Evaluation Criteria In Solid Tumors (RECIST) or death from any cause, whichever occurred first.
Time Frame	Baseline to the end of the study (up to 2 years 10 months)
Safety Issue?	No

Analysis Population Description

Intent-to-treat population: All participants who were enrolled in the study.

Reporting Groups

	Description
Bevacizumab + Paclitaxel + Gemcitabine	Participants received bevacizumab 10 mg/kg intravenously (IV), paclitaxel 150 mg/m^2 IV, and gemcitabine 2000 mg/m^2 IV on Day 1 and Day 15 of each 4-week cycle until disease progression, unacceptable toxicity, or withdrawal of consent.

Measured Values

	Bevacizumab + Paclitaxel + Gemcitabine
Number of Participants Analyzed	90
Progression-free Survival [units: Months] Median (95% Confidence Interval)	11.51 (9.01 to 17.59)

2. Secondary Outcome Measure:

Measure Title	Percentage of Participants With an Objective Response
Measure Description	An objective response was defined as a complete or partial response determined on 2 consecutive occasions ≥ 4 weeks apart using Response Evaluation Criteria in Solid Tumors (RECIST). Complete response was defined as the disappearance of all target and non-target lesions. Any pathological lymph nodes (whether target or non-target) must be < 10 mm on the short axis. Partial response was defined as at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum.
Time Frame	Baseline to the end of the study (up to 2 years 10 months)
Safety Issue?	No

Analysis Population Description

Intent-to-treat population: All participants who were enrolled in the study. Only participants who had a response evaluation were included in the analysis.

Reporting Groups

	Description
Bevacizumab + Paclitaxel + Gemcitabine	Participants received bevacizumab 10 mg/kg intravenously (IV), paclitaxel 150 mg/m^2 IV, and gemcitabine 2000 mg/m^2 IV on Day 1 and Day 15 of each 4-week cycle until disease progression, unacceptable toxicity, or withdrawal of consent.

Measured Values

	Bevacizumab + Paclitaxel + Gemcitabine
Number of Participants Analyzed	76
Percentage of Participants With an Objective Response [units: Percentage of participants] Number (95% Confidence Interval)	72.37 (60.91 to 82.01)

3. Secondary Outcome Measure:

Measure Title	Duration of the Objective Response
Measure Description	Duration of the objective response is defined as the time from a complete or partial response to disease progression or death due to disease.
Time Frame	Baseline to the end of the study (up to 2 years 10 months)
Safety Issue?	No

Analysis Population Description

Intent-to-treat population: All participants who were enrolled in the study. Only participants who had a response were included in the analysis.

Reporting Groups

	Description
Bevacizumab + Paclitaxel + Gemcitabine	Participants received bevacizumab 10 mg/kg intravenously (IV), paclitaxel 150 mg/m^2 IV, and gemcitabine 2000 mg/m^2 IV on Day 1 and Day 15 of each 4-week cycle until disease progression, unacceptable toxicity, or withdrawal of consent.

Measured Values

	Bevacizumab + Paclitaxel + Gemcitabine
Number of Participants Analyzed	55
Duration of the Objective Response [units: Months]	12.39 (7.63 to 15.16)

	Bevacizumab + Paclitaxel + Gemcitabine
Median (95% Confidence Interval)	

4. Secondary Outcome Measure:

Measure Title	Overall Survival
Measure Description	Overall survival is defined as the time from the first dose of study medication until death.
Time Frame	Baseline to the end of the study (up to 2 years 10 months)
Safety Issue?	No

Analysis Population Description

Intent-to-treat population: All participants who were enrolled in the study.

Reporting Groups

	Description
Bevacizumab + Paclitaxel + Gemcitabine	Participants received bevacizumab 10 mg/kg intravenously (IV), paclitaxel 150 mg/m^2 IV, and gemcitabine 2000 mg/m^2 IV on Day 1 and Day 15 of each 4-week cycle until disease progression, unacceptable toxicity, or withdrawal of consent.

Measured Values

	Bevacizumab + Paclitaxel + Gemcitabine
Number of Participants Analyzed	90
Overall Survival [units: Months] Median (95% Confidence Interval)	27.39 (21.86 to NA) [1]

[1] The upper limit of the confidence interval could not be calculated due to too few events.

Reported Adverse Events

Time Frame	[Not specified]

Additional Description	Safety population: All enrolled participants who receive at least 1 dose of medication and who satisfied all inclusion criteria and none of the exclusion criteria. 7 participants did not receive at least 1 dose of medication and 1 participant did not satisfy an inclusion criterion. These 8 participants were not included in the safety population.

Reporting Groups

	Description
Bevacizumab + Paclitaxel + Gemcitabine	Participants received bevacizumab 10 mg/kg intravenously (IV), paclitaxel 150 mg/m^2 IV, and gemcitabine 2000 mg/m^2 IV on Day 1 and Day 15 of each 4-week cycle until disease progression, unacceptable toxicity, or withdrawal of consent.

Serious Adverse Events

	Bevacizumab + Paclitaxel + Gemcitabine
	Affected/At Risk (%)
Total	21/82 (25.61%)
Blood and lymphatic system disorders	
Neutrophils count decreased [A] †	1/82 (1.22%)
Cardiac disorders	
Cardiac ischemia/infarction [A] †	1/82 (1.22%)
Hypertension [A] †	1/82 (1.22%)
Left ventricular systolic dysfunction [A] †	1/82 (1.22%)
Supraventricular and nodal arrhythmia [A] †	1/82 (1.22%)
Gastrointestinal disorders	
Anorexia [A] †	1/82 (1.22%)
Dehydration [A] †	1/82 (1.22%)
Diarrhoea [A] †	1/82 (1.22%)
Gastrointestinal perforation [A] †	1/82 (1.22%)
Vomiting [A] †	1/82 (1.22%)
Infections and infestations	
Catheter site infection [A] †	2/82 (2.44%)

	Bevacizumab + Paclitaxel + Gemcitabine
	Affected/At Risk (%)
Febrile neutropenia [A] †	1/82 (1.22%)
Fever [A] †	4/82 (4.88%)
Infection [A] †	1/82 (1.22%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	
Secondary Malignancy - possibly related to cancer treatment [A] †	1/82 (1.22%)
Nervous system disorders	
Confusion [A] †	1/82 (1.22%)
Dizziness [A] †	1/82 (1.22%)
Respiratory, thoracic and mediastinal disorders	
Dyspnoea [A] †	1/82 (1.22%)
Pleural effusion (non-malignant) [A] †	1/82 (1.22%)
Pneumothorax [A] †	1/82 (1.22%)

† Indicates events were collected by systematic assessment.
A Term from vocabulary, MedDRA (Unspecified)

Other Adverse Events

Frequency Threshold Above Which Other Adverse Events are Reported: 0%

	Bevacizumab + Paclitaxel + Gemcitabine
	Affected/At Risk (%)
Total	82/82 (100%)
Blood and lymphatic system disorders	
Blood/bone marrow , other [A] †	3/82 (3.66%)
Haemoglobin decreased [A] †	15/82 (18.29%)
Leukocytes low [A] †	6/82 (7.32%)

	Bevacizumab + Paclitaxel + Gemcitabine
	Affected/At Risk (%)
Neutrophils low [A] †	26/82 (31.71%)
Platelets low [A] †	6/82 (7.32%)
Cardiac disorders	
Bradycardia [A] †	1/82 (1.22%)
Cardiac ischemia/infarction [A] †	1/82 (1.22%)
Hypertension [A] †	13/82 (15.85%)
Left ventricular systolic dysfunction [A] †	2/82 (2.44%)
Pulmonary hypertension [A] †	1/82 (1.22%)
Supraventricular and nodal arrhythmia [A] †	1/82 (1.22%)
Endocrine disorders	
Hot flashes [A] †	1/82 (1.22%)
Irregular menses [A] †	2/82 (2.44%)
Eye disorders	
Eye disorder [A] †	1/82 (1.22%)
Ocular/visual [A] †	1/82 (1.22%)
Ophthalmoplegia/diplopia [A] †	1/82 (1.22%)
Watery eye [A] †	1/82 (1.22%)
Gastrointestinal disorders	
Anorexia [A] †	10/82 (12.2%)
Ascites (non-malignant) [A] †	1/82 (1.22%)
Constipation [A] †	13/82 (15.85%)
Dehydration [A] †	1/82 (1.22%)
Dental: teeth [A] †	1/82 (1.22%)

	Bevacizumab + Paclitaxel + Gemcitabine
	Affected/At Risk (%)
Diarrhoea [A] †	20/82 (24.39%)
Distension/bloating, abdominal [A] †	2/82 (2.44%)
Dysgeusia [A] †	5/82 (6.1%)
Dyspepsia [A] †	4/82 (4.88%)
Flatulence [A] †	2/82 (2.44%)
Mucositis [A] †	1/82 (1.22%)
Nausea [A] †	27/82 (32.93%)
Pain abdomen [A] †	13/82 (15.85%)
Pain abdomen [A] †	1/82 (1.22%)
Pain uterus [A] †	1/82 (1.22%)
Perforation, GI [A] †	1/82 (1.22%)
Periodontal disease [A] †	2/82 (2.44%)
Vomiting [A] †	25/82 (30.49%)
General disorders	
Chest/thorax [A] †	2/82 (2.44%)
Constitutional symptoms, other [A] †	2/82 (2.44%)
Diaphoresis [A] †	1/82 (1.22%)
Fatigue [A] †	54/82 (65.85%)
Fatigue (asthenia, lethargy, malaise) [A] †	1/82 (1.22%)
Fever [A] †	15/82 (18.29%)
Pain extremity limb [A] †	5/82 (6.1%)
Pain oral-gums [A] †	28/82 (34.15%)

	Bevacizumab + Paclitaxel + Gemcitabine
	Affected/At Risk (%)
Pain, other [A] †	3/82 (3.66%)
Immune system disorders	
Allergic reaction [A] †	1/82 (1.22%)
Allergic reaction/hypersensitivity [A] †	2/82 (2.44%)
Infections and infestations	
Febrile neutropenia [A] †	2/82 (2.44%)
Infection bladder (urinary) [A] †	5/82 (6.1%)
Infection other conjunctiva [A] †	3/82 (3.66%)
Infection pharynx [A] †	3/82 (3.66%)
Infection sexual/reproductive function vaginal [A] †	1/82 (1.22%)
Infection vaginal [A] †	1/82 (1.22%)
Infection with unknown absolute neutrophil count [A] †	4/82 (4.88%)
Infection - other general catheter-related [A] †	3/82 (3.66%)
Infection - other general oral cavity-gums [A] †	2/82 (2.44%)
Infection - other nose [A] †	4/82 (4.88%)
Infection, other [A] †	4/82 (4.88%)
Investigations	
Alanine transaminase [A] †	1/82 (1.22%)
Alanine transaminase, serum glutamic pyruvic transaminase [A] †	2/82 (2.44%)
Alanine transaminase/aspartate aminotransferase high [A] †	1/82 (1.22%)

	Bevacizumab + Paclitaxel + Gemcitabine
	Affected/At Risk (%)
Alkaline phosphatase [A] †	1/82 (1.22%)
Aspartate aminotransferase [A] †	2/82 (2.44%)
Metabolic, other [A] †	2/82 (2.44%)
Proteinuria [A] †	3/82 (3.66%)
Uric acid, serum-high [A] †	1/82 (1.22%)
Metabolism and nutrition disorders	
Lymphatics - other lymphangitis [A] †	1/82 (1.22%)
Oedema: limb [A] †	8/82 (9.76%)
Musculoskeletal and connective tissue disorders	
Cervical spine-range of motion [A] †	1/82 (1.22%)
Muscle weakness- extremity lower [A] †	1/82 (1.22%)
Osteonecrosis (avascular necrosis) [A] †	1/82 (1.22%)
Pain back [A] †	9/82 (10.98%)
Pain bone [A] †	3/82 (3.66%)
Pain joint [A] †	12/82 (14.63%)
Pain muscle [A] †	18/82 (21.95%)
Pain neck [A] †	1/82 (1.22%)
Pain other back [A] †	1/82 (1.22%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	
Secondary malignancy - possibly related to cancer treatment [A] †	2/82 (2.44%)
Nervous system disorders	
Confusion [A] †	1/82 (1.22%)

	Bevacizumab + Paclitaxel + Gemcitabine
	Affected/At Risk (%)
Dizziness [A] †	4/82 (4.88%)
Memory impairment [A] †	1/82 (1.22%)
Mood alteration [A] †	5/82 (6.1%)
Neuropathy: cranial optic [A] †	1/82 (1.22%)
Neuropathy: sensory [A] †	62/82 (75.61%)
Pain head/headache [A] †	7/82 (8.54%)
Psychiatric disorders	
Insomnia [A] †	1/82 (1.22%)
Renal and urinary disorders	
Bladder spasms [A] †	1/82 (1.22%)
Cystitis [A] †	2/82 (2.44%)
Pain bladder [A] †	3/82 (3.66%)
Reproductive system and breast disorders	
Sexual/reproductive, other [A] †	1/82 (1.22%)
Vaginal dryness [A] †	1/82 (1.22%)
Respiratory, thoracic and mediastinal disorders	
Cough [A] †	4/82 (4.88%)
Dysarthria [A] †	8/82 (9.76%)
Dyspnoea [A] †	9/82 (10.98%)
Nasal/paranasal reactions [A] †	2/82 (2.44%)
Pleural effusion (non-malignant) [A] †	2/82 (2.44%)
Pneumothorax [A] †	1/82 (1.22%)
Skin and subcutaneous tissue disorders	

	Bevacizumab + Paclitaxel + Gemcitabine
	Affected/At Risk (%)
Acne [A] †	4/82 (4.88%)
Alteration in scarring [A] †	1/82 (1.22%)
Dermatitis associated with radiation [A] †	1/82 (1.22%)
Dermatology/skin, other [A] †	5/82 (6.1%)
Dry skin [A] †	2/82 (2.44%)
Hair loss/alopecia (scalp or body) [A] †	28/82 (34.15%)
Hand-foot [A] †	4/82 (4.88%)
Nail changes [A] †	17/82 (20.73%)
Pruritus [A] †	7/82 (8.54%)
Rash/desquamation [A] †	20/82 (24.39%)
Rash: acne/acneiform [A] †	8/82 (9.76%)
Vascular disorders	
Haemorrhage, gastrointestinal oral cavity [A] †	4/82 (4.88%)
Haemorrhage, gastrointestinal rectum [A] †	2/82 (2.44%)
Haemorrhage, gastrointestinal varices (rectal) [A] †	1/82 (1.22%)
Haemorrhage, genitourinary bladder [A] †	2/82 (2.44%)
Haemorrhage, genitourinary uterus [A] †	1/82 (1.22%)
Haemorrhage, pulmonary/upper respiratory lung [A] †	2/82 (2.44%)
Haemorrhage, pulmonary/upper respiratory nose [A] †	30/82 (36.59%)
Haemorrhage/bleeding, other [A] †	1/82 (1.22%)

	Bevacizumab + Paclitaxel + Gemcitabine
	Affected/At Risk (%)
Hot flashes [A] †	1/82 (1.22%)
Phlebitis [A] †	1/82 (1.22%)

† Indicates events were collected by systematic assessment.
A Term from vocabulary, MedDRA (Unspecified)

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.

The 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.

Results Point of Contact:

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