ClinicalTrials.gov Protocol and Results Registration System (PRS) Receipt
Release Date: 07/22/2015

A Study of Avastin (Bevacizumab) in Women With HER2 Negative Metastatic Breast Cancer

This study has been completed.

Sponsor:	Hoffmann-La Roche
Collaborators:	
Information provided by (Responsible Party):	Hoffmann-La Roche
ClinicalTrials.gov Identifier:	NCT00333775

Purpose

This study will evaluate the efficacy and safety of 2 doses of Avastin in combination with docetaxel, versus docetaxel plus placebo, in patients with metastatic HER2 negative breast cancer who are candidates for taxane-based chemotherapy but who have not received prior chemotherapy for metastatic disease. The anticipated time on treatment is 1-2 years and the target sample size is 500+ individuals.

Condition	Intervention	Phase
Breast Cancer	Drug: Docetaxel Drug: Placebo to bevacizumab Drug: Bevacizumab	Phase 3

Study Type: Interventional
Study Design: Treatment, Parallel Assignment, Double Blind (Subject, Investigator), Randomized, Safety/Efficacy Study
Official Title: A Randomised, Double Blind, Placebo Controlled, Multicentre Study to Evaluate the Efficacy and Safety of Bevacizumab in Combination With Docetaxel in Comparison With Docetaxel Plus Placebo, as First Line Treatment for Patients With HER2 Negative Metastatic and Locally Recurrent Breast Cancer.

Further study details as provided by Hoffmann-La Roche:

Primary Outcome Measure:

- Progression-free Survival [Time Frame: Baseline to the 30Apr2009 (up to 3 years, 1 month)] [Designated as safety issue: No]

Progression-free survival was defined as the time from randomization to the time of the first documented disease progression or death, whichever occurred first.

Secondary Outcome Measures:

- Percentage of Participants With a Complete Response or a Partial Response [Time Frame: Baseline to the 30 April 2009 cut-off date (up to 3 years, 1 month)] [Designated as safety issue: No]
  A complete response was defined as the disappearance of all target lesions or the disappearance of all non-target lesions and normalization of tumor marker level. A partial response was defined as at least a 30% decrease in the sum of the longest diameter of target lesions, taking as reference the baseline sum longest diameter. Best overall response (OR) was assessed by RECIST criteria. Patients were classified as responders if their best overall response was either confirmed CR or confirmed PR. Responses were evaluated using the Response Evaluation Criteria in Solid Tumors.
- Duration of Response [Time Frame: Baseline to the 15 September 2008 cut-off date (up to 2 years, 6 months)] [Designated as safety issue: No]
  Duration of response was defined as the time from the first documented complete response or partial response to disease progression or death. A complete response was defined as the disappearance of all target lesions or the disappearance of all non-target lesions and normalization of tumor marker level. A partial response was defined as at least a 30% decrease in the sum of the longest diameter of target lesions, taking as reference the baseline sum longest diameter. Best overall response (OR) was assessed by RECIST criteria. Patients were classified as responders if their best overall response was either confirmed CR or confirmed PR. Responses were evaluated using the Response Evaluation Criteria in Solid Tumors.
- Time to Treatment Failure [Time Frame: Baseline to the 15 September 2008 cut-off date (up to 2 years, 6 months)] [Designated as safety issue: No]
  Time to treatment failure was defined as time from randomization to the date of disease progression, death, or withdrawal of treatment due to an adverse event, withdrawal of informed consent, insufficient therapeutic response, refusal of treatment/failure to co-operate, or failure to return, whichever occurred first.
- Overall Survival [Time Frame: Baseline to the 30 Apr 2009 (up to 3 years, 1 month)] [Designated as safety issue: No]
  Overall survival was defined as the time from randomization to death from any cause.

Enrollment: 735
Study Start Date: March 2006
Primary Completion Date: October 2013
Study Completion Date: October 2013

Arms	Assigned Interventions
Experimental: Docetaxel 100 mg/m^2 plus placebo Participants received docetaxel 100 mg/m^2 intravenously on Day 1 of each 3 week cycle for a maximum of 27 weeks (9 cycles). In addition, participants received placebo to bevacizumab intravenously on Day 1 of each 3 week cycle until disease progression, unacceptable toxicity, or participant withdrawal.	Drug: Docetaxel Docetaxel was supplied in 2 vials, 1 containing docetaxel and 1 containing a solvent, for intravenous infusion Drug: Placebo to bevacizumab Placebo to bevacizumab was supplied as a sterile liquid for intravenous infusion in single-use vials.
Experimental: Docetaxel 100 mg/m^2 plus bevacizumab 7.5 mg/kg Participants received docetaxel 100 mg/m^2 intravenously on Day 1 of each 3 week cycle for a maximum of 27 weeks (9	Drug: Docetaxel Docetaxel was supplied in 2 vials, 1 containing docetaxel and 1 containing a solvent, for intravenous infusion

Arms	Assigned Interventions
cycles). In addition, participants received bevacizumab 7.5 mg/kg intravenously on Day 1 of each 3 week cycle until disease progression, unacceptable toxicity, or participant withdrawal.	Drug: Bevacizumab 7.5 mg/kg iv on day 1 of each 3 week cycle Other Names: Avastin Bevacizumab was supplied as a sterile liquid for intravenous infusion in single-use vials.
Experimental: Docetaxel 100 mg/m^2 plus bevacizumab 15.0 mg/kg Participants received docetaxel 100 mg/m^2 intravenously on Day 1 of each 3 week cycle for a maximum of 27 weeks (9 cycles). In addition, participants received bevacizumab 15.0 mg/kg intravenously on Day 1 of each 3 week cycle until disease progression, unacceptable toxicity, or participant withdrawal.	Drug: Docetaxel Docetaxel was supplied in 2 vials, 1 containing docetaxel and 1 containing a solvent, for intravenous infusion Drug: Bevacizumab 7.5 mg/kg iv on day 1 of each 3 week cycle Other Names: Avastin Bevacizumab was supplied as a sterile liquid for intravenous infusion in single-use vials.

Eligibility

Ages Eligible for Study: 18 Years and older
Genders Eligible for Study: Female
Accepts Healthy Volunteers: No

Criteria

Inclusion Criteria:

- female patients >= 18 years of age;
- HER2 negative cancer of the breast with locally recurrent or metastatic disease, suitable for chemotherapy;
- no adjuvant chemotherapy within 6 months before randomization, and no taxane-based chemotherapy within 12 months before randomization;
- ECOG performance status 0-1.

Exclusion Criteria:

- previous chemotherapy for metastatic or locally recurrent breast cancer;
- radiotherapy for treatment of metastatic disease;
- other primary tumors within last 5 years, except for controlled limited basal cell or squamous cancer of the skin, or cancer in situ of the cervix;
- spinal cord compression or brain metastases;
- major surgical procedure, open biopsy or significant traumatic injury within 28 days prior to randomization;
- inadequate bone marrow, liver or renal function;
- uncontrolled hypertension.

Contacts and Locations

Locations

- Australia, New South Wales
  - Adelaide, New South Wales, Australia, 5011
  - Camperdown, New South Wales, Australia, 2050
  - Westmead, New South Wales, Australia, 2145
- Australia, Queensland
  - Auchenflower, Queensland, Australia, 4066
- Australia, Victoria
  - Box Hill, Victoria, Australia, 3128
  - Fitzroy, Victoria, Australia, 3065
  - Ringwood East, Victoria, Australia, 3135
- Australia, Western Australia
  - Perth, Western Australia, Australia, 6000
- Austria
  - Graz, Austria, 8036
  - Salzburg, Austria, 5020
  - Vöcklabruck, Austria, 4840
  - Wien, Austria, 1090
- Belgium
  - Bruxelles, Belgium, 1000
  - Wilrijk, Belgium, 2610
- Brazil
  - Goiania, GO, Brazil, 74605-070
  - Belo Horizonte, MG, Brazil, 31190-131
  - Porto Alegre, RS, Brazil, 90610-000
  - Florianopolis, SC, Brazil, 88034-000
  - Barretos, SP, Brazil, 14784-400
  - Sao Paulo, SP, Brazil, 01509-010
- Canada, Alberta
  - Calgary, Alberta, Canada, T2N 4N2
  - Edmonton, Alberta, Canada, T6G 1Z2
- Canada, British Columbia
  - Vancouver, British Columbia, Canada, V5Z 4E6
- Canada, Nova Scotia
  - Halifax, Nova Scotia, Canada, B3H 1V7
- Canada, Ontario
  - Ottawa, Ontario, Canada, K1H 8L6
  - Sudbury, Ontario, Canada, P3E 5J1
  - Toronto, Ontario, Canada, M4N 3M5
- Canada, Quebec
  - Montreal, Quebec, Canada, H4J 1C5
  - Quebec, Quebec, Canada, G1S 4L8

China
- Beijing, China, 100021

France
- Besancon, France, 25030
- Bordeaux, France, 33076
- Caen, France, 14076
- Clermont Ferrand, France, 63011
- Dijon, France, 21079
- Lille, France, 59020
- Montpellier, France, 34298
- Villejuif, France, 94805

Germany
- Ansbach, Germany, 91522
- Berlin, Germany, 14195
- Düsseldorf, Germany, 40225
- Erlangen, Germany, 91054
- Frankfurt, Germany, 60596
- Frankfurt am Main, Germany, 60389
- Halle, Germany, 06120
- Hamburg, Germany, 20246
- Heidelberg, Germany, 69120
- Jena, Germany, 07743
- Lemgo, Germany, 32657
- München, Germany, 81675
- Stuttgart, Germany, 70376
- Trier, Germany, 54290
- Tübingen, Germany, 72076
- Ulm, Germany, 89075

Italy
- Bologna, Emilia-Romagna, Italy, 40138
- Modena, Emilia-Romagna, Italy, 41100
- Parma, Emilia-Romagna, Italy, 43100
- Trieste, Friuli-Venezia Giulia, Italy, 34100
- Udine, Friuli-Venezia Giulia, Italy, 33100
- Treviglio, Lombardia, Italy, 24047
- Macerata, Marche, Italy, 62100
- Biella, Piemonte, Italy, 13900
- Taormina, Sicilia, Italy, 98030

Korea, Republic of
- Seoul, Korea, Republic of, 138-736
- Seoul, Korea, Republic of, 135-710
- Seoul, Korea, Republic of, 120-752

Lithuania
- Kaunas, Lithuania, 50009
- Vilnius, Lithuania, 08660

Mexico
- Merida, Mexico, 97500
- Mexicali, Mexico, 21100
- Mexico City, Mexico, 06760
- Monterrey, Mexico, 64380
- Obregon, Mexico, 85000
- Puebla, Mexico, 72530

Netherlands
- Sittard, Netherlands, 6131 BK
- Utrecht, Netherlands, 3582 KE

Panama
- Panama City, Panama, 83-0669

Poland
- Krakow, Poland, 31-826
- Olsztyn, Poland, 10-513
- Poznan, Poland, 60-569
- Warszawa, Poland, 02-781
- Wroclaw, Poland, 53-413

Portugal
- Coimbra, Portugal, 3000-075
- Lisboa, Portugal, 1099-023

Romania
- Bucuresti, Romania, 022328

South Africa
- Pretoria, South Africa, 0002
- Sandton, South Africa, 2196

Spain
- Barcelona, Barcelona, Spain, 08907
- Barcelona, Barcelona, Spain, 08035
- Barcelona, Barcelona, Spain, 08036
- Barcelona, Barcelona, Spain, 08003
- Jaen, Jaen, Spain, 23007
- Madrid, Madrid, Spain, 28041
- Malaga, Malaga, Spain, 29010

Sweden
- Linkoeping, Sweden, 58185
- Lund, Sweden, 22185
- Umea, Sweden, 90185

Switzerland
- Chur, Switzerland, 7000

Taiwan
- Kaohsiung, Taiwan, 813
- Taipei, Taiwan, 100
- Taipei, Taiwan, 114

Thailand

Bangkok, Thailand, 10700
Bangkok, Thailand, 10400
Bangkok, Thailand, 10400
Khon Kaen, Thailand, 40002

United Kingdom

Bournemouth, United Kingdom, BH7 7DW
Cambridge, United Kingdom, CB2 2QQ
Edinburgh, United Kingdom, EH4 2XU
Leeds, United Kingdom, LS9 7TF
Leeds, United Kingdom, LS16 5WW
London, United Kingdom, SE1 7EH
Manchester, United Kingdom, M20 4BX
Middlesex, United Kingdom, HA6 2RN
Newcastle Upon Tyne, United Kingdom, NE7 7DN
Truro, United Kingdom, TR1 3LJ

Investigators

Study Director:	Clinical Trials	Hoffmann-La Roche

More Information

Responsible Party:	Hoffmann-La Roche
Study ID Numbers:	BO17708 2005-003862-40 [EudraCT Number]
Health Authority:	France: AFSSAPS (Agence francaise de securite sanitaire des produits de Sante)

Study Results

Participant Flow

Reporting Groups

	Description
Docetaxel 100 mg/m^2 Plus Placebo	Participants received docetaxel 100 mg/m^2 intravenously on Day 1 of each 3 week cycle for a maximum of 27 weeks (9 cycles). In addition, participants received placebo to bevacizumab intravenously on Day 1 of each 3 week cycle until disease progression, unacceptable toxicity, or participant withdrawal.
Docetaxel 100 mg/m^2 Plus Bevacizumab 7.5 mg/kg	Participants received docetaxel 100 mg/m^2 intravenously on Day 1 of each 3 week cycle for a maximum of 27 weeks (9 cycles). In addition, participants received bevacizumab 7.5 mg/kg intravenously on Day 1 of each 3 week cycle until disease progression, unacceptable toxicity, or participant withdrawal.

	Description
Docetaxel 100 mg/m^2 Plus Bevacizumab 15.0 mg/kg	Participants received docetaxel 100 mg/m^2 intravenously on Day 1 of each 3 week cycle for a maximum of 27 weeks (9 cycles). In addition, participants received bevacizumab 15.0 mg/kg intravenously on Day 1 of each 3 week cycle until disease progression, unacceptable toxicity, or participant withdrawal.

Overall Study

	Docetaxel 100 mg/ m^2 Plus Placebo	Docetaxel 100 mg/m^2 Plus Bevacizumab 7.5 mg/kg	Docetaxel 100 mg/m^2 Plus Bevacizumab 15.0 mg/kg
Started	241	248	247
Received Treatment	238	247	245
Completed	56	70	73
Not Completed	185	178	174

Baseline Characteristics

Reporting Groups

	Description
Docetaxel 100 mg/m^2 Plus Placebo	Participants received docetaxel 100 mg/m^2 intravenously on Day 1 of each 3 week cycle for a maximum of 27 weeks (9 cycles). In addition, participants received placebo to bevacizumab intravenously on Day 1 of each 3 week cycle until disease progression, unacceptable toxicity, or participant withdrawal.
Docetaxel 100 mg/m^2 Plus Bevacizumab 7.5 mg/kg	Participants received docetaxel 100 mg/m^2 intravenously on Day 1 of each 3 week cycle for a maximum of 27 weeks (9 cycles). In addition, participants received bevacizumab 7.5 mg/kg intravenously on Day 1 of each 3 week cycle until disease progression, unacceptable toxicity, or participant withdrawal.
Docetaxel 100 mg/m^2 Plus Bevacizumab 15.0 mg/kg	Participants received docetaxel 100 mg/m^2 intravenously on Day 1 of each 3 week cycle for a maximum of 27 weeks (9 cycles). In addition, participants received bevacizumab 15.0 mg/kg intravenously on Day 1 of each 3 week cycle until disease progression, unacceptable toxicity, or participant withdrawal.

Baseline Measures

	Docetaxel 100 mg/ m^2 Plus Placebo	Docetaxel 100 mg/m^2 Plus Bevacizumab 7.5 mg/kg	Docetaxel 100 mg/m^2 Plus Bevacizumab 15.0 mg/kg	Total
Number of Participants	241	248	247	736
Age, Continuous [units: years] Mean (Standard Deviation)	53.5 (10.47)	53.9 (10.61)	53.6 (10.78)	53.7 (10.61)
Gender, Male/Female [units: participants]				

	Docetaxel 100 mg/ m^2 Plus Placebo	Docetaxel 100 mg/m^2 Plus Bevacizumab 7.5 mg/kg	Docetaxel 100 mg/m^2 Plus Bevacizumab 15.0 mg/kg	Total
Female	241	248	247	736
Male	0	0	0	0

Outcome Measures

1. Primary Outcome Measure:

Measure Title	Progression-free Survival
Measure Description	Progression-free survival was defined as the time from randomization to the time of the first documented disease progression or death, whichever occurred first.
Time Frame	Baseline to the 30Apr2009 (up to 3 years, 1 month)
Safety Issue?	No

Analysis Population Description

Intent-to-treat population: All randomized participants, regardless of whether they received study drug or not.

Reporting Groups

	Description
Docetaxel 100 mg/m^2 Plus Placebo	Participants received docetaxel 100 mg/m^2 intravenously on Day 1 of each 3 week cycle for a maximum of 27 weeks (9 cycles). In addition, participants received placebo to bevacizumab intravenously on Day 1 of each 3 week cycle until disease progression, unacceptable toxicity, or participant withdrawal.
Docetaxel 100 mg/m^2 Plus Bevacizumab 7.5 mg/kg	Participants received docetaxel 100 mg/m^2 intravenously on Day 1 of each 3 week cycle for a maximum of 27 weeks (9 cycles). In addition, participants received bevacizumab 7.5 mg/kg intravenously on Day 1 of each 3 week cycle until disease progression, unacceptable toxicity, or participant withdrawal.
Docetaxel 100 mg/m^2 Plus Bevacizumab 15.0 mg/kg	Participants received docetaxel 100 mg/m^2 intravenously on Day 1 of each 3 week cycle for a maximum of 27 weeks (9 cycles). In addition, participants received bevacizumab 15.0 mg/kg intravenously on Day 1 of each 3 week cycle until disease progression, unacceptable toxicity, or participant withdrawal.

Measured Values

	Docetaxel 100 mg/ m^2 Plus Placebo	Docetaxel 100 mg/m^2 Plus Bevacizumab 7.5 mg/kg	Docetaxel 100 mg/m^2 Plus Bevacizumab 15.0 mg/kg
Number of Participants Analyzed	241	248	247
Progression-free Survival [units: months] Median (95% Confidence Interval)	8.1 (7.3 to 8.4)	9.0 (8.3 to 10.6)	10.0 (8.5 to 10.7)

Statistical Analysis 1 for Progression-free Survival

Statistical Analysis Overview	Comparison Groups	Docetaxel 100 mg/m^2 Plus Placebo, Docetaxel 100 mg/m^2 Plus Bevacizumab 7.5 mg/kg
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	0.045
	Comments	[Not specified]
	Method	Log Rank
	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Hazard Ratio (HR)
	Estimated Value	0.80
	Confidence Interval	(2-Sided) 95% 0.65 to 1.00
	Estimation Comments	[Not specified]

Statistical Analysis 2 for Progression-free Survival

Statistical Analysis Overview	Comparison Groups	Docetaxel 100 mg/m^2 Plus Placebo, Docetaxel 100 mg/m^2 Plus Bevacizumab 15.0 mg/kg
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	0.0002
	Comments	[Not specified]
	Method	Log Rank
	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Hazard Ratio, log
	Estimated Value	0.67

	Confidence Interval	(2-Sided) 95% 0.54 to 0.83
	Estimation Comments	[Not specified]

2. Secondary Outcome Measure:

Measure Title	Percentage of Participants With a Complete Response or a Partial Response
Measure Description	A complete response was defined as the disappearance of all target lesions or the disappearance of all non-target lesions and normalization of tumor marker level. A partial response was defined as at least a 30% decrease in the sum of the longest diameter of target lesions, taking as reference the baseline sum longest diameter. Best overall response (OR) was assessed by RECIST criteria. Patients were classified as responders if their best overall response was either confirmed CR or confirmed PR. Responses were evaluated using the Response Evaluation Criteria in Solid Tumors.
Time Frame	Baseline to the 30 April 2009 cut-off date (up to 3 years, 1 month)
Safety Issue?	No

Analysis Population Description

Intent-to-treat population: All randomized participants, regardless of whether they received study drug or not. Only participants with measurable disease at Baseline were included in the analysis.

Reporting Groups

	Description
Docetaxel 100 mg/m^2 Plus Placebo	Participants received docetaxel 100 mg/m^2 intravenously on Day 1 of each 3 week cycle for a maximum of 27 weeks (9 cycles). In addition, participants received placebo to bevacizumab intravenously on Day 1 of each 3 week cycle until disease progression, unacceptable toxicity, or participant withdrawal.
Docetaxel 100 mg/m^2 Plus Bevacizumab 7.5 mg/kg	Participants received docetaxel 100 mg/m^2 intravenously on Day 1 of each 3 week cycle for a maximum of 27 weeks (9 cycles). In addition, participants received bevacizumab 7.5 mg/kg intravenously on Day 1 of each 3 week cycle until disease progression, unacceptable toxicity, or participant withdrawal.
Docetaxel 100 mg/m^2 Plus Bevacizumab 15.0 mg/kg	Participants received docetaxel 100 mg/m^2 intravenously on Day 1 of each 3 week cycle for a maximum of 27 weeks (9 cycles). In addition, participants received bevacizumab 15.0 mg/kg intravenously on Day 1 of each 3 week cycle until disease progression, unacceptable toxicity, or participant withdrawal.

Measured Values

	Docetaxel 100 mg/ m^2 Plus Placebo	Docetaxel 100 mg/m^2 Plus Bevacizumab 7.5 mg/kg	Docetaxel 100 mg/m^2 Plus Bevacizumab 15.0 mg/kg
Number of Participants Analyzed	207	201	206
Percentage of Participants With a Complete Response or a Partial Response [units: Percentage of participants]			

	Docetaxel 100 mg/ m^2 Plus Placebo	Docetaxel 100 mg/m^2 Plus Bevacizumab 7.5 mg/kg	Docetaxel 100 mg/m^2 Plus Bevacizumab 15.0 mg/kg
Number (95% Confidence Interval)			
Complete response	1.0 (0.1 to 3.4)	4.5 (2.1 to 8.3)	2.9 (1.1 to 6.2)
Partial response	45.4 (38.5 to 52.5)	50.7 (43.6 to 57.9)	61.2 (54.1 to 67.9)

Statistical Analysis 1 for Percentage of Participants With a Complete Response or a Partial Response

Statistical Analysis Overview	Comparison Groups	Docetaxel 100 mg/m^2 Plus Placebo, Docetaxel 100 mg/m^2 Plus Bevacizumab 7.5 mg/kg
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.0739
	Comments	[Not specified]
	Method	Chi-squared
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Other [Hauck-Anderson method]
	Estimated Value	8.85
	Confidence Interval	(2-Sided) 95% -1.1 to 18.8
	Estimation Comments	[Not specified]

Statistical Analysis 2 for Percentage of Participants With a Complete Response or a Partial Response

Statistical Analysis Overview	Comparison Groups	Docetaxel 100 mg/m^2 Plus Placebo, Docetaxel 100 mg/m^2 Plus Bevacizumab 15.0 mg/kg
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.0003
	Comments	[Not specified]
	Method	Chi-squared
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Other [Hauck-Anderson method]
	Estimated Value	17.7
	Confidence Interval	(2-Sided) 95% 8 to 27.4
	Estimation Comments	[Not specified]

3. Secondary Outcome Measure:

Measure Title	Duration of Response
Measure Description	Duration of response was defined as the time from the first documented complete response or partial response to disease progression or death. A complete response was defined as the disappearance of all target lesions or the disappearance of all non-target lesions and normalization of tumor marker level. A partial response was defined as at least a 30% decrease in the sum of the longest diameter of target lesions, taking as reference the baseline sum longest diameter. Best overall response (OR) was assessed by RECIST criteria. Patients were classified as responders if their best overall response was either confirmed CR or confirmed PR. Responses were evaluated using the Response Evaluation Criteria in Solid Tumors.
Time Frame	Baseline to the 15 September 2008 cut-off date (up to 2 years, 6 months)
Safety Issue?	No

Analysis Population Description

Intent-to-treat population: All randomized participants, regardless of whether they received study drug or not. Only participants with measurable disease at Baseline who had a complete response or a partial response were included in the analysis.

Reporting Groups

	Description
Docetaxel 100 mg/m^2 Plus Placebo	Participants received docetaxel 100 mg/m^2 intravenously on Day 1 of each 3 week cycle for a maximum of 27 weeks (9 cycles). In addition, participants received placebo to bevacizumab intravenously on Day 1 of each 3 week cycle until disease progression, unacceptable toxicity, or participant withdrawal.
Docetaxel 100 mg/m^2 Plus Bevacizumab 7.5 mg/kg	Participants received docetaxel 100 mg/m^2 intravenously on Day 1 of each 3 week cycle for a maximum of 27 weeks (9 cycles). In addition, participants received bevacizumab 7.5 mg/kg intravenously on Day 1 of each 3 week cycle until disease progression, unacceptable toxicity, or participant withdrawal.

	Description
Docetaxel 100 mg/m^2 Plus Bevacizumab 15.0 mg/kg	Participants received docetaxel 100 mg/m^2 intravenously on Day 1 of each 3 week cycle for a maximum of 27 weeks (9 cycles). In addition, participants received bevacizumab 15.0 mg/kg intravenously on Day 1 of each 3 week cycle until disease progression, unacceptable toxicity, or participant withdrawal.

Measured Values

	Docetaxel 100 mg/ m^2 Plus Placebo	Docetaxel 100 mg/m^2 Plus Bevacizumab 7.5 mg/kg	Docetaxel 100 mg/m^2 Plus Bevacizumab 15.0 mg/kg
Number of Participants Analyzed	95	112	134
Duration of Response [units: months] Median (95% Confidence Interval)	6.5 (6.1 to 7.8)	8.1 (6.8 to 9.1)	8.2 (6.5 to 8.9)

Statistical Analysis 1 for Duration of Response

Statistical Analysis Overview	Comparison Groups	Docetaxel 100 mg/m^2 Plus Placebo, Docetaxel 100 mg/m^2 Plus Bevacizumab 7.5 mg/kg
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Hazard Ratio (HR)
	Estimated Value	0.89
	Confidence Interval	(2-Sided) 95% 0.66 to 1.19
	Estimation Comments	[Not specified]

Statistical Analysis 2 for Duration of Response

Statistical Analysis Overview	Comparison Groups	Docetaxel 100 mg/m^2 Plus Placebo, Docetaxel 100 mg/m^2 Plus Bevacizumab 15.0 mg/kg
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Hazard Ratio (HR)

	Estimated Value	0.79
	Confidence Interval	(2-Sided) 95% 0.6 to 1.06
	Estimation Comments	[Not specified]

4. Secondary Outcome Measure:

Measure Title	Time to Treatment Failure
Measure Description	Time to treatment failure was defined as time from randomization to the date of disease progression, death, or withdrawal of treatment due to an adverse event, withdrawal of informed consent, insufficient therapeutic response, refusal of treatment/failure to co-operate, or failure to return, whichever occurred first.
Time Frame	Baseline to the 15 September 2008 cut-off date (up to 2 years, 6 months)
Safety Issue?	No

Analysis Population Description

Intent-to-treat population: All randomized participants, regardless of whether they received study drug or not.

Reporting Groups

	Description
Docetaxel 100 mg/m^2 Plus Placebo	Participants received docetaxel 100 mg/m^2 intravenously on Day 1 of each 3 week cycle for a maximum of 27 weeks (9 cycles). In addition, participants received placebo to bevacizumab intravenously on Day 1 of each 3 week cycle until disease progression, unacceptable toxicity, or participant withdrawal.
Docetaxel 100 mg/m^2 Plus Bevacizumab 7.5 mg/kg	Participants received docetaxel 100 mg/m^2 intravenously on Day 1 of each 3 week cycle for a maximum of 27 weeks (9 cycles). In addition, participants received bevacizumab 7.5 mg/kg intravenously on Day 1 of each 3 week cycle until disease progression, unacceptable toxicity, or participant withdrawal.
Docetaxel 100 mg/m^2 Plus Bevacizumab 15.0 mg/kg	Participants received docetaxel 100 mg/m^2 intravenously on Day 1 of each 3 week cycle for a maximum of 27 weeks (9 cycles). In addition, participants received bevacizumab 15.0 mg/kg intravenously on Day 1 of each 3 week cycle until disease progression, unacceptable toxicity, or participant withdrawal.

Measured Values

	Docetaxel 100 mg/ m^2 Plus Placebo	Docetaxel 100 mg/m^2 Plus Bevacizumab 7.5 mg/kg	Docetaxel 100 mg/m^2 Plus Bevacizumab 15.0 mg/kg
Number of Participants Analyzed	241	248	247
Time to Treatment Failure [units: months] Median (95% Confidence Interval)	6.3 (5.9 to 7.6)	7.7 (6.7 to 8.3)	7.9 (7.7 to 8.4)

Statistical Analysis 1 for Time to Treatment Failure

Statistical Analysis Overview	Comparison Groups	Docetaxel 100 mg/m^2 Plus Placebo, Docetaxel 100 mg/m^2 Plus Bevacizumab 7.5 mg/kg
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	0.0899
	Comments	[Not specified]
	Method	Log Rank
	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Hazard Ratio (HR)
	Estimated Value	0.86
	Confidence Interval	(2-Sided) 95% 0.71 to 1.03
	Estimation Comments	[Not specified]

Statistical Analysis 2 for Time to Treatment Failure

Statistical Analysis Overview	Comparison Groups	Docetaxel 100 mg/m^2 Plus Placebo, Docetaxel 100 mg/m^2 Plus Bevacizumab 15.0 mg/kg
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	0.0119
	Comments	[Not specified]
	Method	Log Rank
	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Hazard Ratio (HR)
	Estimated Value	0.79

	Confidence Interval	(2-Sided) 95% 0.66 to 0.95
	Estimation Comments	[Not specified]

5. Secondary Outcome Measure:

Measure Title	Overall Survival
Measure Description	Overall survival was defined as the time from randomization to death from any cause.
Time Frame	Baseline to the 30 Apr 2009 (up to 3 years, 1 month)
Safety Issue?	No

Analysis Population Description

Intent-to-treat population: All randomized participants, regardless of whether they received study drug or not.

Reporting Groups

	Description
Docetaxel 100 mg/m^2 Plus Placebo	Participants received docetaxel 100 mg/m^2 intravenously on Day 1 of each 3 week cycle for a maximum of 27 weeks (9 cycles). In addition, participants received placebo to bevacizumab intravenously on Day 1 of each 3 week cycle until disease progression, unacceptable toxicity, or participant withdrawal.
Docetaxel 100 mg/m^2 Plus Bevacizumab 7.5 mg/kg	Participants received docetaxel 100 mg/m^2 intravenously on Day 1 of each 3 week cycle for a maximum of 27 weeks (9 cycles). In addition, participants received bevacizumab 7.5 mg/kg intravenously on Day 1 of each 3 week cycle until disease progression, unacceptable toxicity, or participant withdrawal.
Docetaxel 100 mg/m^2 Plus Bevacizumab 15.0 mg/kg	Participants received docetaxel 100 mg/m^2 intravenously on Day 1 of each 3 week cycle for a maximum of 27 weeks (9 cycles). In addition, participants received bevacizumab 15.0 mg/kg intravenously on Day 1 of each 3 week cycle until disease progression, unacceptable toxicity, or participant withdrawal.

Measured Values

	Docetaxel 100 mg/ m^2 Plus Placebo	Docetaxel 100 mg/m^2 Plus Bevacizumab 7.5 mg/kg	Docetaxel 100 mg/m^2 Plus Bevacizumab 15.0 mg/kg
Number of Participants Analyzed	241	248	247
Overall Survival [units: months] Median (95% Confidence Interval)	31.9 (26.9 to NA) [1]	30.8 (25.4 to 35.8)	30.2 (25.9 to 36.4)

[1] Due to the low number of events, median duration of overall survival could not yet be determined.

Statistical Analysis 1 for Overall Survival

Statistical Analysis Overview	Comparison Groups	Docetaxel 100 mg/m^2 Plus Placebo, Docetaxel 100 mg/m^2 Plus Bevacizumab 7.5 mg/kg
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.7198
	Comments	[Not specified]
	Method	Log Rank
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Hazard Ratio (HR)
	Estimated Value	1.05
	Confidence Interval	(2-Sided) 95% 0.81 to 1.36
	Estimation Comments	[Not specified]

Statistical Analysis 2 for Overall Survival

Statistical Analysis Overview	Comparison Groups	Docetaxel 100 mg/m^2 Plus Placebo, Docetaxel 100 mg/m^2 Plus Bevacizumab 15.0 mg/kg
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.8528
	Comments	[Not specified]
	Method	Log Rank
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Hazard Ratio (HR)
	Estimated Value	1.03
	Confidence Interval	(2-Sided) 95% 0.79 to 1.33

	Estimation Comments	[Not specified]

Reported Adverse Events

Time Frame	Baseline to the 24 Oct 2013 cut-off date (up to and 21 day(s) after last dose)
Additional Description	[Not specified]

Reporting Groups

	Description
Docetaxel 100 mg/m^2 Plus Placebo	Participants received docetaxel 100 mg/m^2 intravenously on Day 1 of each 3 week cycle for a maximum of 27 weeks (9 cycles). In addition, participants received placebo to bevacizumab intravenously on Day 1 of each 3 week cycle until disease progression, unacceptable toxicity, or participant withdrawal.
Docetaxel 100 mg/m^2 Plus Bevacizumab 7.5 mg/kg	Participants received docetaxel 100 mg/m^2 intravenously on Day 1 of each 3 week cycle for a maximum of 27 weeks (9 cycles). In addition, participants received bevacizumab 7.5 mg/kg intravenously on Day 1 of each 3 week cycle until disease progression, unacceptable toxicity, or participant withdrawal.
Docetaxel 100 mg/m^2 Plus Bevacizumab 15.0 mg/kg	Participants received docetaxel 100 mg/m^2 intravenously on Day 1 of each 3 week cycle for a maximum of 27 weeks (9 cycles). In addition, participants received bevacizumab 15.0 mg/kg intravenously on Day 1 of each 3 week cycle until disease progression, unacceptable toxicity, or participant withdrawal.

Serious Adverse Events

	Docetaxel 100 mg/ m^2 Plus Placebo	Docetaxel 100 mg/m^2 Plus Bevacizumab 7.5 mg/kg	Docetaxel 100 mg/m^2 Plus Bevacizumab 15.0 mg/kg
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Total	82/217 (37.79%)	106/252 (42.06%)	120/261 (45.98%)
Blood and lymphatic system disorders			
Anaemia [A] †	1/217 (0.46%)	0/252 (0%)	0/261 (0%)
Febrile neutropenia [A] †	21/217 (9.68%)	29/252 (11.51%)	37/261 (14.18%)
Leukopenia [A] †	0/217 (0%)	3/252 (1.19%)	1/261 (0.38%)
Neutropenia [A] †	4/217 (1.84%)	13/252 (5.16%)	18/261 (6.9%)
Thrombocytopenia [A] †	0/217 (0%)	1/252 (0.4%)	0/261 (0%)
Cardiac disorders			

	Docetaxel 100 mg/ m^2 Plus Placebo	Docetaxel 100 mg/m^2 Plus Bevacizumab 7.5 mg/kg	Docetaxel 100 mg/m^2 Plus Bevacizumab 15.0 mg/kg
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Arrhythmia [A] †	1/217 (0.46%)	0/252 (0%)	0/261 (0%)
Arteriospasm coronary [A] †	0/217 (0%)	1/252 (0.4%)	0/261 (0%)
Atrial fibrillation [A] †	0/217 (0%)	1/252 (0.4%)	1/261 (0.38%)
Atrioventricular block first degree [A] †	0/217 (0%)	1/252 (0.4%)	0/261 (0%)
Cardiac failure [A] †	0/217 (0%)	1/252 (0.4%)	0/261 (0%)
Left ventricular dysfunction [A] †	0/217 (0%)	1/252 (0.4%)	0/261 (0%)
Myocardial infarction [A] †	0/217 (0%)	1/252 (0.4%)	0/261 (0%)
Tachycardia paroxysmal [A] †	0/217 (0%)	1/252 (0.4%)	0/261 (0%)
Ear and labyrinth disorders			
Vertigo [A] †	0/217 (0%)	1/252 (0.4%)	0/261 (0%)
Eye disorders			
Cataract [A] †	0/217 (0%)	1/252 (0.4%)	0/261 (0%)
Visual acuity reduced [A] †	0/217 (0%)	1/252 (0.4%)	0/261 (0%)
Vitreous detachment [A] †	0/217 (0%)	0/252 (0%)	1/261 (0.38%)
Gastrointestinal disorders			
Abdominal pain [A] †	4/217 (1.84%)	3/252 (1.19%)	2/261 (0.77%)
Anal fissure [A] †	0/217 (0%)	0/252 (0%)	1/261 (0.38%)
Colitis [A] †	1/217 (0.46%)	0/252 (0%)	0/261 (0%)
Constipation [A] †	1/217 (0.46%)	0/252 (0%)	1/261 (0.38%)
Diarrhoea [A] †	3/217 (1.38%)	6/252 (2.38%)	8/261 (3.07%)
Diverticular perforation [A] †	0/217 (0%)	1/252 (0.4%)	0/261 (0%)
Enteritis [A] †	0/217 (0%)	1/252 (0.4%)	0/261 (0%)

	Docetaxel 100 mg/ m^2 Plus Placebo	Docetaxel 100 mg/m^2 Plus Bevacizumab 7.5 mg/kg	Docetaxel 100 mg/m^2 Plus Bevacizumab 15.0 mg/kg
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Enterocolitis [A] †	0/217 (0%)	1/252 (0.4%)	0/261 (0%)
Gastric perforation [A] †	0/217 (0%)	0/252 (0%)	1/261 (0.38%)
Gastric ulcer [A] †	0/217 (0%)	1/252 (0.4%)	0/261 (0%)
Gastric ulcer haemorrhage [A] †	0/217 (0%)	0/252 (0%)	1/261 (0.38%)
Gastritis [A] †	1/217 (0.46%)	0/252 (0%)	0/261 (0%)
Gastritis erosive [A] †	0/217 (0%)	2/252 (0.79%)	0/261 (0%)
Gastritis haemorrhagic [A] †	1/217 (0.46%)	0/252 (0%)	0/261 (0%)
Gastroduodenal ulcer [A] †	0/217 (0%)	0/252 (0%)	1/261 (0.38%)
Gastrointestinal haemorrhage [A] †	1/217 (0.46%)	2/252 (0.79%)	3/261 (1.15%)
Gastrointestinal perforation [A] †	0/217 (0%)	0/252 (0%)	1/261 (0.38%)
Gastrointestinal ulcer [A] †	0/217 (0%)	0/252 (0%)	1/261 (0.38%)
Ileus [A] †	0/217 (0%)	1/252 (0.4%)	1/261 (0.38%)
Intestinal obstruction [A] †	0/217 (0%)	1/252 (0.4%)	2/261 (0.77%)
Intestinal perforation [A] †	1/217 (0.46%)	0/252 (0%)	0/261 (0%)
Large intestine perforation [A] †	1/217 (0.46%)	0/252 (0%)	0/261 (0%)
Nausea [A] †	0/217 (0%)	0/252 (0%)	2/261 (0.77%)
Pancreatitis necrotising [A] †	0/217 (0%)	1/252 (0.4%)	0/261 (0%)
Rectal haemorrhage [A] †	0/217 (0%)	1/252 (0.4%)	0/261 (0%)
Small intestinal obstruction [A] †	1/217 (0.46%)	0/252 (0%)	0/261 (0%)
Stomatitis [A] †	0/217 (0%)	3/252 (1.19%)	4/261 (1.53%)
Vomiting [A] †	2/217 (0.92%)	0/252 (0%)	1/261 (0.38%)

	Docetaxel 100 mg/ m^2 Plus Placebo	Docetaxel 100 mg/m^2 Plus Bevacizumab 7.5 mg/kg	Docetaxel 100 mg/m^2 Plus Bevacizumab 15.0 mg/kg
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
General disorders			
Asthenia [A] †	1/217 (0.46%)	6/252 (2.38%)	4/261 (1.53%)
Catheter related complication [A] †	0/217 (0%)	1/252 (0.4%)	0/261 (0%)
Chest pain [A] †	0/217 (0%)	1/252 (0.4%)	0/261 (0%)
Death [A] †	1/217 (0.46%)	0/252 (0%)	0/261 (0%)
Face oedema [A] †	0/217 (0%)	0/252 (0%)	1/261 (0.38%)
Fatigue [A] †	0/217 (0%)	2/252 (0.79%)	0/261 (0%)
General physical health deterioration [A] †	1/217 (0.46%)	0/252 (0%)	1/261 (0.38%)
Ill−defined disorder [A] †	0/217 (0%)	1/252 (0.4%)	0/261 (0%)
Impaired healing [A] †	0/217 (0%)	1/252 (0.4%)	0/261 (0%)
Inflammation [A] †	1/217 (0.46%)	0/252 (0%)	0/261 (0%)
Mucosal inflammation [A] †	1/217 (0.46%)	1/252 (0.4%)	2/261 (0.77%)
Multi−organ failure [A] †	0/217 (0%)	1/252 (0.4%)	0/261 (0%)
Oedema [A] †	0/217 (0%)	1/252 (0.4%)	0/261 (0%)
Oedema peripheral [A] †	2/217 (0.92%)	1/252 (0.4%)	0/261 (0%)
Pain [A] †	1/217 (0.46%)	1/252 (0.4%)	0/261 (0%)
Pyrexia [A] †	3/217 (1.38%)	6/252 (2.38%)	7/261 (2.68%)
Hepatobiliary disorders			
Biliary colic [A] †	0/217 (0%)	1/252 (0.4%)	0/261 (0%)
Cholangitis [A] †	0/217 (0%)	1/252 (0.4%)	0/261 (0%)
Cholecystitis [A] †	0/217 (0%)	0/252 (0%)	1/261 (0.38%)
Hepatic pain [A] †	0/217 (0%)	0/252 (0%)	1/261 (0.38%)

	Docetaxel 100 mg/ m^2 Plus Placebo	Docetaxel 100 mg/m^2 Plus Bevacizumab 7.5 mg/kg	Docetaxel 100 mg/m^2 Plus Bevacizumab 15.0 mg/kg
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Hepatitis [A] †	0/217 (0%)	1/252 (0.4%)	0/261 (0%)
Hepatorenal failure [A] †	1/217 (0.46%)	0/252 (0%)	0/261 (0%)
Hyperbilirubinaemia [A] †	0/217 (0%)	1/252 (0.4%)	0/261 (0%)
Jaundice cholestatic [A] †	0/217 (0%)	0/252 (0%)	1/261 (0.38%)
Immune system disorders			
Anaphylactic reaction [A] †	0/217 (0%)	1/252 (0.4%)	0/261 (0%)
Drug hypersensitivity [A] †	0/217 (0%)	1/252 (0.4%)	1/261 (0.38%)
Hypersensitivity [A] †	0/217 (0%)	1/252 (0.4%)	2/261 (0.77%)
Infections and infestations			
Anal abscess [A] †	0/217 (0%)	2/252 (0.79%)	2/261 (0.77%)
Anal infection [A] †	0/217 (0%)	0/252 (0%)	1/261 (0.38%)
Anorectal infection [A] †	0/217 (0%)	1/252 (0.4%)	0/261 (0%)
Appendicitis perforated [A] †	1/217 (0.46%)	0/252 (0%)	0/261 (0%)
Arthritis infective [A] †	0/217 (0%)	1/252 (0.4%)	0/261 (0%)
Bacteraemia [A] †	0/217 (0%)	0/252 (0%)	1/261 (0.38%)
Bacterial sepsis [A] †	1/217 (0.46%)	0/252 (0%)	0/261 (0%)
Breast abscess [A] †	0/217 (0%)	1/252 (0.4%)	0/261 (0%)
Bronchitis [A] †	0/217 (0%)	0/252 (0%)	1/261 (0.38%)
Catheter bacteraemia [A] †	0/217 (0%)	0/252 (0%)	1/261 (0.38%)
Catheter related infection [A] †	0/217 (0%)	0/252 (0%)	1/261 (0.38%)
Catheter sepsis [A] †	0/217 (0%)	1/252 (0.4%)	0/261 (0%)
Cellulitis [A] †	1/217 (0.46%)	0/252 (0%)	1/261 (0.38%)

	Docetaxel 100 mg/ m^2 Plus Placebo	Docetaxel 100 mg/m^2 Plus Bevacizumab 7.5 mg/kg	Docetaxel 100 mg/m^2 Plus Bevacizumab 15.0 mg/kg
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Central line infection [A] †	0/217 (0%)	2/252 (0.79%)	2/261 (0.77%)
Clostridial infection [A] †	1/217 (0.46%)	0/252 (0%)	1/261 (0.38%)
Diverticulitis [A] †	0/217 (0%)	0/252 (0%)	1/261 (0.38%)
Endophthalmitis [A] †	1/217 (0.46%)	0/252 (0%)	0/261 (0%)
Erysipelas [A] †	0/217 (0%)	1/252 (0.4%)	0/261 (0%)
Gastroenteritis viral [A] †	0/217 (0%)	0/252 (0%)	1/261 (0.38%)
Infection [A] †	5/217 (2.3%)	3/252 (1.19%)	2/261 (0.77%)
Lower respiratory tract infection [A] †	0/217 (0%)	0/252 (0%)	1/261 (0.38%)
Lung abscess [A] †	0/217 (0%)	0/252 (0%)	1/261 (0.38%)
Lung infection [A] †	1/217 (0.46%)	0/252 (0%)	0/261 (0%)
Nail bed infection [A] †	1/217 (0.46%)	0/252 (0%)	0/261 (0%)
Neutropenic infection [A] †	2/217 (0.92%)	2/252 (0.79%)	1/261 (0.38%)
Neutropenic sepsis [A] †	2/217 (0.92%)	3/252 (1.19%)	2/261 (0.77%)
Oral candidiasis [A] †	1/217 (0.46%)	0/252 (0%)	0/261 (0%)
Paronychia [A] †	0/217 (0%)	0/252 (0%)	2/261 (0.77%)
Periodontal infection [A] †	0/217 (0%)	1/252 (0.4%)	0/261 (0%)
Peritonsillar abscess [A] †	1/217 (0.46%)	0/252 (0%)	0/261 (0%)
Pneumonia [A] †	4/217 (1.84%)	2/252 (0.79%)	1/261 (0.38%)
Postoperative wound infection [A] †	1/217 (0.46%)	0/252 (0%)	1/261 (0.38%)
Purulent discharge [A] †	0/217 (0%)	0/252 (0%)	1/261 (0.38%)
Respiratory tract infection [A] †	2/217 (0.92%)	0/252 (0%)	0/261 (0%)

	Docetaxel 100 mg/ m^2 Plus Placebo	Docetaxel 100 mg/m^2 Plus Bevacizumab 7.5 mg/kg	Docetaxel 100 mg/m^2 Plus Bevacizumab 15.0 mg/kg
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Sepsis [A] †	0/217 (0%)	1/252 (0.4%)	2/261 (0.77%)
Septic shock [A] †	0/217 (0%)	1/252 (0.4%)	0/261 (0%)
Sinusitis [A] †	1/217 (0.46%)	0/252 (0%)	0/261 (0%)
Staphylococcal sepsis [A] †	0/217 (0%)	2/252 (0.79%)	0/261 (0%)
Stent related infection [A] †	0/217 (0%)	1/252 (0.4%)	0/261 (0%)
Subcutaneous abscess [A] †	0/217 (0%)	1/252 (0.4%)	0/261 (0%)
Upper respiratory tract infection [A] †	1/217 (0.46%)	0/252 (0%)	0/261 (0%)
Urinary tract infection [A] †	1/217 (0.46%)	3/252 (1.19%)	0/261 (0%)
Wound infection [A] †	1/217 (0.46%)	0/252 (0%)	0/261 (0%)
Injury, poisoning and procedural complications			
Dislocation of joint prosthesis [A] †	0/217 (0%)	1/252 (0.4%)	0/261 (0%)
Fall [A] †	0/217 (0%)	1/252 (0.4%)	1/261 (0.38%)
Femoral neck fracture [A] †	2/217 (0.92%)	0/252 (0%)	1/261 (0.38%)
Hip fracture [A] †	1/217 (0.46%)	1/252 (0.4%)	0/261 (0%)
Joint dislocation [A] †	1/217 (0.46%)	0/252 (0%)	0/261 (0%)
Narcotic intoxication [A] †	0/217 (0%)	0/252 (0%)	1/261 (0.38%)
Procedural complication [A] †	0/217 (0%)	1/252 (0.4%)	0/261 (0%)
Spinal fracture [A] †	0/217 (0%)	1/252 (0.4%)	0/261 (0%)
Wound dehiscence [A] †	0/217 (0%)	0/252 (0%)	1/261 (0.38%)
Wrist fracture [A] †	0/217 (0%)	1/252 (0.4%)	0/261 (0%)
Metabolism and nutrition disorders			
Decreased appetite [A] †	0/217 (0%)	1/252 (0.4%)	0/261 (0%)

	Docetaxel 100 mg/ m^2 Plus Placebo	Docetaxel 100 mg/m^2 Plus Bevacizumab 7.5 mg/kg	Docetaxel 100 mg/m^2 Plus Bevacizumab 15.0 mg/kg
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Dehydration [A] †	0/217 (0%)	3/252 (1.19%)	1/261 (0.38%)
Fluid retention [A] †	0/217 (0%)	0/252 (0%)	1/261 (0.38%)
Hypercalcaemia [A] †	2/217 (0.92%)	1/252 (0.4%)	1/261 (0.38%)
Hyperglycaemia [A] †	1/217 (0.46%)	1/252 (0.4%)	0/261 (0%)
Hypocalcaemia [A] †	0/217 (0%)	0/252 (0%)	1/261 (0.38%)
Hyponatraemia [A] †	0/217 (0%)	0/252 (0%)	1/261 (0.38%)
Musculoskeletal and connective tissue disorders			
Arthralgia [A] †	0/217 (0%)	0/252 (0%)	1/261 (0.38%)
Back pain [A] †	1/217 (0.46%)	0/252 (0%)	0/261 (0%)
Bone pain [A] †	0/217 (0%)	1/252 (0.4%)	2/261 (0.77%)
Musculoskeletal pain [A] †	0/217 (0%)	1/252 (0.4%)	1/261 (0.38%)
Osteoarthritis [A] †	0/217 (0%)	0/252 (0%)	1/261 (0.38%)
Osteonecrosis [A] †	0/217 (0%)	0/252 (0%)	1/261 (0.38%)
Pain in extremity [A] †	0/217 (0%)	0/252 (0%)	1/261 (0.38%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Colon cancer [A] †	1/217 (0.46%)	0/252 (0%)	0/261 (0%)
Inflammatory carcinoma of the breast [A] †	0/217 (0%)	1/252 (0.4%)	0/261 (0%)
Non−hodgkin's lymphoma [A] †	0/217 (0%)	0/252 (0%)	1/261 (0.38%)
Nervous system disorders			
Cauda equina syndrome [A] †	1/217 (0.46%)	0/252 (0%)	0/261 (0%)
Cerebral infarction [A] †	0/217 (0%)	0/252 (0%)	1/261 (0.38%)
Cerebral ischaemia [A] †	0/217 (0%)	0/252 (0%)	3/261 (1.15%)

	Docetaxel 100 mg/ m^2 Plus Placebo	Docetaxel 100 mg/m^2 Plus Bevacizumab 7.5 mg/kg	Docetaxel 100 mg/m^2 Plus Bevacizumab 15.0 mg/kg
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Cerebrovascular accident [A] †	1/217 (0.46%)	0/252 (0%)	0/261 (0%)
Convulsion [A] †	0/217 (0%)	0/252 (0%)	1/261 (0.38%)
Cranial nerve palsies multiple [A] †	0/217 (0%)	1/252 (0.4%)	0/261 (0%)
Dizziness [A] †	0/217 (0%)	1/252 (0.4%)	0/261 (0%)
Headache [A] †	0/217 (0%)	1/252 (0.4%)	1/261 (0.38%)
Migraine [A] †	0/217 (0%)	1/252 (0.4%)	0/261 (0%)
Nervous system disorder [A] †	0/217 (0%)	1/252 (0.4%)	1/261 (0.38%)
Peripheral sensory neuropathy [A] †	1/217 (0.46%)	0/252 (0%)	0/261 (0%)
Presyncope [A] †	0/217 (0%)	1/252 (0.4%)	0/261 (0%)
Syncope [A] †	0/217 (0%)	3/252 (1.19%)	0/261 (0%)
Psychiatric disorders			
Depression [A] †	0/217 (0%)	1/252 (0.4%)	0/261 (0%)
Mood altered [A] †	0/217 (0%)	1/252 (0.4%)	0/261 (0%)
Renal and urinary disorders			
Renal colic [A] †	0/217 (0%)	1/252 (0.4%)	0/261 (0%)
Renal failure [A] †	0/217 (0%)	1/252 (0.4%)	0/261 (0%)
Reproductive system and breast disorders			
Uterine prolapse [A] †	0/217 (0%)	0/252 (0%)	1/261 (0.38%)
Vaginal haemorrhage [A] †	1/217 (0.46%)	1/252 (0.4%)	0/261 (0%)
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure [A] †	0/217 (0%)	1/252 (0.4%)	0/261 (0%)
Asthmatic crisis [A] †	0/217 (0%)	1/252 (0.4%)	0/261 (0%)

	Docetaxel 100 mg/ m^2 Plus Placebo	Docetaxel 100 mg/m^2 Plus Bevacizumab 7.5 mg/kg	Docetaxel 100 mg/m^2 Plus Bevacizumab 15.0 mg/kg
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Dyspnoea [A] †	2/217 (0.92%)	3/252 (1.19%)	3/261 (1.15%)
Dyspnoea exertional [A] †	0/217 (0%)	1/252 (0.4%)	0/261 (0%)
Epistaxis [A] †	0/217 (0%)	1/252 (0.4%)	1/261 (0.38%)
Haemoptysis [A] †	0/217 (0%)	0/252 (0%)	1/261 (0.38%)
Interstitial lung disease [A] †	0/217 (0%)	0/252 (0%)	1/261 (0.38%)
Lung disorder [A] †	1/217 (0.46%)	0/252 (0%)	0/261 (0%)
Nasal septum ulceration [A] †	0/217 (0%)	0/252 (0%)	1/261 (0.38%)
Pleural effusion [A] †	1/217 (0.46%)	1/252 (0.4%)	3/261 (1.15%)
Pneumonitis [A] †	0/217 (0%)	1/252 (0.4%)	0/261 (0%)
Pneumothorax [A] †	3/217 (1.38%)	0/252 (0%)	0/261 (0%)
Pulmonary embolism [A] †	3/217 (1.38%)	0/252 (0%)	2/261 (0.77%)
Respiratory failure [A] †	0/217 (0%)	1/252 (0.4%)	0/261 (0%)
Skin and subcutaneous tissue disorders			
Skin toxicity [A] †	0/217 (0%)	0/252 (0%)	1/261 (0.38%)
Stevens−Johnson syndrome [A] †	1/217 (0.46%)	0/252 (0%)	0/261 (0%)
Surgical and medical procedures			
Central venous catheter removal [A] †	0/217 (0%)	0/252 (0%)	1/261 (0.38%)
Vertebroplasty [A] †	0/217 (0%)	1/252 (0.4%)	0/261 (0%)
Vascular disorders			
Deep vein thrombosis [A] †	2/217 (0.92%)	1/252 (0.4%)	0/261 (0%)
Embolism venous [A] †	1/217 (0.46%)	0/252 (0%)	0/261 (0%)
Flushing [A] †	0/217 (0%)	0/252 (0%)	1/261 (0.38%)

	Docetaxel 100 mg/ m^2 Plus Placebo	Docetaxel 100 mg/m^2 Plus Bevacizumab 7.5 mg/kg	Docetaxel 100 mg/m^2 Plus Bevacizumab 15.0 mg/kg
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Hypertension [A] †	0/217 (0%)	2/252 (0.79%)	2/261 (0.77%)
Hypertensive crisis [A] †	0/217 (0%)	1/252 (0.4%)	0/261 (0%)
Jugular vein thrombosis [A] †	0/217 (0%)	0/252 (0%)	1/261 (0.38%)
Microangiopathy [A] †	2/217 (0.92%)	0/252 (0%)	0/261 (0%)
Orthostatic hypotension [A] †	1/217 (0.46%)	0/252 (0%)	0/261 (0%)
Peripheral ischaemia [A] †	0/217 (0%)	1/252 (0.4%)	0/261 (0%)
Phlebitis [A] †	1/217 (0.46%)	0/252 (0%)	0/261 (0%)
Thrombophlebitis [A] †	0/217 (0%)	1/252 (0.4%)	0/261 (0%)
Venous thrombosis [A] †	1/217 (0.46%)	0/252 (0%)	0/261 (0%)

† Indicates events were collected by systematic assessment.
A Term from vocabulary, MedDRA 16.1

Other Adverse Events

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

	Docetaxel 100 mg/ m^2 Plus Placebo	Docetaxel 100 mg/m^2 Plus Bevacizumab 7.5 mg/kg	Docetaxel 100 mg/m^2 Plus Bevacizumab 15.0 mg/kg
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Total	216/217 (99.54%)	251/252 (99.6%)	260/261 (99.62%)
Blood and lymphatic system disorders			
Anaemia [A] †	37/217 (17.05%)	34/252 (13.49%)	32/261 (12.26%)
Leukopenia [A] †	14/217 (6.45%)	21/252 (8.33%)	20/261 (7.66%)
Neutropenia [A] †	44/217 (20.28%)	51/252 (20.24%)	53/261 (20.31%)
Ear and labyrinth disorders			
Vertigo [A] †	10/217 (4.61%)	11/252 (4.37%)	15/261 (5.75%)
Eye disorders			

	Docetaxel 100 mg/ m^2 Plus Placebo	Docetaxel 100 mg/m^2 Plus Bevacizumab 7.5 mg/kg	Docetaxel 100 mg/m^2 Plus Bevacizumab 15.0 mg/kg
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Conjunctivitis [A] †	11/217 (5.07%)	16/252 (6.35%)	39/261 (14.94%)
Lacrimation increased [A] †	63/217 (29.03%)	114/252 (45.24%)	120/261 (45.98%)
Gastrointestinal disorders			
Abdominal pain [A] †	39/217 (17.97%)	45/252 (17.86%)	58/261 (22.22%)
Abdominal pain upper [A] †	34/217 (15.67%)	24/252 (9.52%)	32/261 (12.26%)
Constipation [A] †	64/217 (29.49%)	89/252 (35.32%)	77/261 (29.5%)
Diarrhoea [A] †	106/217 (48.85%)	143/252 (56.75%)	140/261 (53.64%)
Dry mouth [A] †	8/217 (3.69%)	15/252 (5.95%)	12/261 (4.6%)
Dyspepsia [A] †	27/217 (12.44%)	36/252 (14.29%)	43/261 (16.48%)
Dysphagia [A] †	12/217 (5.53%)	13/252 (5.16%)	13/261 (4.98%)
Gingivitis [A] †	4/217 (1.84%)	11/252 (4.37%)	16/261 (6.13%)
Haemorrhoids [A] †	14/217 (6.45%)	22/252 (8.73%)	22/261 (8.43%)
Nausea [A] †	117/217 (53.92%)	115/252 (45.63%)	132/261 (50.57%)
Stomatitis [A] †	60/217 (27.65%)	127/252 (50.4%)	115/261 (44.06%)
Toothache [A] †	13/217 (5.99%)	13/252 (5.16%)	14/261 (5.36%)
Vomiting [A] †	59/217 (27.19%)	64/252 (25.4%)	75/261 (28.74%)
General disorders			
Asthenia [A] †	83/217 (38.25%)	88/252 (34.92%)	97/261 (37.16%)
Chest pain [A] †	19/217 (8.76%)	10/252 (3.97%)	20/261 (7.66%)
Fatigue [A] †	96/217 (44.24%)	105/252 (41.67%)	109/261 (41.76%)
Malaise [A] †	6/217 (2.76%)	10/252 (3.97%)	15/261 (5.75%)
Mucosal inflammation [A] †	48/217 (22.12%)	87/252 (34.52%)	78/261 (29.89%)

	Docetaxel 100 mg/ m^2 Plus Placebo	Docetaxel 100 mg/m^2 Plus Bevacizumab 7.5 mg/kg	Docetaxel 100 mg/m^2 Plus Bevacizumab 15.0 mg/kg
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Oedema [A] †	32/217 (14.75%)	12/252 (4.76%)	21/261 (8.05%)
Oedema peripheral [A] †	89/217 (41.01%)	63/252 (25%)	61/261 (23.37%)
Pain [A] †	20/217 (9.22%)	16/252 (6.35%)	16/261 (6.13%)
Pyrexia [A] †	45/217 (20.74%)	61/252 (24.21%)	63/261 (24.14%)
Infections and infestations			
Influenza [A] †	12/217 (5.53%)	26/252 (10.32%)	15/261 (5.75%)
Nasopharyngitis [A] †	14/217 (6.45%)	20/252 (7.94%)	35/261 (13.41%)
Rhinitis [A] †	9/217 (4.15%)	11/252 (4.37%)	18/261 (6.9%)
Sinusitis [A] †	8/217 (3.69%)	10/252 (3.97%)	19/261 (7.28%)
Upper respiratory tract infection [A] †	23/217 (10.6%)	22/252 (8.73%)	28/261 (10.73%)
Urinary tract infection [A] †	18/217 (8.29%)	27/252 (10.71%)	20/261 (7.66%)
Investigations			
Weight decreased [A] †	12/217 (5.53%)	29/252 (11.51%)	30/261 (11.49%)
Weight increased [A] †	16/217 (7.37%)	5/252 (1.98%)	7/261 (2.68%)
Metabolism and nutrition disorders			
Decreased appetite [A] †	58/217 (26.73%)	78/252 (30.95%)	85/261 (32.57%)
Musculoskeletal and connective tissue disorders			
Arthralgia [A] †	48/217 (22.12%)	74/252 (29.37%)	90/261 (34.48%)
Back pain [A] †	45/217 (20.74%)	36/252 (14.29%)	44/261 (16.86%)
Bone pain [A] †	38/217 (17.51%)	35/252 (13.89%)	42/261 (16.09%)
Muscular weakness [A] †	9/217 (4.15%)	16/252 (6.35%)	9/261 (3.45%)
Musculoskeletal chest pain [A] †	13/217 (5.99%)	12/252 (4.76%)	12/261 (4.6%)

	Docetaxel 100 mg/ m^2 Plus Placebo	Docetaxel 100 mg/m^2 Plus Bevacizumab 7.5 mg/kg	Docetaxel 100 mg/m^2 Plus Bevacizumab 15.0 mg/kg
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Musculoskeletal pain [A] †	23/217 (10.6%)	34/252 (13.49%)	36/261 (13.79%)
Myalgia [A] †	80/217 (36.87%)	82/252 (32.54%)	88/261 (33.72%)
Neck pain [A] †	8/217 (3.69%)	14/252 (5.56%)	17/261 (6.51%)
Pain in extremity [A] †	37/217 (17.05%)	56/252 (22.22%)	44/261 (16.86%)
Nervous system disorders			
Dizziness [A] †	25/217 (11.52%)	26/252 (10.32%)	31/261 (11.88%)
Dysgeusia [A] †	59/217 (27.19%)	77/252 (30.56%)	63/261 (24.14%)
Headache [A] †	56/217 (25.81%)	86/252 (34.13%)	79/261 (30.27%)
Hypoaesthesia [A] †	11/217 (5.07%)	2/252 (0.79%)	6/261 (2.3%)
Neuropathy peripheral [A] †	30/217 (13.82%)	35/252 (13.89%)	26/261 (9.96%)
Paraesthesia [A] †	40/217 (18.43%)	46/252 (18.25%)	51/261 (19.54%)
Peripheral sensory neuropathy [A] †	60/217 (27.65%)	67/252 (26.59%)	63/261 (24.14%)
Psychiatric disorders			
Anxiety [A] †	8/217 (3.69%)	11/252 (4.37%)	16/261 (6.13%)
Depression [A] †	11/217 (5.07%)	13/252 (5.16%)	13/261 (4.98%)
Insomnia [A] †	34/217 (15.67%)	31/252 (12.3%)	35/261 (13.41%)
Renal and urinary disorders			
Proteinuria [A] †	8/217 (3.69%)	12/252 (4.76%)	24/261 (9.2%)
Respiratory, thoracic and mediastinal disorders			
Cough [A] †	42/217 (19.35%)	67/252 (26.59%)	61/261 (23.37%)
Dysphonia [A] †	10/217 (4.61%)	24/252 (9.52%)	28/261 (10.73%)
Dyspnoea [A] †	49/217 (22.58%)	44/252 (17.46%)	60/261 (22.99%)

	Docetaxel 100 mg/ m^2 Plus Placebo	Docetaxel 100 mg/m^2 Plus Bevacizumab 7.5 mg/kg	Docetaxel 100 mg/m^2 Plus Bevacizumab 15.0 mg/kg
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Epistaxis [A] †	47/217 (21.66%)	123/252 (48.81%)	128/261 (49.04%)
Nasal dryness [A] †	3/217 (1.38%)	13/252 (5.16%)	12/261 (4.6%)
Oropharyngeal pain [A] †	19/217 (8.76%)	27/252 (10.71%)	28/261 (10.73%)
Pleural effusion [A] †	13/217 (5.99%)	10/252 (3.97%)	17/261 (6.51%)
Rhinorrhoea [A] †	19/217 (8.76%)	26/252 (10.32%)	38/261 (14.56%)
Skin and subcutaneous tissue disorders			
Alopecia [A] †	154/217 (70.97%)	181/252 (71.83%)	183/261 (70.11%)
Dry skin [A] †	32/217 (14.75%)	33/252 (13.1%)	25/261 (9.58%)
Erythema [A] †	20/217 (9.22%)	26/252 (10.32%)	33/261 (12.64%)
Nail disorder [A] †	87/217 (40.09%)	118/252 (46.83%)	118/261 (45.21%)
Nail toxicity [A] †	15/217 (6.91%)	16/252 (6.35%)	12/261 (4.6%)
Onycholysis [A] †	9/217 (4.15%)	21/252 (8.33%)	25/261 (9.58%)
Palmar−plantar erythrodysaesthesia syndrome [A] †	47/217 (21.66%)	80/252 (31.75%)	70/261 (26.82%)
Pruritus [A] †	19/217 (8.76%)	28/252 (11.11%)	23/261 (8.81%)
Rash [A] †	43/217 (19.82%)	43/252 (17.06%)	47/261 (18.01%)
Skin exfoliation [A] †	11/217 (5.07%)	21/252 (8.33%)	20/261 (7.66%)
Skin hyperpigmentation [A] †	8/217 (3.69%)	14/252 (5.56%)	10/261 (3.83%)
Vascular disorders			
Flushing [A] †	12/217 (5.53%)	15/252 (5.95%)	19/261 (7.28%)
Hot flush [A] †	16/217 (7.37%)	16/252 (6.35%)	19/261 (7.28%)
Hypertension [A] †	32/217 (14.75%)	44/252 (17.46%)	66/261 (25.29%)

	Docetaxel 100 mg/ m^2 Plus Placebo	Docetaxel 100 mg/m^2 Plus Bevacizumab 7.5 mg/kg	Docetaxel 100 mg/m^2 Plus Bevacizumab 15.0 mg/kg
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Lymphoedema [A] †	15/217 (6.91%)	19/252 (7.54%)	8/261 (3.07%)

† Indicates events were collected by systematic assessment.
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.

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.

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