ClinicalTrials.gov Protocol and Results Registration System (PRS) Receipt
Release Date: 05/21/2015

ClinicalTrials.gov ID: NCT00448591

Study Identification

Unique Protocol ID:	MO19391
Brief Title:	A Study of Avastin (Bevacizumab) Plus Taxane-Based Therapy in Patients With Locally Recurrent or Metastatic Breast Cancer.
Official Title:	An Open-label Study to Evaluate the Safety and Effect on Disease Progression and Overall Survival of Avastin Plus Taxane-based Chemotherapy in Patients With Locally Recurrent or Metastatic Breast Cancer
Secondary IDs:	

Study Status

Record Verification:	May 2015
Overall Status:	Completed
Study Start:	September 2006
Primary Completion:	February 2013 [Actual]
Study Completion:	February 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: Unknown Board Name: Joint Hospitals' Ethics Committee Board Affiliation: Unknown Phone: +02 6051 7111 Email:
Data Monitoring?:	
Plan to Share Data?:	
Oversight Authorities:	Australia: Joint Human Research Ethics Committee

Study Description

Brief Summary:	This single arm study will assess the safety and efficacy of a regimen of Avastin plus a taxane, with or without additional chemotherapy, as first-line treatment in patients with locally recurrent or metastatic breast cancer. All patients will receive Avastin (10mg/kg iv every 2 weeks, or 15 mg/kg iv every 3 weeks) plus taxane-based chemotherapy. If taxanes are contraindicated, alternative chemotherapy (other than anthracyclines or pegylated liposomal doxorubicin) may be used. The anticipated time on study treatment is until disease progression, and the target sample size is 500+ individuals.
Detailed Description:	

Conditions

Conditions:	Breast Cancer
Keywords:	

Study Design

Study Type:	Interventional
Primary Purpose:	Treatment
Study Phase:	Phase 3
Intervention Model:	Single Group Assignment
Number of Arms:	1
Masking:	Open Label
Allocation:	N/A
Endpoint Classification:	Safety/Efficacy Study
Enrollment:	2296 [Actual]

Arms and Interventions

Arms	Assigned Interventions
Experimental: 1	Drug: bevacizumab [Avastin] 10mg/kg iv on day 1 of each 3 week cycle, or 15mg/kg iv on day 1 of each 2 week cycle Drug: Taxane-based chemotherapy As prescribed

Outcome Measures

[See Results Section.]

Eligibility

Minimum Age: 18 Years

Maximum Age:

Gender: Both

Accepts Healthy Volunteers?: No

Criteria: Inclusion Criteria:

- patients, >=18 years of age;
- HER-2 negative adenocarcinoma of the breast, with locally recurrent or metastatic disease; (HER-2 positive patients only if previously treated with Herceptin in the adjuvant setting;
- candidates for chemotherapy.

Exclusion Criteria:

- previous chemotherapy for metastatic or locally recurrent breast cancer;
- concomitant hormonal therapy for metastatic or locally recurrent disease;
- concomitant Herceptin therapy for treatment of metastatic or locally recurrent HER-2 positive disease;
- previous radiotherapy for treatment of metastatic disease;
- evidence of CNS metastases.

Contacts/Locations

Study Officials: Clinical Trials
Study Director
Hoffmann-La Roche

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Suzhou, China, 215006

Shanghai, China, 200032

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Rabat, Morocco, 21000

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Zams, Austria, 6511

Bludesch, Austria, 6712

Bregenz, Austria, 6900

Wien, Austria, 1030

Wien, Austria, 1130

St Veit An Der Glan, Austria, 9300

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- Klagenfurt, Austria, 9026
- Wien, Austria, 1160
- Wien, Austria, 1220
- Wien, Austria, 1140
- St Pölten, Austria, 3100
- Wiener Neustadt, Austria, 2700
- Leoben, Austria, 8700
- Wels, Austria, 4600
- Linz, Austria, 4010
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- Ried-innkreis, Austria, 4910
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- Magdeburg, Germany, 39108
- Bochum, Germany, 44787
- Bad Saarow, Germany, 15526
- Wuppertal, Germany, 42105
- Troisdorf, Germany, 53804
- Lübeck, Germany, 23562

Rostock, Germany, 18059

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Augsburg, Germany, 86150

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Regensburg, Germany, 93053

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Essen, Germany, 45122

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Dresden, Germany, 01307

Kiel, Germany, 24105

Leipzig, Germany, 04129

Wuerselen, Germany, 52146

Freiburg, Germany, 79106

Frankfurt, Germany, 65929

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Terrassa, Spain, 08227

Terrassa, Spain, 08221

Salamanca, Spain, 37007

Madrid, Spain, 28905

Madrid, Spain, 28943

Sabadell, Barcelona, Spain, 08208

Alcorcon, Spain, 28922

Madrid, Spain, 28041

Las Palmas de Gran Canaria, Spain, 35016

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Montpellier, France, 34967

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Tours, France, 37044

Marseille, France, 13285

Grenoble, France, 38043

Mantes La Jolie, France, 78201

Paris, France, 75012

Toulouse, France, 31052

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Bordeaux, France, 33077

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Angers, France, 49933

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Strasbourg, France, 67065

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Safed, Israel, 13110

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Israel
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Roma, Italy, 00153

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France
Angers, France, 49933

Pontoise, France, 95300

Vandoeuvre Les Nancy, France, 54511

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Vigo, Spain, 36204

Pontevedra, Spain, 36002

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Murcia, Spain, 30008

References

Citations:

Links:

Study Data/Documents:

Study Results

Participant Flow

Reporting Groups

	Description
Bevacizumab	Participants received bevacizumab 15 milligrams per kilogram (mg/kg) intravenously (iv) on Day 1 of each 3 week cycle, or 10 mg/kg iv on Day 1 of each 2 week cycle (weekly equivalent dose of 5 mg/kg/week) until disease progression, unacceptable toxicity or withdrawal, along with Taxane-based chemotherapy or in combination with other chemotherapy as prescribed.

Overall Study

	Bevacizumab
Started	2296
Completed	0
Not Completed	2296
Withdrawal by Subject	178
Progressive Disease	1382
Adverse Event	382
Protocol Violation	41
Lost to Follow-up	19

	Bevacizumab
Treatment Regimen Completed	70
Not specified	154
Termination of Study	70

Baseline Characteristics

Analysis Population Description

The safety/intent-to-treat (ITT) population was defined as all participants who had signed informed consent, with at least one valid post-baseline assessment and who received at least one dose of bevacizumab.

Reporting Groups

	Description
Bevacizumab	Participants received bevacizumab 15 mg/kg iv on day 1 of each 3 week cycle, or 10 mg/kg iv on day 1 of each 2 week cycle (weekly equivalent dose of 5 mg/kg/week) until disease progression, unacceptable toxicity or withdrawal, along with Taxane-based chemotherapy as prescribed

Baseline Measures

	Bevacizumab
Number of Participants	2264
Age, Continuous [units: years] Mean (Standard Deviation)	53.2 (11.0)
Gender, Male/Female [units: participants]	
Female	2252
Male	12

Outcome Measures

1. Primary Outcome Measure:

Measure Title	Percentage of Participants With Adverse Events (AEs) and Serious AEs (SAEs) Related to Bevacizumab, Death, and AEs of Special Interest (AESIs)
Measure Description	Adverse events (including laboratory abnormalities) were assessed by the investigator according to the National Cancer Institute - Common Toxicity Criteria (NCI-CTC) grading systems.

Time Frame	Day 1 of Cycles 1, 2, 3, 4, 5, and 6 up to 6 months after the last bevacizumab infusion
Safety Issue?	Yes

Analysis Population Description
Safety Population

Reporting Groups

	Description
Bevacizumab	Participants received bevacizumab 15 mg/kg iv on Day 1 of each 3 week cycle, or 10 mg/kg iv on Day 1 of each 2 week cycle (weekly equivalent dose of 5 mg/kg/week) along with Taxane-based chemotherapy as prescribed

Measured Values

	Bevacizumab
Number of Participants Analyzed	2264
Percentage of Participants With Adverse Events (AEs) and Serious AEs (SAEs) Related to Bevacizumab, Death, and AEs of Special Interest (AESIs) [units: percentage of participants]	
Any AE	95.4
CTC grade 3, 4 or 5 AE	57.6
Bevacizumab-related AE	64.2
Any Serious AE	29.7
Bevacizumab-related serious SAE	7.6
All deaths	53.1
AESIs	71.8

2. Secondary Outcome Measure:

Measure Title	Percentage of Participants With Disease Progression
Measure Description	Disease progression was assessed by the investigator per standard clinical practice using Response Evaluation Criteria In Solid Tumors (RECIST) criteria.
Time Frame	Baseline, Day 1 of Cycle 4, final visit and every 3 months during follow-up until disease progression or death up to 45 months

Safety Issue?	No

Analysis Population Description
ITT Population

Reporting Groups

	Description
Bevacizumab	Participants received bevacizumab 15 mg/kg iv on Day 1 of each 3 week cycle, or 10 mg/kg iv on Day 1 of each 2 week cycle (weekly equivalent dose of 5 mg/kg/week) along with Taxane-based chemotherapy as prescribed

Measured Values

	Bevacizumab
Number of Participants Analyzed	2264
Percentage of Participants With Disease Progression [units: percentage of participants]	72.44

3. Secondary Outcome Measure:

Measure Title	Time to Progression (TTP)
Measure Description	TTP was defined as the time period from the start of first-line therapy to investigator-assessed disease progression. Tumor assessments were performed according to standard clinical practice using NCI criteria. Participants who had not progressed at the time of analysis (including those who died before progressive disease [PD]) or who were lost to follow-up were censored at the last bevacizumab administration date. Time to disease progression was determined by Kaplan-Meier estimates.
Time Frame	Baseline, Day 1 of Cycle 4, final visit and every 3 months during follow-up until disease progression or death up to 45 months
Safety Issue?	No

Analysis Population Description
ITT Population

Reporting Groups

	Description
Bevacizumab	Participants received bevacizumab 15 mg/kg iv on day 1 of each 3 week cycle, or 10 mg/kg iv on day 1 of each 2 week cycle (weekly equivalent dose of 5 mg/kg/week) until disease progression, unacceptable toxicity or withdrawal, along with Taxane-based chemotherapy as prescribed

Measured Values

	Bevacizumab
Number of Participants Analyzed	2264
Time to Progression (TTP) [units: months] Median (Full Range)	9.7 (9.4 to 10.1)

4. Secondary Outcome Measure:

Measure Title	Percentage of Participants With Recorded Death
Measure Description	
Time Frame	Baseline, Day 1 of Cycle 4, final visit and every 3 months during follow-up until disease progression or death up to 45 months
Safety Issue?	No

Analysis Population Description

ITT Population

Reporting Groups

	Description
Bevacizumab	Participants received bevacizumab 15 mg/kg iv on Day 1 of each 3 week cycle, or 10 mg/kg iv on Day 1 of each 2 week cycle (weekly equivalent dose of 5 mg/kg/week) along with Taxane-based chemotherapy as prescribed

Measured Values

	Bevacizumab
Number of Participants Analyzed	2264
Percentage of Participants With Recorded Death [units: percentage of participants]	53.14

5. Secondary Outcome Measure:

Measure Title	Overall Survival

Measure Description	Overall Survival was defined as the time from start of first-line therapy to death due to any cause. Participants for whom no death was captured in the clinical database were censored at the last date they were known to be alive. Median time to overall survival was calculated by Kaplan Meier estimates.
Time Frame	Baseline, Day 1 of Cycle 4, Final Visit and every 3 months during follow-up until death up to 45 months
Safety Issue?	No

Analysis Population Description
ITT Population

Reporting Groups

	Description
Bevacizumab	Participants received bevacizumab 15 mg/kg iv on Day 1 of each 3 week cycle, or 10 mg/kg iv on Day 1 of each 2 week cycle (weekly equivalent dose of 5 mg/kg/week) until disease progression, unacceptable toxicity or withdrawal, along with Taxane-based chemotherapy as prescribed

Measured Values

	Bevacizumab
Number of Participants Analyzed	2264
Overall Survival [units: months] Median (Full Range)	25.2 (24.0 to 26.3)

6. Secondary Outcome Measure:

Measure Title	Percentage of Participants by Best Overall Response to Treatment
Measure Description	Best overall response is defined as the best response shown throughout the study. Tumor assessment was performed by the investigator using standard clinical practice.
Time Frame	Baseline, Day 1 of Cycle 4, final visit and every 3 months during follow-up until disease progression or death up to 45 months
Safety Issue?	No

Analysis Population Description
ITT Population

Reporting Groups

	Description
Bevacizumab	Participants received bevacizumab 15 mg/kg iv on Day 1 of each 3 week cycle, or 10 mg/kg iv on Day 1 of each 2 week cycle (weekly equivalent dose of 5 mg/kg/week) along with Taxane-based chemotherapy as prescribed

Measured Values

	Bevacizumab
Number of Participants Analyzed	2264
Percentage of Participants by Best Overall Response to Treatment [units: percentage of participants]	
Complete response	9.0
Partial response	45.1
Stable disease	32.4
Progressive disease	9.1
Not evaluable	0.1
Assessment not done	4.2

Reported Adverse Events

Time Frame	Adverse events were recorded throughout the study from date of first dose of drug administration until follow up visits.
Additional Description	[Not specified]

Reporting Groups

	Description
Bevacizumab	Participants received bevacizumab 15 mg/kg iv on Day 1 of each 3 week cycle, or 10 mg/kg iv on Day 1 of each 2 week cycle (weekly equivalent dose of 5 mg/kg/week) until disease progression, unacceptable toxicity or withdrawal, along with Taxane-based chemotherapy as prescribed

Serious Adverse Events

	Bevacizumab
	Affected/At Risk (%)
Total	672/2264 (29.68%)
Blood and lymphatic system disorders	
Agranulocytosis [A] *	1/2264 (0.04%)
Anaemia [A] *	8/2264 (0.35%)
Bone marrow failure [A] *	1/2264 (0.04%)
Disseminated intravascular coagulation [A] *	3/2264 (0.13%)
Febrile bone marrow aplasia [A] *	14/2264 (0.62%)
Febrile neutropenia [A] *	117/2264 (5.17%)
Leukopenia [A] *	8/2264 (0.35%)
Lymphopenia [A] *	1/2264 (0.04%)
Neutropenia [A] *	98/2264 (4.33%)
Thrombocytopenia [A] *	6/2264 (0.27%)
Thrombotic microangiopathy [A] *	1/2264 (0.04%)
Thrombotic thrombocytopenic purpura [A] *	1/2264 (0.04%)
Cardiac disorders	
Acute myocardial infarction [A] *	1/2264 (0.04%)
Angina unstable [A] *	2/2264 (0.09%)
Arrhythmia [A] *	1/2264 (0.04%)
Atrial fibrillation [A] *	3/2264 (0.13%)
Atrial flutter [A] *	1/2264 (0.04%)
Cardiac arrest [A] *	2/2264 (0.09%)
Cardiac failure [A] *	4/2264 (0.18%)

	Bevacizumab
	Affected/At Risk (%)
Cardiac failure congestive [A] *	4/2264 (0.18%)
Cardiogenic shock [A] *	1/2264 (0.04%)
Cardiomyopathy [A] *	1/2264 (0.04%)
Cardiotoxicity [A] *	1/2264 (0.04%)
Congestive cardiomyopathy [A] *	1/2264 (0.04%)
Coronary artery disease [A] *	1/2264 (0.04%)
Diastolic dysfunction [A] *	1/2264 (0.04%)
Myocardial infarction [A] *	4/2264 (0.18%)
Myocardial ischaemia [A] *	1/2264 (0.04%)
Palpitations [A] *	2/2264 (0.09%)
Pericardial effusion [A] *	1/2264 (0.04%)
Sinus tachycardia [A] *	1/2264 (0.04%)
Tachycardia [A] *	1/2264 (0.04%)
Ventricular arrhythmia [A] *	1/2264 (0.04%)
Ear and labyrinth disorders	
Deafness [A] *	2/2264 (0.09%)
Eye disorders	
Blindness [A] *	1/2264 (0.04%)
Diplopia [A] *	2/2264 (0.09%)
Keratitis [A] *	1/2264 (0.04%)
Pupils unequal [A] *	1/2264 (0.04%)
Retinal detachment [A] *	1/2264 (0.04%)

	Bevacizumab
	Affected/At Risk (%)
Gastrointestinal disorders	
Abdominal pain [A] *	7/2264 (0.31%)
Abdominal pain upper [A] *	1/2264 (0.04%)
Anal fissure [A] *	1/2264 (0.04%)
Anal fistula [A] *	3/2264 (0.13%)
Ascites [A] *	2/2264 (0.09%)
Colitis [A] *	2/2264 (0.09%)
Colitis ulcerative [A] *	1/2264 (0.04%)
Constipation [A] *	5/2264 (0.22%)
Dental caries [A] *	1/2264 (0.04%)
Diarrhoea [A] *	13/2264 (0.57%)
Diarrhoea haemorrhagic [A] *	2/2264 (0.09%)
Diverticulum intestinal haemorrhagic [A] *	1/2264 (0.04%)
Duodenal perforation [A] *	1/2264 (0.04%)
Duodenal ulcer [A] *	1/2264 (0.04%)
Dysphagia [A] *	1/2264 (0.04%)
Enteritis [A] *	1/2264 (0.04%)
Gastric haemorrhage [A] *	1/2264 (0.04%)
Gastric perforation [A] *	1/2264 (0.04%)
Gastritis [A] *	1/2264 (0.04%)
Gastrointestinal disorder [A] *	1/2264 (0.04%)
Gastrointestinal haemorrhage [A] *	9/2264 (0.4%)

	Bevacizumab
	Affected/At Risk (%)
Gastrointestinal obstruction [A] *	1/2264 (0.04%)
Gastrointestinal pain [A] *	1/2264 (0.04%)
Gastrointestinal perforation [A] *	3/2264 (0.13%)
Gastrointestinal toxicity [A] *	1/2264 (0.04%)
Gingivitis [A] *	1/2264 (0.04%)
Haematemesis [A] *	2/2264 (0.09%)
Haematochezia [A] *	1/2264 (0.04%)
Ileal perforation [A] *	1/2264 (0.04%)
Intestinal obstruction [A] *	1/2264 (0.04%)
Intestinal perforation [A] *	2/2264 (0.09%)
Irritable bowel syndrome [A] *	1/2264 (0.04%)
Large intestine perforation [A] *	2/2264 (0.09%)
Lower gastrointestinal haemorrhage [A] *	1/2264 (0.04%)
Melaena [A] *	1/2264 (0.04%)
Nausea [A] *	6/2264 (0.27%)
Oesophageal fistula [A] *	1/2264 (0.04%)
Oesophageal stenosis [A] *	1/2264 (0.04%)
Oesophagitis [A] *	1/2264 (0.04%)
Pancreatitis [A] *	1/2264 (0.04%)
Peritonitis [A] *	2/2264 (0.09%)
Pneumoperitoneum [A] *	1/2264 (0.04%)
Proctalgia [A] *	1/2264 (0.04%)

	Bevacizumab
	Affected/At Risk (%)
Proctocolitis [A] *	1/2264 (0.04%)
Rectal haemorrhage [A] *	4/2264 (0.18%)
Sigmoiditis [A] *	1/2264 (0.04%)
Stomatitis [A] *	4/2264 (0.18%)
Subileus [A] *	3/2264 (0.13%)
Vomiting [A] *	20/2264 (0.88%)
General disorders	
Aplasia [A] *	1/2264 (0.04%)
Asthenia [A] *	5/2264 (0.22%)
Chest pain [A] *	6/2264 (0.27%)
Death [A] *	2/2264 (0.09%)
Discomfort [A] *	1/2264 (0.04%)
Extravasation [A] *	1/2264 (0.04%)
Fatigue [A] *	3/2264 (0.13%)
General physical health deterioration [A] *	6/2264 (0.27%)
Hyperthermia [A] *	1/2264 (0.04%)
Impaired healing [A] *	9/2264 (0.4%)
Malaise [A] *	3/2264 (0.13%)
Mucosal inflammation [A] *	1/2264 (0.04%)
Necrosis [A] *	1/2264 (0.04%)
Oedema peripheral [A] *	2/2264 (0.09%)
Pain [A] *	3/2264 (0.13%)

	Bevacizumab
	Affected/At Risk (%)
Pelvic mass [A] *	1/2264 (0.04%)
Pyrexia [A] *	26/2264 (1.15%)
Hepatobiliary disorders	
Cholangitis [A] *	1/2264 (0.04%)
Cholecystitis [A] *	3/2264 (0.13%)
Cholecystitis acute [A] *	1/2264 (0.04%)
Hepatic atrophy [A] *	1/2264 (0.04%)
Hepatic failure [A] *	3/2264 (0.13%)
Hepatic functional abnormal [A] *	1/2264 (0.04%)
Hepatitis toxic [A] *	1/2264 (0.04%)
Hepatotoxicity [A] *	1/2264 (0.04%)
Hyperbilirubinaemia [A] *	3/2264 (0.13%)
Jaundice hepatocellular [A] *	1/2264 (0.04%)
Portal vein thrombosis [A] *	1/2264 (0.04%)
Immune system disorders	
Hypersensitivity [A] *	3/2264 (0.13%)
Infections and infestations	
Abscess [A] *	2/2264 (0.09%)
Abscess limb [A] *	4/2264 (0.18%)
Abscess soft tissue [A] *	1/2264 (0.04%)
Anal abscess [A] *	5/2264 (0.22%)
Anal infection [A] *	1/2264 (0.04%)

	Bevacizumab
	Affected/At Risk (%)
Appendicitis [A] *	2/2264 (0.09%)
Arthritis infective [A] *	1/2264 (0.04%)
Bronchitis [A] *	3/2264 (0.13%)
Catheter sepsis [A] *	1/2264 (0.04%)
Catheter site infection [A] *	2/2264 (0.09%)
Cellulitis [A] *	3/2264 (0.13%)
Clostridial infection [A] *	1/2264 (0.04%)
Clostridium difficile colitis [A] *	1/2264 (0.04%)
Device related infection [A] *	16/2264 (0.71%)
Diverticulitis [A] *	4/2264 (0.18%)
Endocarditis [A] *	1/2264 (0.04%)
Erysipelas [A] *	4/2264 (0.18%)
Escherichia infection [A] *	1/2264 (0.04%)
Febrile infection [A] *	3/2264 (0.13%)
Gastroenteritis [A] *	1/2264 (0.04%)
Gastrointestinal infection [A] *	1/2264 (0.04%)
Herpes zoster [A] *	2/2264 (0.09%)
Infected cyst [A] *	1/2264 (0.04%)
Infection [A] *	15/2264 (0.66%)
Influenza [A] *	1/2264 (0.04%)
Kidney infection [A] *	1/2264 (0.04%)
Klebsiella sepsis [A] *	1/2264 (0.04%)

	Bevacizumab
	Affected/At Risk (%)
Laryngitis [A] *	1/2264 (0.04%)
Liver abscess [A] *	1/2264 (0.04%)
Lower respiratory infection [A] *	3/2264 (0.13%)
Lung infection [A] *	2/2264 (0.09%)
Neutropenic infection [A] *	1/2264 (0.04%)
Neutropenic sepsis [A] *	8/2264 (0.35%)
Osteomyelitis [A] *	1/2264 (0.04%)
Otitis media [A] *	1/2264 (0.04%)
Parotid abscess [A] *	1/2264 (0.04%)
Perianal abscess [A] *	1/2264 (0.04%)
Periodontal infection [A] *	1/2264 (0.04%)
Peritonsillar abscess [A] *	1/2264 (0.04%)
Pneumonia [A] *	17/2264 (0.75%)
Postoperative wound infection [A] *	1/2264 (0.04%)
Pseudomonas infection [A] *	1/2264 (0.04%)
Pyelonephritis [A] *	1/2264 (0.04%)
Renal cyst infection [A] *	1/2264 (0.04%)
Respiratory moniliasis [A] *	1/2264 (0.04%)
Sepsis [A] *	17/2264 (0.75%)
Septic shock [A] *	1/2264 (0.04%)
Sinusitis [A] *	1/2264 (0.04%)
Skin infection [A] *	1/2264 (0.04%)

	Bevacizumab
	Affected/At Risk (%)
Soft tissue infection [A] *	2/2264 (0.09%)
Staphylococcal sepsis [A] *	1/2264 (0.04%)
Tonsillitis [A] *	1/2264 (0.04%)
Tooth infection [A] *	1/2264 (0.04%)
Tuberculous pleurisy [A] *	1/2264 (0.04%)
Upper respiratory tract infection [A] *	1/2264 (0.04%)
Urinary tract infection [A] *	9/2264 (0.4%)
Urosepsis [A] *	1/2264 (0.04%)
Varicella [A] *	1/2264 (0.04%)
Viral infection [A] *	1/2264 (0.04%)
Wound abscess [A] *	1/2264 (0.04%)
Injury, poisoning and procedural complications	
Contusion [A] *	1/2264 (0.04%)
Device breakage [A] *	1/2264 (0.04%)
Device leakage [A] *	1/2264 (0.04%)
Fall [A] *	4/2264 (0.18%)
Femoral neck fracture [A] *	2/2264 (0.09%)
Femur fracture [A] *	2/2264 (0.09%)
Fracture [A] *	1/2264 (0.04%)
Haemothorax [A] *	1/2264 (0.04%)
Head injury [A] *	2/2264 (0.09%)
Hepatic rupture [A] *	1/2264 (0.04%)

	Bevacizumab
	Affected/At Risk (%)
Humerus fracture [A] *	3/2264 (0.13%)
Joint dislocation [A] *	2/2264 (0.09%)
Lumbar vertebral fracture [A] *	1/2264 (0.04%)
Medical device complication [A] *	1/2264 (0.04%)
Patella fracture [A] *	1/2264 (0.04%)
Procedural complication [A] *	1/2264 (0.04%)
Procedural pain [A] *	2/2264 (0.09%)
Radiation injury [A] *	1/2264 (0.04%)
Radiation oesophagitis [A] *	1/2264 (0.04%)
Radius fracture [A] *	1/2264 (0.04%)
Rib fracture [A] *	1/2264 (0.04%)
Subcutaneous haematoma [A] *	1/2264 (0.04%)
Thrombosis in device [A] *	1/2264 (0.04%)
Wound [A] *	1/2264 (0.04%)
Wound dehiscence [A] *	1/2264 (0.04%)
Investigations	
Granulocyte count decreased [A] *	1/2264 (0.04%)
Haemoglobin decreased [A] *	2/2264 (0.09%)
Neutrophil count abnormal [A] *	1/2264 (0.04%)
Neutrophil count decreased [A] *	3/2264 (0.13%)
Platelet count decreased [A] *	2/2264 (0.09%)
Scan myocardial perfusion abnormal [A] *	1/2264 (0.04%)

	Bevacizumab
	Affected/At Risk (%)
Transaminases increased [A] *	2/2264 (0.09%)
White blood cell count abnormal [A] *	1/2264 (0.04%)
White blood cell count decreased [A] *	4/2264 (0.18%)
Metabolism and nutrition disorders	
Anorexia [A] *	2/2264 (0.09%)
Dehydration [A] *	5/2264 (0.22%)
Diabetes mellitus [A] *	1/2264 (0.04%)
Gout [A] *	1/2264 (0.04%)
Hypercalcaemia [A] *	4/2264 (0.18%)
Hyperkalaemia [A] *	1/2264 (0.04%)
Hypernatraemia [A] *	1/2264 (0.04%)
Hypocalcaemia [A] *	1/2264 (0.04%)
Hypoglycaemia [A] *	1/2264 (0.04%)
Hypokalaemia [A] *	3/2264 (0.13%)
Hyponatraemia [A] *	1/2264 (0.04%)
Hypovolaemia [A] *	1/2264 (0.04%)
Metabolic acidosis [A] *	2/2264 (0.09%)
Musculoskeletal and connective tissue disorders	
Arthralgia [A] *	1/2264 (0.04%)
Back pain [A] *	8/2264 (0.35%)
Bone disorder [A] *	1/2264 (0.04%)
Bone pain [A] *	2/2264 (0.09%)

	Bevacizumab
	Affected/At Risk (%)
Fistula [A] *	1/2264 (0.04%)
Joint destruction [A] *	1/2264 (0.04%)
Musculoskeletal pain [A] *	4/2264 (0.18%)
Neck pain [A] *	1/2264 (0.04%)
Osteitis [A] *	1/2264 (0.04%)
Osteoarthritis [A] *	1/2264 (0.04%)
Osteolysis [A] *	1/2264 (0.04%)
Osteonecrosis [A] *	6/2264 (0.27%)
Pain in extremity [A] *	2/2264 (0.09%)
Pathological fracture [A] *	3/2264 (0.13%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	
Breast cancer [A] *	1/2264 (0.04%)
Cervix carcinoma [A] *	1/2264 (0.04%)
Metastases to bladder [A] *	1/2264 (0.04%)
Metastases to meninges [A] *	1/2264 (0.04%)
Uterine leiomyoma [A] *	1/2264 (0.04%)
Uterine prolapse [A] *	1/2264 (0.04%)
Nervous system disorders	
Cerebral haemorrhage [A] *	2/2264 (0.09%)
Cerebral ischaemia [A] *	1/2264 (0.04%)
Cerebral microangiopathy [A] *	1/2264 (0.04%)
Cerebrovascular accident [A] *	4/2264 (0.18%)

	Bevacizumab
	Affected/At Risk (%)
Convulsion [A] *	3/2264 (0.13%)
Cranial nerve paralysis [A] *	1/2264 (0.04%)
Dementia alzheimer's type [A] *	1/2264 (0.04%)
Dizziness [A] *	2/2264 (0.09%)
Epilepsy [A] *	1/2264 (0.04%)
Facial palsy [A] *	3/2264 (0.13%)
Headache [A] *	6/2264 (0.27%)
Hemiparesis [A] *	2/2264 (0.09%)
Intracranial pressure increased [A] *	1/2264 (0.04%)
Movement disorder [A] *	1/2264 (0.04%)
Neuropathy peripheral [A] *	2/2264 (0.09%)
Optic neuritis retrobulbar [A] *	1/2264 (0.04%)
Paraesthesia [A] *	2/2264 (0.09%)
Paraplegia [A] *	1/2264 (0.04%)
Peripheral motor neuropathy [A] *	1/2264 (0.04%)
Pneumocephalus [A] *	1/2264 (0.04%)
Presyncope [A] *	1/2264 (0.04%)
Reversible ischaemic neurological deficit [A] *	1/2264 (0.04%)
Syncope [A] *	2/2264 (0.09%)
Transient ischaemic attack [A] *	2/2264 (0.09%)
Psychiatric disorders	
Acute psychosis [A] *	1/2264 (0.04%)

	Bevacizumab
	Affected/At Risk (%)
Confusional state [A] *	2/2264 (0.09%)
Depression [A] *	4/2264 (0.18%)
Drug abuse [A] *	1/2264 (0.04%)
Insomnia related to another mental condition [A] *	1/2264 (0.04%)
Major depression [A] *	1/2264 (0.04%)
Mental disorder [A] *	1/2264 (0.04%)
Renal and urinary disorders	
Haematuria [A] *	2/2264 (0.09%)
Hydronephrosis [A] *	1/2264 (0.04%)
Hydroureter [A] *	1/2264 (0.04%)
Nephrotic syndrome [A] *	3/2264 (0.13%)
Obstrucive uropathy [A] *	1/2264 (0.04%)
Proteinuria [A] *	5/2264 (0.22%)
Renal colic [A] *	1/2264 (0.04%)
Renal failure [A] *	3/2264 (0.13%)
Ureteric obstruction [A] *	1/2264 (0.04%)
Urethral pain [A] *	1/2264 (0.04%)
Reproductive system and breast disorders	
Pelvic pain [A] *	1/2264 (0.04%)
Uterine disorder [A] *	1/2264 (0.04%)
Uterine haemorrhage [A] *	1/2264 (0.04%)
Respiratory, thoracic and mediastinal disorders	

	Bevacizumab
	Affected/At Risk (%)
Aspiration [A] *	1/2264 (0.04%)
Dyspnoea [A] *	23/2264 (1.02%)
Dyspnoea exertional [A] *	1/2264 (0.04%)
Epistaxis [A] *	9/2264 (0.4%)
Haemoptysis [A] *	5/2264 (0.22%)
Hypoventilation [A] *	1/2264 (0.04%)
Hypoxia [A] *	1/2264 (0.04%)
Lung disorder [A] *	3/2264 (0.13%)
Nasal septum perforation [A] *	3/2264 (0.13%)
Non-cardiogenic pulmonary oedema [A] *	1/2264 (0.04%)
Pharyngeal inflammation [A] *	1/2264 (0.04%)
Pleural effusion [A] *	9/2264 (0.4%)
Pneumonia aspiration [A] *	1/2264 (0.04%)
Pneumothorax [A] *	6/2264 (0.27%)
Pulmonary embolism [A] *	21/2264 (0.93%)
Pulmonary infarction [A] *	1/2264 (0.04%)
Pulmonary oedema [A] *	2/2264 (0.09%)
Pulmonary thrombosis [A] *	1/2264 (0.04%)
Respiratory failure [A] *	2/2264 (0.09%)
Skin and subcutaneous tissue disorders	
Drug eruption [A] *	1/2264 (0.04%)
Intertrigo [A] *	1/2264 (0.04%)

	Bevacizumab
	Affected/At Risk (%)
Leukocytoclastic vasculitis [A] *	1/2264 (0.04%)
Palmar-plantar erythrodysaesthesia syndrome [A] *	2/2264 (0.09%)
Pruritus [A] *	1/2264 (0.04%)
Skin necrosis [A] *	1/2264 (0.04%)
Skin toxicity [A] *	1/2264 (0.04%)
Skin ulcer [A] *	2/2264 (0.09%)
Surgical and medical procedures	
Breast lump removal [A] *	1/2264 (0.04%)
Catheter removal [A] *	1/2264 (0.04%)
Hepatectomy [A] *	2/2264 (0.09%)
Hip surgery [A] *	1/2264 (0.04%)
Laryngeal operation [A] *	1/2264 (0.04%)
Mastectomy [A] *	3/2264 (0.13%)
Thoractomy [A] *	1/2264 (0.04%)
Vascular disorders	
Aortic stenosis [A] *	1/2264 (0.04%)
Axillary vein thrombosis [A] *	1/2264 (0.04%)
Deep vein thrombosis [A] *	12/2264 (0.53%)
Haemodynamic instability [A] *	1/2264 (0.04%)
Haemorrhage [A] *	3/2264 (0.13%)
Hypertension [A] *	16/2264 (0.71%)
Hypertensive crisis [A] *	3/2264 (0.13%)

	Bevacizumab
	Affected/At Risk (%)
Peripheral ischaemia [A] *	2/2264 (0.09%)
Phlebitis [A] *	2/2264 (0.09%)
Thrombophlebitis superficial [A] *	1/2264 (0.04%)
Thrombosis [A] *	4/2264 (0.18%)
Vena cava thrombosis [A] *	1/2264 (0.04%)
Venous thrombosis [A] *	2/2264 (0.09%)
Venous thrombosis limb [A] *	4/2264 (0.18%)

* Indicates events were collected by non-systematic methods.
A Term from vocabulary, MedDRA (10.1)

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

	Bevacizumab
	Affected/At Risk (%)
Total	2095/2264 (92.54%)
Eye disorders	
Lacrimation increased [A] *	212/2264 (9.36%)
Gastrointestinal disorders	
Abdominal pain [A] *	210/2264 (9.28%)
Abdominal pain upper [A] *	153/2264 (6.76%)
Constipation [A] *	415/2264 (18.33%)
Diarrhoea [A] *	613/2264 (27.08%)
Dyspepsia [A] *	119/2264 (5.26%)
Gingival bleeding [A] *	131/2264 (5.79%)
Nausea [A] *	667/2264 (29.46%)

	Bevacizumab
	Affected/At Risk (%)
Stomatitis [A] *	657/2264 (29.02%)
Vomiting [A] *	352/2264 (15.55%)
General disorders	
Fatigue [A] *	1111/2264 (49.07%)
Oedema peripheral [A] *	202/2264 (8.92%)
Pyrexia [A] *	361/2264 (15.95%)
Infections and infestations	
Nasopharyngitis [A] *	124/2264 (5.48%)
Urinary tract infection [A] *	142/2264 (6.27%)
Investigations	
Alanine aminotransferase increased [A] *	293/2264 (12.94%)
Aspartate aminotransferase increased [A] *	259/2264 (11.44%)
Blood alkaline phosphatase increased [A] *	202/2264 (8.92%)
Blood lactate dehydrogenase increased [A] *	114/2264 (5.04%)
Gamma-glutamyltransferase increased [A] *	184/2264 (8.13%)
Haemoglobin decreased [A] *	416/2264 (18.37%)
Neutrophil count decreased [A] *	587/2264 (25.93%)
Platelet count decreased [A] *	166/2264 (7.33%)
White blood cell count decreased [A] *	566/2264 (25%)
Metabolism and nutrition disorders	
Anorexia [A] *	423/2264 (18.68%)
Hyperglycaemia [A] *	144/2264 (6.36%)
Musculoskeletal and connective tissue disorders	

	Bevacizumab
	Affected/At Risk (%)
Arthralgia [A] *	339/2264 (14.97%)
Back pain [A] *	305/2264 (13.47%)
Bone pain [A] *	247/2264 (10.91%)
Musculoskeletal pain [A] *	198/2264 (8.75%)
Myalgia [A] *	270/2264 (11.93%)
Pain in extremity [A] *	277/2264 (12.23%)
Nervous system disorders	
Dizziness [A] *	120/2264 (5.3%)
Dysgeusia [A] *	168/2264 (7.42%)
Headache [A] *	409/2264 (18.07%)
Neuropathy [A] *	446/2264 (19.7%)
Neuropathy peripheral [A] *	165/2264 (7.29%)
Paraesthesia [A] *	158/2264 (6.98%)
Psychiatric disorders	
Insomnia [A] *	136/2264 (6.01%)
Renal and urinary disorders	
Proteinuria [A] *	618/2264 (27.3%)
Respiratory, thoracic and mediastinal disorders	
Cough [A] *	338/2264 (14.93%)
Dysphonia [A] *	149/2264 (6.58%)
Dyspnoea [A] *	312/2264 (13.78%)
Epistaxis [A] *	867/2264 (38.3%)
Skin and subcutaneous tissue disorders	

	Bevacizumab
	Affected/At Risk (%)
Alopecia [A] *	934/2264 (41.25%)
Nail disorder [A] *	272/2264 (12.01%)
Palmar-plantar erythrodysaesthesia syndrome [A] *	234/2264 (10.34%)
Rash [A] *	207/2264 (9.14%)
Vascular disorders	
Hypertension [A] *	760/2264 (33.57%)

* Indicates events were collected by non-systematic methods.
A Term from vocabulary, MedDRA (10.1)

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 after the first publication or presentation that involves the overall study. 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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