Clinical trial results:
A Single Arm, Open-Label, Phase II Study of Bevacizumab in Combination With Trastuzumab and Capecitabine as First-Line Treatment of Patients With HER2-Positive Locally Recurrent or Metastatic Breast Cancer

Summary

EudraCT number	2008-003283-20
Trial protocol	ES FR SE SK DK
Global end of trial date	

Results information

Result version number	v1 (current)
This version publication date	07 May 2016
First version publication date	07 May 2016

Trial information

Trial identification

Sponsor protocol code	MO21926

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00811135
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 61 6878333, global.trial_information@roche.com
Scientific contact	Roche Trial Information Hotline, F.Hoffmann-La Roche AG, +41 61 6878333, 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	Interim
Date of interim/final analysis	14 March 2013
Is this the analysis of the primary completion data?	Yes
Primary completion date	14 March 2013
Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

The study was designed to evaluate the efficacy, safety and tolerability of combining bevacizumab with trastuzumab and capecitabine in a single treatment regimen for the treatment of participants with human epidermal growth factor 2 (HER2)-positive locally recurrent or metastatic breast cancer.

Protection of trial subjects:

This study was fully adhered to the principles outlined in "Guideline for Good Clinical Practice" International Conference on Harmonization (ICH) Tripartite Guideline (January 1997) or with local law.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	29 December 2008
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Slovakia: 3
Country: Number of subjects enrolled	Spain: 12
Country: Number of subjects enrolled	Sweden: 4
Country: Number of subjects enrolled	Denmark: 4
Country: Number of subjects enrolled	France: 20
Country: Number of subjects enrolled	Russian Federation: 45
Worldwide total number of subjects	88
EEA total number of subjects	43

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)	75

From 65 to 84 years	13
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Screening details were taken 28 days prior to baseline. There were 88 participants included from 23 centers.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Trastuzumab + Bevacizumab + Capecitabine

Arm description:

Participants received intravenous (IV) trastuzumab 8 milligrams per kilogram (mg/kg) for first cycle and then 6 mg/kg for subsequent cycles followed by bevacizumab 15 mg/kg on Day 1 of each treatment cycles along with capecitabine administered orally to participants at a dose of 1000 milligrams per meter square (mg/m^2) twice daily (BID) on Days 1 to 14 of each treatment cycle until disease progression, unmanageable toxicity or participant request for discontinuation. Treatment cycles were of 3 weeks.

Arm type	Experimental
Investigational medicinal product name	Trastuzumab
Investigational medicinal product code	
Other name	Herceptin
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Participants received IV trastuzumab (8 mg/kg) on Day 1 of first cycle and then 6 mg/kg for subsequent cycles until disease progression, unmanageable toxicity or participant request for discontinuation.

Investigational medicinal product name	Bevacizumab
Investigational medicinal product code	
Other name	Avastin
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Participants received IV bevacizumab (15 mg/kg) on Day 1 of each treatment cycle until disease progression, unmanageable toxicity or participant request for discontinuation.

Investigational medicinal product name	Capecitabine
Investigational medicinal product code	
Other name	Xeloda
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Participants received capecitabine (1000 mg/m^2) BID orally on Day 1 to 14 of each treatment cycle until disease progression, unmanageable toxicity or participant request for discontinuation.

Number of subjects in period 1	Trastuzumab + Bevacizumab + Capecitabine
Started	88
Completed	0
Not completed	88
Administrative/other unspecified	11
Adverse event/intercurrent illness	8
Protocol violation	2
Death	3
Refused treatment	1
Ongoing	59
Violation of selection criteria	1
Withdrew consent	3

Baseline characteristics

Reporting groups	
Reporting group title	Overall Study

Reporting group description: -

Reporting group values	Overall Study	Total	
Number of subjects	88	88	
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	53		
standard deviation	± 10.94	-	
Gender categorical Units: Subjects			
Female	87	87	
Male	1	1	

End points

End points reporting groups

Reporting group title	Trastuzumab + Bevacizumab + Capecitabine

Reporting group description:

Participants received intravenous (IV) trastuzumab 8 milligrams per kilogram (mg/kg) for first cycle and then 6 mg/kg for subsequent cycles followed by bevacizumab 15 mg/kg on Day 1 of each treatment cycles along with capecitabine administered orally to participants at a dose of 1000 milligrams per meter square (mg/m^2) twice daily (BID) on Days 1 to 14 of each treatment cycle until disease progression, unmanageable toxicity or participant request for discontinuation. Treatment cycles were of 3 weeks.

Primary: Percentage of Participants with a Best Overall Response (BOR) of Confirmed Complete Response (CR) or Partial Response (PR)

End point title	Percentage of Participants with a Best Overall Response (BOR) of Confirmed Complete Response (CR) or Partial Response (PR)[1]

End point description:

Tumor response was assessed using the Response Evaluation Criteria in Solid Tumors (RECIST), Version 1.0. BOR was defined as the best response recorded for a participant from the start of treatment until disease progression/recurrence. Percentage of participants with a BOR of confirmed CR or PR (responders) was reported. CR: disappearance of all target and non-target lesions and normalization of tumor marker level; PR: at least a 30 percent (%) decrease in the sum of the longest diameter (LD) of target lesions taking as reference the baseline sum LD. Confirmed responses were those which were confirmed by a repeat assessment, performed 4 weeks after the criteria for response first met. Intention-to-treat (ITT) population included all participants enrolled in the study who receive at least one dose of any study medication.

End point type	Primary

End point timeframe:

Screening until disease progression (assessed at screening, every 6 weeks up to Week 36, thereafter every 9 weeks during treatment period, and then every 3 months during follow-up, up to approximately 4 years)

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: No statistical analyses have been specified for this primary endpoint due to single arm group study.

End point values	Trastuzumab + Bevacizumab + Capecitabine			
Subject group type	Reporting group			
Number of subjects analysed	88			
Units: percentage of participants				
number (confidence interval 95%)	75 (64.6 to 83.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Disease Progression or Death

End point title	Number of Participants With Disease Progression or Death

End point description:

Disease progression was defined as at least a 20% increase in the sum of LD of target lesions taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. ITT population.

End point type	Secondary

End point timeframe:

Screening until disease progression (assessed at screening, every 6 weeks up to Week 36, thereafter every 9 weeks during treatment period, and then every 3 months during follow-up, up to approximately 4 years)

End point values	Trastuzumab + Bevacizumab + Capecitabine			
Subject group type	Reporting group			
Number of subjects analysed	88			
Units: participants				
number (not applicable)	70			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival (PFS)

End point title	Progression Free Survival (PFS)

End point description:

PFS was defined as the time from enrollment to time of first documented disease progression or death due to any cause, whichever occurred first. Progression: at least a 20% increase in the sum of LD of target lesions taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. PFS was estimated using Kaplan-Meier methods. ITT population.

End point type	Secondary

End point timeframe:

Screening until disease progression (assessed at screening, every 6 weeks up to Week 36, thereafter every 9 weeks during treatment period, and then every 3 months during follow-up, up to approximately 4 years)

End point values	Trastuzumab + Bevacizumab + Capecitabine			
Subject group type	Reporting group			
Number of subjects analysed	88			
Units: months				
median (confidence interval 95%)	14.2 (10.5 to 14.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Overall Survival (OS)

End point title	Number of Participants With Overall Survival (OS)

End point description:

OS was defined as the time from enrollment to death from any cause where enrollment was defined as successfully passed screening visit, enrolled in the study and received first dose of study treatment. Here, number of participants with OS was reported. ITT population.

End point type	Secondary

End point timeframe:

Screening until disease progression (assessed at screening, every 6 weeks up to Week 36, thereafter every 9 weeks during treatment period, and then every 3 months during follow-up, up to approximately 4 years)

End point values	Trastuzumab + Bevacizumab + Capecitabine			
Subject group type	Reporting group			
Number of subjects analysed	88			
Units: participants				
number (not applicable)	40			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival

End point title	Overall Survival

End point description:

OS was defined as the time from enrollment to death from any cause where enrollment was defined as successfully passed screening visit, enrolled in the study and received first dose of study treatment. OS was estimated using Kaplan-Meier methods. ITT population.

End point type	Secondary

End point timeframe:

Screening until disease progression (assessed at screening, every 6 weeks up to Week 36, thereafter every 9 weeks during treatment period, and then every 3 months during follow-up, up to approximately 4 years)

End point values	Trastuzumab + Bevacizumab + Capecitabine			
Subject group type	Reporting group			
Number of subjects analysed	88			
Units: months				
median (confidence interval 95%)	31.8 (26.3 to			

38.2)

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Time to Progression (TTP)

End point title	Number of Participants With Time to Progression (TTP)

End point description:

TTP was defined as the time from enrollment to first documented disease progression. Progression: at least a 20% increase in the sum of LD of target lesions taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. ITT population.

End point type	Secondary

End point timeframe:

Screening until disease progression (assessed at screening, every 6 weeks up to Week 36, thereafter every 9 weeks during treatment period, and then every 3 months during follow-up, up to approximately 4 years)

End point values	Trastuzumab + Bevacizumab + Capecitabine			
Subject group type	Reporting group			
Number of subjects analysed	88			
Units: participants				
number (not applicable)	62			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Progression (TTP)

End point title	Time to Progression (TTP)

End point description:

TTP was defined as the time from enrollment to first documented disease progression. Progression: at least a 20% increase in the sum of LD of target lesions taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. TTP was estimated using Kaplan-Meier method. ITT population.

End point type	Secondary

End point timeframe:

Screening until disease progression (assessed at screening, every 6 weeks up to Week 36, thereafter every 9 weeks during treatment period, and then every 3 months during follow-up, up to approximately 4 years)

End point values	Trastuzumab + Bevacizumab + Capecitabine			
Subject group type	Reporting group			
Number of subjects analysed	88			
Units: months				
median (confidence interval 95%)	14.5 (11 to 17)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Response

End point title	Number of Participants With Response

End point description:

Participants who had CR or PR were considered as responders. CR: disappearance of all target and non-target lesions and normalization of tumor marker level; PR: at least a 30% decrease in the sum of the LD of target lesions taking as reference the baseline sum LD. ITT population.

End point type	Secondary

End point timeframe:

Screening until disease progression (assessed at screening, every 6 weeks up to Week 36, thereafter every 9 weeks during treatment period, and then every 3 months during follow-up, up to approximately 4 years)

End point values	Trastuzumab + Bevacizumab + Capecitabine			
Subject group type	Reporting group			
Number of subjects analysed	88			
Units: participants				
number (not applicable)	66			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DR)

End point title	Duration of Response (DR)

End point description:

DR was defined as the time from the first recorded response (CR/PR) to the date of first documented progression or death. CR: disappearance of all target lesions and non-target lesions and normalization of tumor marker level. PR: at least a 30% decrease in the sum of the LD of target lesions taking as reference the baseline sum LD. Progression: at least a 20% increase in the sum of LD of target lesions

taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. DR was estimated using Kaplan-Meier methods. ITT population.

End point type	Secondary

End point timeframe:

Screening until disease progression (assessed at screening, every 6 weeks up to Week 36, thereafter every 9 weeks during treatment period, and then every 3 months during follow-up, up to approximately 4 years)

End point values	Trastuzumab + Bevacizumab + Capecitabine			
Subject group type	Reporting group			
Number of subjects analysed	88			
Units: months				
median (confidence interval 95%)	12.7 (10.2 to 17.7)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 28 days after the last study treatment dose (maximum treatment time = approximately 44 months)

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	13.0

Reporting groups

Reporting group title	Trastuzumab + Bevacizumab + Capecitabine

Reporting group description:

Participants received IV trastuzumab (8 mg/kg) for first cycle and then 6 mg/kg for subsequent cycles followed by bevacizumab (15 mg/kg) on Day 1 of each treatment cycles along with capecitabine administered orally to participants at a dose of 1000 mg/m^2 BID on Days 1 to 14 of each treatment cycle until disease progression, unmanageable toxicity or participant request for discontinuation. Treatment cycles were of 3 weeks.

Serious adverse events	Trastuzumab + Bevacizumab + Capecitabine		
Total subjects affected by serious adverse events			
subjects affected / exposed	20 / 88 (22.73%)		
number of deaths (all causes)	40		
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Abdominal wound dehiscence			
subjects affected / exposed	1 / 88 (1.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Fall			
subjects affected / exposed	1 / 88 (1.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Embolism			
subjects affected / exposed	1 / 88 (1.14%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			

Cardiac failure				
subjects affected / exposed	2 / 88 (2.27%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 1			
Intracardiac thrombus				
subjects affected / exposed	1 / 88 (1.14%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Cerebral ischaemia				
subjects affected / exposed	1 / 88 (1.14%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Presyncope				
subjects affected / exposed	1 / 88 (1.14%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Sensory disturbance				
subjects affected / exposed	1 / 88 (1.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pregnancy, puerperium and perinatal conditions				
Abortion spontaneous				
subjects affected / exposed	1 / 88 (1.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
Chest pain				
subjects affected / exposed	1 / 88 (1.14%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Death				

subjects affected / exposed	1 / 88 (1.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	2 / 88 (2.27%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		
Enteritis			
subjects affected / exposed	1 / 88 (1.14%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Intestinal perforation			
subjects affected / exposed	1 / 88 (1.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Abdominal pain			
subjects affected / exposed	1 / 88 (1.14%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 88 (1.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary embolism			
subjects affected / exposed	2 / 88 (2.27%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Respiratory failure			
subjects affected / exposed	1 / 88 (1.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		

Renal and urinary disorders			
Haematuria			
subjects affected / exposed	1 / 88 (1.14%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Renal failure			
subjects affected / exposed	1 / 88 (1.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Musculoskeletal and connective tissue disorders			
Osteoarthritis			
subjects affected / exposed	1 / 88 (1.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Erysipelas			
subjects affected / exposed	1 / 88 (1.14%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	1 / 88 (1.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Trastuzumab + Bevacizumab + Capecitabine		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	81 / 88 (92.05%)		
Investigations			
Weight decreased			
subjects affected / exposed	6 / 88 (6.82%)		
occurrences (all)	6		
Vascular disorders			

Hypertension			
subjects affected / exposed	34 / 88 (38.64%)		
occurrences (all)	58		
Nervous system disorders			
Headache			
subjects affected / exposed	14 / 88 (15.91%)		
occurrences (all)	28		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	32 / 88 (36.36%)		
occurrences (all)	54		
Pyrexia			
subjects affected / exposed	18 / 88 (20.45%)		
occurrences (all)	18		
Fatigue			
subjects affected / exposed	11 / 88 (12.50%)		
occurrences (all)	17		
Mucosal inflammation			
subjects affected / exposed	10 / 88 (11.36%)		
occurrences (all)	12		
Oedema peripheral			
subjects affected / exposed	6 / 88 (6.82%)		
occurrences (all)	9		
Chest pain			
subjects affected / exposed	6 / 88 (6.82%)		
occurrences (all)	6		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	37 / 88 (42.05%)		
occurrences (all)	82		
Nausea			
subjects affected / exposed	24 / 88 (27.27%)		
occurrences (all)	38		
Vomiting			
subjects affected / exposed	15 / 88 (17.05%)		
occurrences (all)	19		

Stomatitis subjects affected / exposed occurrences (all)	10 / 88 (11.36%) 14		
Abdominal pain upper subjects affected / exposed occurrences (all)	9 / 88 (10.23%) 12		
Gingival bleeding subjects affected / exposed occurrences (all)	9 / 88 (10.23%) 11		
Constipation subjects affected / exposed occurrences (all)	9 / 88 (10.23%) 9		
Dry mouth subjects affected / exposed occurrences (all)	5 / 88 (5.68%) 5		
Haemorrhoids subjects affected / exposed occurrences (all)	5 / 88 (5.68%) 5		
Respiratory, thoracic and mediastinal disorders			
Epistaxis subjects affected / exposed occurrences (all)	35 / 88 (39.77%) 56		
Cough subjects affected / exposed occurrences (all)	11 / 88 (12.50%) 14		
Dyspnoea subjects affected / exposed occurrences (all)	7 / 88 (7.95%) 9		
Skin and subcutaneous tissue disorders			
Palmar-plantar erythrodysaesthesia syndrome subjects affected / exposed occurrences (all)	65 / 88 (73.86%) 227		
Nail disorder subjects affected / exposed occurrences (all)	14 / 88 (15.91%) 16		
Renal and urinary disorders			

Proteinuria subjects affected / exposed occurrences (all)	5 / 88 (5.68%) 19		
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all) Arthralgia subjects affected / exposed occurrences (all) Musculoskeletal pain subjects affected / exposed occurrences (all) Pain in extremity subjects affected / exposed occurrences (all) Myalgia subjects affected / exposed occurrences (all)	 10 / 88 (11.36%) 15 9 / 88 (10.23%) 13 8 / 88 (9.09%) 13 8 / 88 (9.09%) 11 6 / 88 (6.82%) 7		
Infections and infestations Urinary tract infection subjects affected / exposed occurrences (all) Respiratory tract infection viral subjects affected / exposed occurrences (all)	 7 / 88 (7.95%) 10 5 / 88 (5.68%) 7		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	 12 / 88 (13.64%) 18		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 March 2012	Increased the interval duration between tumor assessments after 24 months of study participation from every 9 weeks to every 15 weeks until disease progression, initiation of alternative anticancer medication or death. Increasing the interval for tumor assessment reduced the number of scans a participant had to undergo.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported