Clinical trial results:
Phase II, open label, neoadjuvant study of Bevacizumab in patients with inflammatory or locally advanced breast cancer

Summary

EudraCT number	2006-003291-35
Trial protocol	IT
Global end of trial date	28 July 2015

Results information

Result version number	v2 (current)
This version publication date	17 February 2017
First version publication date	16 November 2016
Version creation reason	• Correction of full data set Update to align with ClinicalTrials.gov registry posting.

Trial information

Trial identification

Sponsor protocol code	ML 19884

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00559845
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	F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.com
Scientific contact	F. Hoffmann-La Roche AG, 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	28 July 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	28 July 2015
Global end of trial reached?	Yes
Global end of trial date	28 July 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine the rate of pathological complete responses (pCR) defined as absence of invasive neoplastic cells at microscopic examination of the tumor remnants after surgery following primary systemic therapy.

Protection of trial subjects:

All study subjects were required to read and sign an informed consent form.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	18 February 2008
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy, Safety
Long term follow-up duration	5 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Italy: 56
Worldwide total number of subjects	56
EEA total number of subjects	56

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)	52
From 65 to 84 years	4
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

56 subjects were enrolled in 8 centers in Italy.

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	Bevacizumab

Arm description:

5-fluorouracil, epidoxorubicin and cyclophosphamide (FEC), followed by paclitaxel, given concomitantly with bevacizumab for approximately 3-12 months.

Arm type	Experimental
Investigational medicinal product name	5-fluorouracil
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous bolus use

Dosage and administration details:

600 milligrams per metre squared (mg/m^2) as an intravenous (i.v.) bolus over ≤15 minutes every 3 weeks for 4 cycles.

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

Dosage and administration details:

90 mg/m^2 as an i.v. infusion over 1 hour every 3 weeks for 4 cycles.

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

Dosage and administration details:

600 mg/m^2 as an i.v. infusion over 1 hour every 3 weeks for 4 cycles.

Investigational medicinal product name	Paclitaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravascular use

Dosage and administration details:

80 mg/m^2 i.v. over 1 hour weekly for 12 weeks.

Investigational medicinal product name	Bevacizumab
Investigational medicinal product code	
Other name	Avastin®
Pharmaceutical forms	Concentrate for emulsion for infusion
Routes of administration	Intravenous use

Dosage and administration details:

10 milligrams per kilogram (mg/kg) i.v. every 2 weeks for 6 cycles.

Number of subjects in period 1	Bevacizumab
Started	56
Completed	49
Not completed	7
Did not attend cycle 6 hospital visit	1
Disease progression	1
Adverse event	3
Premature surgery-investigator decision	1
Withdrew consent	1

Baseline characteristics

Reporting groups	
Reporting group title	Bevacizumab
Reporting group description:	
5-fluorouracil, epidoxorubicin and cyclophosphamide (FEC), followed by paclitaxel, given concomitantly with bevacizumab for approximately 3-12 months.	

Reporting group values	Bevacizumab	Total	
Number of subjects	56	56	
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	50		
standard deviation	± 9.279	-	
Gender categorical			
Units: Subjects			
Female	56	56	
Male	0	0	

End points

End points reporting groups

Reporting group title	Bevacizumab

Reporting group description:

5-fluorouracil, epidoxorubicin and cyclophosphamide (FEC), followed by paclitaxel, given concomitantly with bevacizumab for approximately 3-12 months.

Primary: Percentage of Subjects With Pathological Complete Response Following Principle Investigator Review

End point title	Percentage of Subjects With Pathological Complete Response Following Principle Investigator Review[1]

End point description:

Pathological complete response was defined as absence of invasive neoplastic cells at microscopic examination of the tumor remnants after surgery following primary systemic therapy. Intention-to-Treat (ITT) population, defined as all subjects that were included in the trial and underwent surgery.

End point type	Primary

End point timeframe:

Up to 7.5 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: Only descriptive data was planned to be reported.

End point values	Bevacizumab			
Subject group type	Reporting group			
Number of subjects analysed	56			
Units: percentage of subjects				
number (not applicable)	23.2			

Statistical analyses

No statistical analyses for this end point

Secondary: Objective Response Rate

End point title	Objective Response Rate

End point description:

Objective response rate was defined as the percentage of subjects with a Complete Response (CR) or Partial Response (PR) as defined by the Response Evaluation Criteria in Solid Tumors (RECIST). CR was defined as the disappearance of all target lesions; PR was defined as a 30% decrease in sum of longest diameter of target lesions. ITT population, defined as all subjects that were included in the trial and underwent surgery.

End point type	Secondary

End point timeframe:

Up to 7.5 years

End point values	Bevacizumab			
Subject group type	Reporting group			
Number of subjects analysed	56			
Units: percentage of subjects				
number (not applicable)	59			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Breast-Conserving Surgery

End point title	Percentage of Subjects With Breast-Conserving Surgery

End point description:

Categories breast-conserving procedure, and breast-conserving procedure plus axillary dissection are presented. ITT population, defined as all subjects that were included in the trial and underwent surgery.

End point type	Secondary

End point timeframe:

Up to 7.5 years

End point values	Bevacizumab			
Subject group type	Reporting group			
Number of subjects analysed	56			
Units: percentage of subjects				
number (not applicable)				
Breast-conserving	17			
Breast-conserving plus axillary	13.2			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Disease-Free Interval at Specified Time Points

End point title	Percentage of Subjects With Disease-Free Interval at Specified Time Points

End point description:

Disease-free interval was defined as the time from enrollment until recurrence of tumor or death from any cause, and was estimated using the Kaplan-Meier method. The percentage of subjects without events at Months 12, 24, 36, 48, and 60 is presented. ITT population, defined as all subjects that were included in the trial and underwent surgery.

End point type	Secondary

End point timeframe:
Months 12, 24, 36, 48, and 60

End point values	Bevacizumab			
Subject group type	Reporting group			
Number of subjects analysed	53[2]			
Units: percentage of subjects				
number (confidence interval 95%)				
12 Months	92.2 (85.1 to 99.8)			
24 Months	84.3 (74.9 to 94.9)			
36 Months	80.4 (70.2 to 92.1)			
48 Months	76.5 (65.7 to 89.1)			
60 Months	76.5 (65.7 to 89.1)			

Notes:
[2] - Number of subjects analyzed signifies those subjects who were evaluable for the endpoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival

End point title	Overall Survival

End point description:
Overall survival was defined as the time from enrollment of subject to death from any cause.

End point type	Secondary

End point timeframe:
Up to 7.5 years

End point values	Bevacizumab			
Subject group type	Reporting group			
Number of subjects analysed	0[3]			
Units: months				
median (full range (min-max))	(to)			

Notes:
[3] - Data for the outcome measure was not collected.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Experiencing Any Adverse Event

End point title	Percentage of Subjects Experiencing Any Adverse Event

End point description:

An adverse event was defined as any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. Safety population, defined as all subjects who received at least one infusion of Bevacizumab.

End point type	Secondary

End point timeframe:

Up to 7.5 years

End point values	Bevacizumab			
Subject group type	Reporting group			
Number of subjects analysed	56			
Units: percentage of subjects				
number (not applicable)	100			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 7.5 years

Adverse event reporting additional description:

Safety population, defined as all subjects who received at least one infusion of Bevacizumab.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	13.0

Reporting groups

Reporting group title	Bevacizumab

Reporting group description:

5-fluorouracil, epidoxorubicin and cyclophosphamide (FEC), followed by paclitaxel, given concomitantly with bevacizumab for approximately 3-12 months.

Serious adverse events	Bevacizumab		
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 54 (14.81%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Investigations			
Cardiac imaging procedure abnormal			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant melanoma in situ			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Postoperative wound complication			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			

Anaemia			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Febrile neutropenia			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences causally related to treatment / all	4 / 6		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Retinopathy hypertensive			
subjects affected / exposed	1 / 54 (1.85%)		
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 / 54 (1.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Suicide attempt			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Febrile infection			
subjects affected / exposed	1 / 54 (1.85%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Bevacizumab		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	54 / 54 (100.00%)		

Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	6 / 54 (11.11%)		
occurrences (all)	8		
Ast increased			
subjects affected / exposed	3 / 54 (5.56%)		
occurrences (all)	4		
Vascular disorders			
Hypertension			
subjects affected / exposed	13 / 54 (24.07%)		
occurrences (all)	15		
Phlebitis			
subjects affected / exposed	4 / 54 (7.41%)		
occurrences (all)	4		
Surgical and medical procedures			
Astringent therapy			
subjects affected / exposed	3 / 54 (5.56%)		
occurrences (all)	3		
Nervous system disorders			
Paraesthesia			
subjects affected / exposed	27 / 54 (50.00%)		
occurrences (all)	37		
Headache			
subjects affected / exposed	10 / 54 (18.52%)		
occurrences (all)	16		
Dysgeusia			
subjects affected / exposed	5 / 54 (9.26%)		
occurrences (all)	6		
Syncope			
subjects affected / exposed	3 / 54 (5.56%)		
occurrences (all)	3		
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	22 / 54 (40.74%)		
occurrences (all)	50		
Leukopenia			

subjects affected / exposed	15 / 54 (27.78%)		
occurrences (all)	26		
Anaemia			
subjects affected / exposed	12 / 54 (22.22%)		
occurrences (all)	15		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	30 / 54 (55.56%)		
occurrences (all)	83		
Mucosal inflammation			
subjects affected / exposed	18 / 54 (33.33%)		
occurrences (all)	41		
Pyrexia			
subjects affected / exposed	15 / 54 (27.78%)		
occurrences (all)	27		
Oedema			
subjects affected / exposed	3 / 54 (5.56%)		
occurrences (all)	3		
Pain			
subjects affected / exposed	3 / 54 (5.56%)		
occurrences (all)	4		
Eye disorders			
Conjunctivitis			
subjects affected / exposed	9 / 54 (16.67%)		
occurrences (all)	17		
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	38 / 54 (70.37%)		
occurrences (all)	66		
Diarrhea			
subjects affected / exposed	17 / 54 (31.48%)		
occurrences (all)	27		
Vomiting			
subjects affected / exposed	17 / 54 (31.48%)		
occurrences (all)	28		
Constipation			

subjects affected / exposed	11 / 54 (20.37%)		
occurrences (all)	16		
Stomatitis			
subjects affected / exposed	11 / 54 (20.37%)		
occurrences (all)	14		
Abdominal pain upper			
subjects affected / exposed	7 / 54 (12.96%)		
occurrences (all)	8		
Dyspepsia			
subjects affected / exposed	6 / 54 (11.11%)		
occurrences (all)	7		
Haemorrhoids			
subjects affected / exposed	4 / 54 (7.41%)		
occurrences (all)	4		
Abdominal pain			
subjects affected / exposed	3 / 54 (5.56%)		
occurrences (all)	3		
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	33 / 54 (61.11%)		
occurrences (all)	47		
Cough			
subjects affected / exposed	4 / 54 (7.41%)		
occurrences (all)	4		
Dyspnoea			
subjects affected / exposed	3 / 54 (5.56%)		
occurrences (all)	6		
Oropharyngeal pain			
subjects affected / exposed	3 / 54 (5.56%)		
occurrences (all)	3		
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	36 / 54 (66.67%)		
occurrences (all)	36		
Nail disorder			

subjects affected / exposed	10 / 54 (18.52%)		
occurrences (all)	10		
Rash			
subjects affected / exposed	8 / 54 (14.81%)		
occurrences (all)	11		
Pruritus			
subjects affected / exposed	4 / 54 (7.41%)		
occurrences (all)	5		
Erythema			
subjects affected / exposed	3 / 54 (5.56%)		
occurrences (all)	3		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	4 / 54 (7.41%)		
occurrences (all)	4		
Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	18 / 54 (33.33%)		
occurrences (all)	35		
Bone Pain			
subjects affected / exposed	13 / 54 (24.07%)		
occurrences (all)	24		
Arthralgia			
subjects affected / exposed	3 / 54 (5.56%)		
occurrences (all)	7		
Pain in extremity			
subjects affected / exposed	3 / 54 (5.56%)		
occurrences (all)	3		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 November 2009	1. Better define and specify the objectives of the study 2. Update the duration of the study according to the new definition of "Long-Term Follow-up" for a maximum of 5 years 3. Update the examinations to be performed during the "Long-Term Follow-up" according to the clinical practice

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported