Clinical trial results:
A Randomized Phase III Clinical Study of Bevacizumab Plus Capecitabine vs. Bevacizumab Alone as Maintenance Therapy in Patients with HER2-Negative Metastatic Breast Cancer That Has Not Progressed During First-Line Docetaxel Plus Bevacizumab Therapy

Summary

EudraCT number	2008-006872-31
Trial protocol	ES FR IT
Global end of trial date	14 June 2014

Results information

Result version number	v1 (current)
This version publication date	14 July 2016
First version publication date	06 August 2015

Trial information

Trial identification

Sponsor protocol code	MO22223

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00929240
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	F.Hoffmann-La Roche AG
Sponsor organisation address	Grenzacherstrasse 124, Basel, Switzerland, CH-4070
Public contact	Roche Trial Information Hotline, F. Hoffmann-La Roche AG, 41 616878333, global.trial_information@roche.com
Scientific contact	Roche Trial Information Hotline, F. Hoffmann-La Roche AG, 41 616878333, global.trial_information@roche.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	14 June 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	14 June 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate whether maintenance therapy with bevacizumab plus capecitabine, compared to bevacizumab alone, can further increase Progression-Free Survival (PFS) in patients showing objective response or stable disease following initial therapy with bevacizumab plus (+) docetaxel.

Protection of trial subjects:

The study was conducted in accordance with the principles of the "Declaration of Helsinki" and Good Clinical Practice (GCP) according to the regulations and procedures described in the following sections of the protocol.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	16 July 2009
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 9
Country: Number of subjects enrolled	Spain: 31
Country: Number of subjects enrolled	France: 54
Country: Number of subjects enrolled	Italy: 30
Country: Number of subjects enrolled	Brazil: 40
Country: Number of subjects enrolled	China: 25
Country: Number of subjects enrolled	Egypt: 13
Country: Number of subjects enrolled	India: 48
Country: Number of subjects enrolled	Turkey: 25
Country: Number of subjects enrolled	Hong Kong: 12
Worldwide total number of subjects	287
EEA total number of subjects	124

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0

Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	238
From 65 to 84 years	49
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Screening was performed from Day -28 to Day 1 (Baseline).

Period 1

Period 1 title	Initial Treatment Phase
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Arm title	Initial Treatment Phase: Bevacizumab Plus (+) Docetaxel

Arm description:

During the Initial Phase all participants received bevacizumab 15 milligrams per kilogram (mg/kg) intravenously (IV) on Day 1 of each 3 week cycle for a minimum of 3 cycles and a maximum of 6 cycles or until disease progression, unacceptable toxicity or participant request for withdrawal, whichever occurred first. Participants also received docetaxel, a recommended dose of 100 milligrams per square meter (mg/m^2) IV administered on Day 1 of each cycle. Doses of 75 to 100 mg/m^2 of docetaxel could be administered at investigator's discretion. At the end of the Initial Treatment Phase, participants with an objective response (partial response [PR] or complete response [CR]) or stable disease (SD) following 3-6 cycles of bevacizumab + docetaxel were randomized to receive maintenance therapy with either bevacizumab alone or bevacizumab + capecitabine.

Arm type	Experimental
Investigational medicinal product name	Bevacizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

During the Initial Phase all participants received bevacizumab 15 mg/kg IV on Day 1 of each 3 week cycle for a minimum of 3 cycles and a maximum of 6 cycles or until disease progression, unacceptable toxicity or participant request for withdrawal, whichever occurred first.

Investigational medicinal product name	Docetaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion in pre-filled syringe
Routes of administration	Intravenous use

Dosage and administration details:

Participants received docetaxel, a recommended dose of 100 mg/m^2 IV administered on Day 1 of each cycle. Doses of 75 to 100 mg/m^2 of docetaxel could be administered at investigator's discretion for a minimum of 3 cycles and a maximum of 6 cycles.

Number of subjects in period 1	Initial Treatment Phase: Bevacizumab Plus (+) Docetaxel
Started	287
Completed	185
Not completed	102
Adverse event, serious fatal	2
Consent withdrawn by subject	13
Physician decision	4
Disease progression	41
Health authority/Study termination	3
Adverse event, non-fatal	31
Participants who received no treatment	3
Protocol deviation	5

Period 2

Period 2 title	Maintenance Phase
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Maintenance Phase: Bevacizumab

Arm description:

During the Initial Phase all participants received bevacizumab 15 mg/kg IV on Day 1 of each 3 week cycle for a minimum of 3 cycles and a maximum of 6 cycles or until disease progression, unacceptable toxicity or participant request for withdrawal, whichever occurred first along with docetaxel, a recommended dose of 100 mg/m^2 IV administered on Day 1 of each cycle. Doses of 75 to 100 mg/m^2 of docetaxel could be administered at investigator's discretion. At the end of the Initial Phase, participants with an objective response (PR or CR) or SD received 15 mg/kg bevacizumab IV on Day 1 of each 3 week cycle until disease progression, unacceptable toxicity, participant request for withdrawal or end of study, whichever occurred first.

Arm type	Active comparator
Investigational medicinal product name	Bevacizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

During the Initial Phase all participants received bevacizumab 15 mg/kg IV on Day 1 of each 3 week cycle for a minimum of 3 cycles and a maximum of 6 cycles or until disease progression, unacceptable toxicity or participant request for withdrawal, whichever occurred first.

Investigational medicinal product name	Docetaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion

Routes of administration	Intravenous use

Dosage and administration details:

Participants received docetaxel, a recommended dose of 100 mg/m^2 IV administered on Day 1 of each cycle. Doses of 75 to 100 mg/m^2 of docetaxel could be administered at investigator's discretion.

Arm title	Maintenance Phase: Bevacizumab + Capecitabine

Arm description:

During the Initial Phase participants received bevacizumab 15 mg/kg IV on Day 1 of each 3 week cycle for a minimum of 3 cycles and a maximum of 6 cycles or until disease progression, unacceptable toxicity or withdrawal, whichever occurred first, along with docetaxel, a recommended dose of 100 mg/m^2 IV administered on Day 1 of each cycle. Doses of 75 to 100 mg/m^2 of docetaxel could be administered at investigator's discretion. At the end of the Initial Phase, participants with an objective response were randomized to receive bevacizumab 15 mg/kg IV on Day 1 of each 3-week cycle plus capecitabine 1000 mg/m^2 twice daily on Days 1 to 14 of each 3 week cycle until disease progression, unacceptable toxicity, request for withdrawal or end of study, whichever occurred first. If one of the drugs was discontinued before disease progression, treatment was continued with the second drug until disease progression, unacceptable toxicity, withdrawal or end of study, whichever occurred first.

Arm type	Experimental
Investigational medicinal product name	Bevacizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

During the Initial Phase all participants received bevacizumab 15 milligrams per kilogram (mg/kg) intravenously (IV) on Day 1 of each 3 week cycle for a minimum of 3 cycles and a maximum of 6 cycles or until disease progression, unacceptable toxicity or participant request for withdrawal, whichever occurred first.

Investigational medicinal product name	Docetaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Participants received docetaxel, a recommended dose of 100 mg/m^2 IV administered on Day 1 of each cycle. Doses of 75 to 100 mg/m^2 of docetaxel could be administered at investigator's discretion.

Investigational medicinal product name	Capecitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Participants received capecitabine 1000 mg/m^2 twice daily on Days 1 to 14 of each 3 week cycle until disease progression, unacceptable toxicity, request for withdrawal or end of study, whichever occurred first.

Number of subjects in period 2	Maintenance Phase: Bevacizumab	Maintenance Phase: Bevacizumab + Capecitabine
Started	94	91
Completed	0	0
Not completed	94	91
Consent withdrawn by subject	2	6
Physician decision	2	1
Disease progression	73	60
Adverse event, non-fatal	9	12
Health authority/Study termination	1	2
Treatment ongoing at study termination	-	10
Change of treatment	4	-
Participant not treated	2	-
Protocol deviation	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Initial Treatment Phase

Reporting group description:

During the Initial Phase all participants received bevacizumab 15 mg/kg IV on Day 1 of each 3 week cycle for a minimum of 3 cycles and a maximum of 6 cycles or until disease progression, unacceptable toxicity or participant request for withdrawal, whichever occurred first. Participants also received docetaxel, a recommended dose of 100 mg/m^2 IV administered on Day 1 of each cycle. Doses of 75 to 100 mg/m^2 of docetaxel could be administered at investigator's discretion. At the end of the Initial Treatment Phase, participants with an objective response (PR or CR) or SD following 3-6 cycles of bevacizumab + docetaxel were randomized to receive maintenance therapy with either bevacizumab alone or bevacizumab + capecitabine.

Reporting group values	Initial Treatment Phase	Total	
Number of subjects	287	287	
Age categorical Units: Subjects			

Age continuous Units: years			
arithmetic mean	52.5		
standard deviation	± 11.8	-	
Gender categorical Units: Subjects			
Female	287	287	
Male	0	0	

End points

End points reporting groups

Reporting group title	Initial Treatment Phase: Bevacizumab Plus (+) Docetaxel

Reporting group description:

During the Initial Phase all participants received bevacizumab 15 milligrams per kilogram (mg/kg) intravenously (IV) on Day 1 of each 3 week cycle for a minimum of 3 cycles and a maximum of 6 cycles or until disease progression, unacceptable toxicity or participant request for withdrawal, whichever occurred first. Participants also received docetaxel, a recommended dose of 100 milligrams per square meter (mg/m^2) IV administered on Day 1 of each cycle. Doses of 75 to 100 mg/m^2 of docetaxel could be administered at investigator's discretion. At the end of the Initial Treatment Phase, participants with an objective response (partial response [PR] or complete response [CR]) or stable disease (SD) following 3-6 cycles of bevacizumab + docetaxel were randomized to receive maintenance therapy with either bevacizumab alone or bevacizumab + capecitabine.

Reporting group title	Maintenance Phase: Bevacizumab

Reporting group description:

During the Initial Phase all participants received bevacizumab 15 mg/kg IV on Day 1 of each 3 week cycle for a minimum of 3 cycles and a maximum of 6 cycles or until disease progression, unacceptable toxicity or participant request for withdrawal, whichever occurred first along with docetaxel, a recommended dose of 100 mg/m^2 IV administered on Day 1 of each cycle. Doses of 75 to 100 mg/m^2 of docetaxel could be administered at investigator's discretion. At the end of the Initial Phase, participants with an objective response (PR or CR) or SD received 15 mg/kg bevacizumab IV on Day 1 of each 3 week cycle until disease progression, unacceptable toxicity, participant request for withdrawal or end of study, whichever occurred first.

Reporting group title	Maintenance Phase: Bevacizumab + Capecitabine

Reporting group description:

During the Initial Phase participants received bevacizumab 15 mg/kg IV on Day 1 of each 3 week cycle for a minimum of 3 cycles and a maximum of 6 cycles or until disease progression, unacceptable toxicity or withdrawal, whichever occurred first, along with docetaxel, a recommended dose of 100 mg/m^2 IV administered on Day 1 of each cycle. Doses of 75 to 100 mg/m^2 of docetaxel could be administered at investigator's discretion. At the end of the Initial Phase, participants with an objective response were randomized to receive bevacizumab 15 mg/kg IV on Day 1 of each 3-week cycle plus capecitabine 1000 mg/m^2 twice daily on Days 1 to 14 of each 3 week cycle until disease progression, unacceptable toxicity, request for withdrawal or end of study, whichever occurred first. If one of the drugs was discontinued before disease progression, treatment was continued with the second drug until disease progression, unacceptable toxicity, withdrawal or end of study, whichever occurred first.

Primary: Percentage of Participants With Disease Progression or Death (Maintenance Phase Data Cutoff October 4, 2013)

End point title	Percentage of Participants With Disease Progression or Death (Maintenance Phase Data Cutoff October 4, 2013)[1]

End point description:

Progression Free Survival (PFS) was defined as the time from first study drug dosing (during the maintenance treatment phase) to the first documented disease progression or death, whichever occurred first. Progression was based on tumor assessment made by the investigators according to the Response Evaluation Criteria In Solid Tumors (RECIST). Progressive Disease (PD) was defined as a 20 percent (%) or greater increase in the sum of the Longest Diameter (LD) of the target lesions taking as reference the smallest sum LD recorded or appearance of new lesions.

End point type	Primary

End point timeframe:

Randomization, at the end of every third cycle (every 9 weeks) until the end of maintenance phase and every 3 months until disease progression or death until data cutoff on October 4, 2013, up to 4 year

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical analysis was performed for Progression free survival which is defined as survival without disease progression or death.

End point values	Maintenance Phase: Bevacizumab	Maintenance Phase: Bevacizumab + Capecitabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	94	91		
Units: percentage of participants				
number (not applicable)	88.3	75.8		

Statistical analyses

No statistical analyses for this end point

Primary: Progression Free Survival (Maintenance Phase Data Cutoff October 4, 2013)

End point title	Progression Free Survival (Maintenance Phase Data Cutoff October 4, 2013)

End point description:

PFS was defined as time from first study drug during the maintenance treatment phase dosing to first documented disease progression or death, whichever occurred first. Time to progression was defined as time from randomization to first documented disease progression defined per RECIST 1.0 criteria. Participants without an event at data cut-off or who were withdrawn from study without documented progression were censored at date of last tumor assessment when participant was known to be progression free. Participants who took other non-protocol anti-cancer drugs while being on study medication, and who were still event free were censored on date of first dose of anti-cancer drug. Participants without post-randomization tumor assessments but alive were censored at the time of randomization. Participants without post-randomization assessments, who died after randomization were considered to have the PFS event at date of death. Kaplan-Meier estimation was used for median time to PFS.

End point type	Primary

End point timeframe:

Randomization, at the end of every third cycle (every 9 weeks) until the end of maintenance phase and every 3 months until disease progression or death until data cutoff on October 4, 2013, up to 4 years

End point values	Maintenance Phase: Bevacizumab	Maintenance Phase: Bevacizumab + Capecitabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	94	91		
Units: months				
median (confidence interval 95%)	4.3 (3.9 to 6.8)	11.9 (9.8 to 15.4)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Stratified by estrogen receptor (ER) status, visceral metastasis (yes/no), response to initial phase, and lactate dehydrogenase (LDH) level.

Comparison groups	Maintenance Phase: Bevacizumab v Maintenance Phase: Bevacizumab + Capecitabine
Number of subjects included in analysis	185
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.383
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.266
upper limit	0.551

Secondary: Percentage of Participants With Best Overall Confirmed Objective Response of CR or PR Per RECIST 1.0 (Maintenance Phase Data Cutoff October 4, 2013)

End point title	Percentage of Participants With Best Overall Confirmed Objective Response of CR or PR Per RECIST 1.0 (Maintenance Phase Data Cutoff October 4, 2013)

End point description:

Objective Response was determined by the investigator using modified RECIST criteria, Version 1.0. An objective response was a complete or partial overall confirmed response as determined by investigators. CR was defined as complete disappearance of all target and non-target lesions and no new lesions. PR was defined as greater than or equal to (≥) 30 % decrease in the sum of appropriate diameters of all target measurable lesions, no progress in the non-measurable disease, and no new lesions. PD was defined as 20% increase in the sum of the longest diameter of target lesions and SD was defined as small changes that do not meet above criteria. Pearson-Clopper one-sample method was used for confidence intervals (CIs).

End point type	Secondary

End point timeframe:

Randomization, at the end of every third cycle (every 9 weeks) until the end of maintenance phase and every 3 months until disease progression or death until data cutoff on October 4, 2013, up to 4 years

End point values	Maintenance Phase: Bevacizumab	Maintenance Phase: Bevacizumab + Capecitabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	94	91		
Units: percentage of participants				
number (confidence interval 95%)	76.6 (66.7 to 84.7)	85.7 (76.8 to 92.2)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Maintenance Phase: Bevacizumab + Capecitabine v Maintenance Phase: Bevacizumab
Number of subjects included in analysis	185
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.113
Method	Chi-squared
Parameter estimate	Mean difference (final values)
Point estimate	9.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.1
upper limit	20.3

Secondary: Percentage of Participants With Clinical Benefit (CR, PR and SD) Per RECIST 1.0 (Data Cutoff October 4, 2013)

End point title	Percentage of Participants With Clinical Benefit (CR, PR and SD) Per RECIST 1.0 (Data Cutoff October 4, 2013)

End point description:

CR was defined as complete disappearance of all target and non-target lesions and no new lesions. PR was defined as ≥30% decrease in the sum of appropriate diameters of all target measurable lesions, no progress in the non-measurable disease, and no new lesions. SD was defined as small changes that do not meet above criteria with Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started.

End point type	Secondary

End point timeframe:

Randomization, at the end of every third cycle (every 9 weeks) until the end of maintenance phase and every 3 months until disease progression or death until data cutoff on October 4, 2013, up to 4 years

End point values	Maintenance Phase: Bevacizumab	Maintenance Phase: Bevacizumab + Capecitabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	94	91		
Units: percentage of participants				
number (confidence interval 95%)	97.9 (92.5 to 99.7)	98.9 (94 to 100)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Maintenance Phase: Bevacizumab v Maintenance Phase: Bevacizumab + Capecitabine

Number of subjects included in analysis	185
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.58
Method	Chi-squared
Parameter estimate	Mean difference (final values)
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.6
upper limit	4.6

Secondary: Percentage of Participants Who Died (Maintenance Phase Data Cutoff October 4, 2013)

End point title	Percentage of Participants Who Died (Maintenance Phase Data Cutoff October 4, 2013)

End point description:

End point type	Secondary

End point timeframe:

Randomization, at the end of every third cycle (every 9 weeks) until the end of maintenance phase and every 3 months until disease progression or death until data cutoff on October 4, 2013, up to 4 years

End point values	Maintenance Phase: Bevacizumab	Maintenance Phase: Bevacizumab + Capecitabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	94	91		
Units: percentage of participants				
number (not applicable)	56.4	36.3		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (Maintenance Phase Data Cutoff October 4, 2013)

End point title	Overall Survival (Maintenance Phase Data Cutoff October 4, 2013)

End point description:

Duration of Overall Survival (OS) was defined as the time from randomization to death of any cause. The OS data for participants for whom no death was captured in the clinical database were censored at the last time they were known to be alive. Kaplan Meier estimation was used to determine OS. A value of 999 represents that the upper limit of the confidence interval was inestimable.

End point type	Secondary

End point timeframe:

Randomization, at the end of every third cycle (every 9 weeks) until the end of maintenance phase and every 3 months until disease progression or death until data cutoff on October 4, 2013, up to 4 years

End point values	Maintenance Phase: Bevacizumab	Maintenance Phase: Bevacizumab + Capecitabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	94	91		
Units: Months				
median (confidence interval 95%)	23.7 (18.5 to 31.7)	39 (32.3 to 999)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Maintenance Phase: Bevacizumab + Capecitabine v Maintenance Phase: Bevacizumab
Number of subjects included in analysis	185
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0003 [2]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.425
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.263
upper limit	0.685

Notes:

[2] - Stratified by ER status, visceral metastasis (yes/no), response to initial phase, and LDH level.

Statistical analysis title	Statistical Analysis 2
Comparison groups	Maintenance Phase: Bevacizumab v Maintenance Phase: Bevacizumab + Capecitabine
Number of subjects included in analysis	185
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.002 [3]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.516

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.334
upper limit	0.798

Notes:

[3] - Unstratified analysis

Secondary: Percentage of Participants Expected to Be Alive After 1 and 2 Years on Treatment (Maintenance Phase Data Cutoff October 4, 2013)

End point title	Percentage of Participants Expected to Be Alive After 1 and 2 Years on Treatment (Maintenance Phase Data Cutoff October 4, 2013)

End point description:

Probability of being alive after 1 and 2 years on treatment with 95% CIs was calculated using Kaplan Meier approach with LOGLOG transformation.

End point type	Secondary

End point timeframe:

Years 1 and 2

End point values	Maintenance Phase: Bevacizumab	Maintenance Phase: Bevacizumab + Capecitabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	94	91		
Units: percentage of participants				
number (confidence interval 95%)				
1 Year	71.6 (61.1 to 79.7)	90.4 (81.8 to 95.1)		
2 Years	49.4 (38.5 to 59.3)	69 (57.6 to 77.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage Of Participants With PD or Death Due to PD (Maintenance Phase Data Cutoff October 4, 2013)

End point title	Percentage Of Participants With PD or Death Due to PD (Maintenance Phase Data Cutoff October 4, 2013)

End point description:

PD was defined per RECIST version 1.0 as 20% increase in the sum of the longest diameter of target lesions.

End point type	Secondary

End point timeframe:

Randomization, at the end of every third cycle (every 9 weeks) until the end of maintenance phase and every 3 months until disease progression or death until data cutoff on October 4, 2013

End point values	Maintenance Phase: Bevacizumab	Maintenance Phase: Bevacizumab + Capecitabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	94	91		
Units: percentage of participants				
number (not applicable)	88.3	74.7		

Statistical analyses

No statistical analyses for this end point

Secondary: Time To Progression (Maintenance Phase Data Cutoff October 4, 2013)

End point title	Time To Progression (Maintenance Phase Data Cutoff October 4, 2013)

End point description:

Time to Progression was defined as the time from randomization to the first documented disease progression (using investigator assessments of disease progression by RECIST 1.0). PD was defined as 20% increase in the sum of the longest diameter of target lesions.

End point type	Secondary

End point timeframe:

Randomization, at the end of every third cycle (every 9 weeks) until the end of maintenance phase and every 3 months until disease progression or death until data cutoff on October 4, 2013

End point values	Maintenance Phase: Bevacizumab	Maintenance Phase: Bevacizumab + Capecitabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	94	91		
Units: Months				
median (confidence interval 95%)	4.3 (3.9 to 6.8)	11.9 (9.8 to 15.4)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Maintenance Phase: Bevacizumab v Maintenance Phase: Bevacizumab + Capecitabine

Number of subjects included in analysis	185
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001 [4]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.383
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.266
upper limit	0.551

Notes:

[4] - Stratified by ER status, visceral metastasis (yes/no), response to initial phase, and LDH level.

Statistical analysis title	Statistical Analysis 2
Comparison groups	Maintenance Phase: Bevacizumab v Maintenance Phase: Bevacizumab + Capecitabine
Number of subjects included in analysis	185
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001 [5]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.425
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.305
upper limit	0.591

Notes:

[5] - Unstratified analysis

Secondary: Quality of Life Assessed As Change From Baseline in Global Health Status Using The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - 30 (EORTC QLQ - C30) (Maintenance Phase Data Cutoff October 4, 2013)

End point title	Quality of Life Assessed As Change From Baseline in Global Health Status Using The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - 30 (EORTC QLQ - C30) (Maintenance Phase Data Cutoff October 4, 2013)

End point description:

The EORTC QLQ-C30 incorporates 9 multi-item scales: 5 functional scales (physical, role, cognitive, emotional, and social); 9 symptom scales (fatigue, pain, nausea and vomiting, dyspnoea, insomnia, appetite loss, constipation, diarrhea and financial difficulties); and a global health and quality-of-life scale. Most questions used 4 point scale (1 'Not at all' to 4 'Very much'; 2 questions used 7-point scale (1 'very poor' to 7 'Excellent'). Scores were averaged and transformed to 0-100 scale; higher score=better level of functioning or greater degree of symptoms. The change in global health status was determined to be the difference in values at baseline and each specific visit. The term ‘’baseline’’ refers to the time of randomization to the maintenance phase. Only timepoints with more than 10 participants in each treatment arm are presented. n=number of participants analyzed at the specific visit.

End point type	Secondary

End point timeframe:

Baseline, Randomization and Cycles 3, 6, 9 and 12

End point values	Maintenance Phase: Bevacizumab	Maintenance Phase: Bevacizumab + Capecitabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	83	86		
Units: units on a scale				
number (confidence interval 95%)				
Randomization (n= 83, 86)	-3.51 (-9.63 to 2.6)	-4.46 (-9.4 to 0.48)		
Cycle 3 (n= 44, 52)	0.76 (-6.65 to 8.17)	-3.21 (-9.99 to 3.58)		
Cycle 6 (n= 26, 54)	4.17 (-6.49 to 14.82)	-5.4 (-11.67 to 0.87)		
Cycle 9 (n= 18, 37)	8.8 (-4.57 to 22.17)	-1.8 (-8.92 to 5.32)		
Cycle 12 (n= 12, 31)	0.69 (-17.99 to 19.37)	0 (-8.24 to 8.24)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Best Overall Confirmed Objective Response of CR or PR Per RECIST 1.0 (Initial Treatment Phase)

End point title	Percentage of Participants With Best Overall Confirmed Objective Response of CR or PR Per RECIST 1.0 (Initial Treatment Phase)

End point description:

Objective Response was determined by the investigator using RECIST criteria, Version 1.0. An objective response was a complete or partial overall confirmed response as determined by investigators. CR was defined as complete disappearance of all target and non-target lesions and no new lesions. PR was defined as ≥ 30% decrease in the sum of appropriate diameters of all target measurable lesions, no progress in the non-measurable disease, and no new lesions. Pearson-Clopper one-sample method was used for CI. Only participants who were not randomized at the end of the initial treatment phase were included in this analysis

End point type	Secondary

End point timeframe:

Screening and at the end of every third cycle until randomization for an average of 18 weeks

End point values	Initial Treatment Phase: Bevacizumab Plus (+) Docetaxel			
Subject group type	Reporting group			
Number of subjects analysed	102			
Units: percentage of participants				
number (confidence interval 95%)	8.8 (4.1 to 16.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Clinical Benefit (CR, PR and SD) Per RECIST 1.0 (Initial Treatment Phase)

End point title	Percentage of Participants With Clinical Benefit (CR, PR and SD) Per RECIST 1.0 (Initial Treatment Phase)

End point description:

CR was defined as complete disappearance of all target and non-target lesions and no new lesions. PR was defined as ≥30% decrease in the sum of appropriate diameters of all target measurable lesions, no progress in the non-measurable disease, and no new lesions. SD was defined as small changes that do not meet above criteria. Only participants who were not randomized at the end of the initial treatment phase were included in this analysis.

End point type	Secondary

End point timeframe:

Screening and at the end of every third cycle until randomization for an average of 18 weeks

End point values	Initial Treatment Phase: Bevacizumab Plus (+) Docetaxel			
Subject group type	Reporting group			
Number of subjects analysed	102			
Units: percentage of participants				
number (confidence interval 95%)	56.9 (46.7 to 66.6)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events (AEs) were recorded from the date of randomization until the end of study at the cutoff date of October 4, 2013.

Adverse event reporting additional description:

AEs were recorded for the Safety population (all participants who received at least one dose of study drug during the maintenance phase). Only Grade 3 and above AEs have been captured per protocol.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.0

Reporting groups

Reporting group title	Initial Treatment Phase: Bevacizumab + Docetaxel

Reporting group description:

During the Initial Phase all participants received bevacizumab 15 mg/kg IV on Day 1 of each 3 week cycle for a minimum of 3 cycles and a maximum of 6 cycles or until disease progression, unacceptable toxicity or participant request for withdrawal, whichever occurred first. Participants also received docetaxel, a recommended dose of 100 mg/m^2 IV administered on Day 1 of each cycle. Doses of 75 to 100 mg/m^2 of docetaxel could be administered at investigator's discretion. At the end of the Initial Treatment Phase, participants with an objective response (PR or CR) or SD following 3-6 cycles of bevacizumab + docetaxel were randomized to receive maintenance therapy with either bevacizumab alone or bevacizumab + capecitabine.

Reporting group title	Maintenance Phase: Bevacizumab

Reporting group description:

During the Initial Phase all participants received bevacizumab 15 mg/kg IV on Day 1 of each 3 week cycle for a minimum of 3 cycles and a maximum of 6 cycles or until disease progression, unacceptable toxicity or participant request for withdrawal, whichever occurred first along with docetaxel, a recommended dose of 100 mg/m^2 IV administered on Day 1 of each cycle. Doses of 75 to 100 mg/m^2 of docetaxel could be administered at investigator's discretion. At the end of the Initial Phase, participants with an objective response (PR or CR) or SD received 15 mg/kg bevacizumab IV on Day 1 of each 3 week cycle until disease progression, unacceptable toxicity, participant request for withdrawal or end of study, whichever occurred first.

Reporting group title	Maintenance Phase: Bevacizumab + Capecitabine

Reporting group description:

During the Initial Phase participants received bevacizumab 15 mg/kg IV on Day 1 of each 3 week cycle for a minimum of 3 cycles and a maximum of 6 cycles or until disease progression, unacceptable toxicity or withdrawal, whichever occurred first, along with docetaxel, a recommended dose of 100 mg/m^2 IV administered on Day 1 of each cycle. Doses of 75 to 100 mg/m^2 of docetaxel could be administered at investigator's discretion. At the end of the Initial Phase, participants with an objective response were randomized to receive bevacizumab 15 mg/kg IV on Day 1 of each 3-week cycle plus capecitabine 1000 mg/m^2 twice daily on Days 1 to 14 of each 3 week cycle until disease progression, unacceptable toxicity, request for withdrawal or end of study, whichever occurred first. If one of the drugs was discontinued before disease progression, treatment was continued with the second drug until disease progression, unacceptable toxicity, withdrawal or end of study, whichever occurred first.

Serious adverse events	Initial Treatment Phase: Bevacizumab + Docetaxel	Maintenance Phase: Bevacizumab	Maintenance Phase: Bevacizumab + Capecitabine
Total subjects affected by serious adverse events			
subjects affected / exposed	78 / 284 (27.46%)	7 / 92 (7.61%)	10 / 91 (10.99%)
number of deaths (all causes)	54	51	33
number of deaths resulting from adverse events			

Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Large cell lung cancer			
subjects affected / exposed	1 / 284 (0.35%)	0 / 92 (0.00%)	0 / 91 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 284 (0.00%)	0 / 92 (0.00%)	1 / 91 (1.10%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Embolism			
subjects affected / exposed	1 / 284 (0.35%)	1 / 92 (1.09%)	0 / 91 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Embolism arterial			
subjects affected / exposed	1 / 284 (0.35%)	0 / 92 (0.00%)	0 / 91 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Death			
subjects affected / exposed	1 / 284 (0.35%)	0 / 92 (0.00%)	0 / 91 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Mucosal inflammation			
subjects affected / exposed	4 / 284 (1.41%)	0 / 92 (0.00%)	0 / 91 (0.00%)
occurrences causally related to treatment / all	4 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	3 / 284 (1.06%)	0 / 92 (0.00%)	0 / 91 (0.00%)
occurrences causally related to treatment / all	1 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Asthenia			

subjects affected / exposed	1 / 284 (0.35%)	0 / 92 (0.00%)	0 / 91 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ulcer			
subjects affected / exposed	0 / 284 (0.00%)	0 / 92 (0.00%)	1 / 91 (1.10%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Respiratory distress			
subjects affected / exposed	1 / 284 (0.35%)	0 / 92 (0.00%)	0 / 91 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	2 / 284 (0.70%)	0 / 92 (0.00%)	0 / 91 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epistaxis			
subjects affected / exposed	2 / 284 (0.70%)	0 / 92 (0.00%)	0 / 91 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	2 / 284 (0.70%)	0 / 92 (0.00%)	0 / 91 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	0 / 284 (0.00%)	1 / 92 (1.09%)	0 / 91 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Toxicity to various agents			
subjects affected / exposed	1 / 284 (0.35%)	0 / 92 (0.00%)	0 / 91 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0

Femur fracture			
subjects affected / exposed	1 / 284 (0.35%)	0 / 92 (0.00%)	0 / 91 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Incisional hernia			
subjects affected / exposed	0 / 284 (0.00%)	0 / 92 (0.00%)	1 / 91 (1.10%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound dehiscence			
subjects affected / exposed	1 / 284 (0.35%)	0 / 92 (0.00%)	0 / 91 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Myocardial infarction			
subjects affected / exposed	0 / 284 (0.00%)	0 / 92 (0.00%)	2 / 91 (2.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arrhythmia			
subjects affected / exposed	1 / 284 (0.35%)	0 / 92 (0.00%)	0 / 91 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	1 / 284 (0.35%)	0 / 92 (0.00%)	0 / 91 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery disease			
subjects affected / exposed	0 / 284 (0.00%)	0 / 92 (0.00%)	1 / 91 (1.10%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Left ventricular dysfunction			
subjects affected / exposed	1 / 284 (0.35%)	0 / 92 (0.00%)	0 / 91 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			

Depressed level of consciousness			
subjects affected / exposed	1 / 284 (0.35%)	0 / 92 (0.00%)	0 / 91 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
VIIth nerve paralysis			
subjects affected / exposed	0 / 284 (0.00%)	1 / 92 (1.09%)	0 / 91 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	28 / 284 (9.86%)	0 / 92 (0.00%)	0 / 91 (0.00%)
occurrences causally related to treatment / all	29 / 30	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	17 / 284 (5.99%)	0 / 92 (0.00%)	0 / 91 (0.00%)
occurrences causally related to treatment / all	18 / 18	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Leukopenia			
subjects affected / exposed	3 / 284 (1.06%)	0 / 92 (0.00%)	0 / 91 (0.00%)
occurrences causally related to treatment / all	3 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anaemia			
subjects affected / exposed	2 / 284 (0.70%)	0 / 92 (0.00%)	0 / 91 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	0 / 284 (0.00%)	0 / 92 (0.00%)	1 / 91 (1.10%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 284 (0.35%)	0 / 92 (0.00%)	0 / 91 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Gastrointestinal disorders			
Intestinal perforation			
subjects affected / exposed	2 / 284 (0.70%)	0 / 92 (0.00%)	0 / 91 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestine perforation			
subjects affected / exposed	2 / 284 (0.70%)	0 / 92 (0.00%)	0 / 91 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal obstruction			
subjects affected / exposed	1 / 284 (0.35%)	1 / 92 (1.09%)	0 / 91 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed	1 / 284 (0.35%)	0 / 92 (0.00%)	0 / 91 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticular perforation			
subjects affected / exposed	1 / 284 (0.35%)	0 / 92 (0.00%)	0 / 91 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysphagia			
subjects affected / exposed	0 / 284 (0.00%)	0 / 92 (0.00%)	1 / 91 (1.10%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric haemorrhage			
subjects affected / exposed	0 / 284 (0.00%)	1 / 92 (1.09%)	0 / 91 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis			
subjects affected / exposed	0 / 284 (0.00%)	1 / 92 (1.09%)	0 / 91 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal ulcer haemorrhage			

subjects affected / exposed	0 / 284 (0.00%)	0 / 92 (0.00%)	1 / 91 (1.10%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematemesis			
subjects affected / exposed	1 / 284 (0.35%)	0 / 92 (0.00%)	0 / 91 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subileus			
subjects affected / exposed	1 / 284 (0.35%)	0 / 92 (0.00%)	0 / 91 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper gastrointestinal haemorrhage			
subjects affected / exposed	1 / 284 (0.35%)	0 / 92 (0.00%)	0 / 91 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	0 / 284 (0.00%)	0 / 92 (0.00%)	1 / 91 (1.10%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	0 / 284 (0.00%)	1 / 92 (1.09%)	0 / 91 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Anuria			
subjects affected / exposed	0 / 284 (0.00%)	1 / 92 (1.09%)	0 / 91 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Back pain			

subjects affected / exposed	1 / 284 (0.35%)	0 / 92 (0.00%)	0 / 91 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal pain			
subjects affected / exposed	1 / 284 (0.35%)	0 / 92 (0.00%)	0 / 91 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myalgia			
subjects affected / exposed	1 / 284 (0.35%)	0 / 92 (0.00%)	0 / 91 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia			
subjects affected / exposed	5 / 284 (1.76%)	1 / 92 (1.09%)	0 / 91 (0.00%)
occurrences causally related to treatment / all	2 / 5	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	1 / 284 (0.35%)	0 / 92 (0.00%)	0 / 91 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	2 / 284 (0.70%)	2 / 92 (2.17%)	0 / 91 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	2 / 284 (0.70%)	0 / 92 (0.00%)	0 / 91 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection			
subjects affected / exposed	1 / 284 (0.35%)	0 / 92 (0.00%)	1 / 91 (1.10%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			

subjects affected / exposed	2 / 284 (0.70%)	0 / 92 (0.00%)	0 / 91 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gallbladder empyema			
subjects affected / exposed	1 / 284 (0.35%)	0 / 92 (0.00%)	0 / 91 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection			
subjects affected / exposed	0 / 284 (0.00%)	0 / 92 (0.00%)	1 / 91 (1.10%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meningitis			
subjects affected / exposed	1 / 284 (0.35%)	0 / 92 (0.00%)	0 / 91 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritonitis			
subjects affected / exposed	1 / 284 (0.35%)	0 / 92 (0.00%)	0 / 91 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection			
subjects affected / exposed	1 / 284 (0.35%)	0 / 92 (0.00%)	0 / 91 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 284 (0.35%)	0 / 92 (0.00%)	0 / 91 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypercalcaemia			
subjects affected / exposed	0 / 284 (0.00%)	1 / 92 (1.09%)	0 / 91 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Initial Treatment Phase: Bevacizumab + Docetaxel	Maintenance Phase: Bevacizumab	Maintenance Phase: Bevacizumab + Capecitabine
Total subjects affected by non-serious adverse events			
subjects affected / exposed	40 / 284 (14.08%)	4 / 92 (4.35%)	32 / 91 (35.16%)
Vascular disorders			
Hypertension			
subjects affected / exposed	5 / 284 (1.76%)	3 / 92 (3.26%)	7 / 91 (7.69%)
occurrences (all)	5	4	9
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	29 / 284 (10.21%)	1 / 92 (1.09%)	2 / 91 (2.20%)
occurrences (all)	40	1	5
Skin and subcutaneous tissue disorders			
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	6 / 284 (2.11%)	0 / 92 (0.00%)	29 / 91 (31.87%)
occurrences (all)	7	0	48

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 May 2010	• Addition of biomarker collection to explore potential single-nucleotide polymorphisms (SNPs) that may be associated with efficacy and/or safety of bevacizumab therapy in patients with locally recurrent or metastatic breast cancer. • Inclusion of new guidance for the management of proteinuria in bevacizumab studies, to make the management of proteinuria the same irrespective of whether it was a first or subsequent occurrence. • Inclusion of new guidance to clarify SAE collection throughout the study, from the time informed consent was signed onwards. In addition, the stopping rules for bevacizumab treatment were corrected to include Grade 4 venous thrombosis and a new section regarding reversible posterior leucoencephalopathy syndrome was added for consistency with other bevacizumab studies. • Updated the guidance for capecitabine dosing and dose modifications to include numbers of tablets based on the 500 mg tablet (which was the formulation provided for this study).
12 August 2012	• Updated the patient follow-up for PFS and OS to until 24 months after the last patient had been randomized rather than until at least 24 months after the last patient had been enrolled. Randomization was selected as the reference point (replacing enrolment) as this allowed for a longer follow-up, and therefore more events for the analysis. • For China only, included that assessments such as physical examination, vital signs, ECOG PS, laboratory evaluations (specified parameters) and AEs must be performed at the beginning of each treatment cycle (before study drug administration), rather than only if clinically indicated. • Updated the guidance for deaths and other SAEs to be reported to Roche within 24 hours of the investigator becoming aware of the event rather than being reported within one working day. • Updated the guidance that a pregnancy occurring up to 6 months after completion of bevacizumab must be reported to the investigator rather than the previous interval of up to 90 days. • Established an Independent Data Monitoring Committee (IDMC), to independently evaluate the safety of the patients participating in the study.
06 September 2013	Updated the end of study information to state that the study and investigational sites were to be closed as soon as approval from the regulatory authority and ethics committee occurred. At this time, patients who were still receiving study medication (bevacizumab and/or capecitabine) were to end their study participation. Based on the physician's decision, treatment with bevacizumab and/or capecitabine could be prolonged in accordance with the standard of care and the cost was to be refunded by the Sponsor until disease progression, as initially planned in the protocol. Alternatively, if the Avastin® long-term extension study (AvaLTE / MO25757) was approved in the patients' country, patients were to be offered participation in this study.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported