Clinical trial results:
"Estudio aleatorizado, multicéntrico para evaluar la eficacia y seguridad de bevacizumab en combinación con letrozol comparado con letrozol solo, en mujeres postmenopáusicas con cáncer de mama localmente recurrente o metastásico con indicación de hormonoterapia como tratamiento de primera línea".
"Multicenter, randomized trial to evaluate efficacy and safety of bevacizumab in combination with endocrine treatment compared to endocrine treatment alone, in postmenopausal women with advanced or metastatic breast cancer with indication of hormonotherapy as first-line treatment"

Summary

EudraCT number	2007-002841-19
Trial protocol	ES DE
Global end of trial date	01 September 2013

Results information

Result version number	v1
This version publication date	18 March 2022
First version publication date	18 March 2022

Trial information

Trial identification

Sponsor protocol code	GEICAM/2006-11

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00545077
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	GEICAM (FUNDACIÓN GRUPO ESPAÑOL DE INVESTIGACIÓN EN CÁNCER DE MAMA)
Sponsor organisation address	Avenida de los Pirineos 7, San Sebastián de los Reyes / Madrid, Spain, 28703
Public contact	GEICAM, GEICAM (FUNDACIÓN GRUPO ESPAÑOL DE INVESTIGACIÓN EN CÁNCER DE MAMA), +34 916 592 870, inicio_ensayos@geicam.org
Scientific contact	GEICAM, GEICAM (FUNDACIÓN GRUPO ESPAÑOL DE INVESTIGACIÓN EN CÁNCER DE MAMA), +34 916 592 870, inicio_ensayos@geicam.org

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	12 November 2013
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	01 September 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the progression-free survival (PFS) between both treatment arms

Protection of trial subjects:

Not applicable. It was not necessary to applied extra measures for protection of the subjects out of the good clinical practice environment.

Background therapy:

Bevacizumab is a humanized monoclonal antibody which acts by binding and inhibiting the action of the vascular endothelial growth factor (VEGF).
Bevacizumab and aromatase inhibitors have shown a high activity and an acceptable and manageable Adverse Event profile in the treatment of patients with locally advanced or metastatic breast cancer. It has also been suggested that estrogens modulates the angiogenesis induced by VEGF in pathological and physiological conditions. Clinical data suggest, that the down regulation of VEGF may be able to overcome resistance to hormonal therapy and thus improve efficacy to hormonal therapy. Therefore, a combination of endocrine therapy and an antibody against VEGF such as bevacizumab can be more effective than endocrine therapy as a single agent alone.

Evidence for comparator:

This study proposed evaluating the activity and safety profile of the combination of bevacizumab and endocrine treatment compared with endocrine treatment alone, as first-line treatment for postmenopausal women with positive hormone receptor and negative HER2 status. As some patients may have received aromatase inhibitors in the adjuvant setting, fulvestrant, an estrogen receptor downregulator, could also be administered as endocrine therapy according the physicians decision.

Actual start date of recruitment	06 November 2007
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	Spain: 266
Country: Number of subjects enrolled	Germany: 108
Worldwide total number of subjects	374
EEA total number of subjects	374

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)	185
From 65 to 84 years	174
85 years and over	15

Subject disposition

Recruitment

Recruitment details:

Between November 2007 and August 2011, 380 patients (270 in Spain and 110 in Germany) were recruited and randomly assigned to receive ET (n = 189) or ET-B (n = 191). Six patients, five in the ET arm and one in the ET-B arm, never received treatment; thus, a total of 374 patients (184 on ET and 190 on ET-B) were evaluable for efficacy and safety

Pre-assignment

Screening details:

Between November 2007 and August 2011, 380 patients (270 in Spain and 110 in Germany) were recruited and randomly assigned to receive ET (n = 189) or ET-B (n = 191). Six patients, five in the ET arm and one in the ET-B arm, never received treatment; thus, a total of 374 patients (184 on ET and 190 on ET-B) were evaluable for efficacy and safety

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm A: Endocrine Therapy (ET)

Arm description:

Endocrine Therapy consisting of either letrozole (2.5mg per day) or fulvestrant (250 mg every 4 weeks). The patients received the assigned treatment until the progression of the disease, unacceptable toxicity or withdrawal of the consent.

Arm type	Active comparator
Investigational medicinal product name	Letrozole
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Letrozole 2.5 mg was administered orally as one tablet daily.

Investigational medicinal product name	Fulvestrant
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Fulvestrant 250 mg every 4 weeks.

Arm title	Arm B: ET with Bevacizumab (ET-B)

Arm description:

Endocrine treatment consisted on either letrozole [2.5mg per day] or fulvestrant [250 mg every 4 weeks] plus bevacizumab 15mg/kg i.v. on day 1 every 3 weeks. The patients received the assigned treatment until the progression of the disease, unacceptable toxicity or withdrawal of the consent.

Arm type	Experimental

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

Dosage and administration details:

Letrozole 2.5 mg was administered orally as one tablet daily.

Investigational medicinal product name	Fulvestrant
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Fulvestrant 250 mg every 4 weeks.

Investigational medicinal product name	Bevacizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Bevacizumab 15mg/kg i.v. on day 1 every 3 weeks

Number of subjects in period 1	Arm A: Endocrine Therapy (ET)	Arm B: ET with Bevacizumab (ET-B)
Started	184	190
Completed	41	36
Not completed	143	154
Consent withdrawn by subject	3	13
Physician decision	7	3
Disease progression	131	98
Adverse event, non-fatal	-	38
Death	-	2
Lost to follow-up	2	-

Baseline characteristics

Reporting groups	
Reporting group title	Arm A: Endocrine Therapy (ET)
Reporting group description:	
Endocrine Therapy consisting of either letrozole (2.5mg per day) or fulvestrant (250 mg every 4 weeks). The patients received the assigned treatment until the progression of the disease, unacceptable toxicity or withdrawal of the consent.	
Reporting group title	Arm B: ET with Bevacizumab (ET-B)
Reporting group description:	
Endocrine treatment consisted on either letrozole [2.5mg per day] or fulvestrant [250 mg every 4 weeks] plus bevacizumab 15mg/kg i.v. on day 1 every 3 weeks. The patients received the assigned treatment until the progression of the disease, unacceptable toxicity or withdrawal of the consent.	

Reporting group values	Arm A: Endocrine Therapy (ET)	Arm B: ET with Bevacizumab (ET-B)	Total
Number of subjects	184	190	374
Age categorical Units: Subjects			
Adults (18-64 years)	84	101	185
From 65-84 years	93	81	174
85 years and over	7	8	15
Age continuous Units: years			
median	66	64	
full range (min-max)	39 to 86	38 to 85	-
Gender categorical Units: Subjects			
Female	184	190	374
Male	0	0	0
Eastern Cooperative Oncology Group (ECOG) status			
ECOG score runs from 0 to 5, with 0 denoting perfect health and 5 death. 0 - Asymptomatic 1 - Symptomatic but completely ambulatory 2 - Symptomatic, <50% in bed during the day 3 - Symptomatic, >50% in bed, but not bedbound 4 - Bedbound 5 - Death			
Units: Subjects			
ECOG 0	131	139	270
ECOG 1	53	51	104
Previous (neo)adjuvant chemotherapy Units: Subjects			
Taxanes, anthracyclines, or both	66	65	131
Cyclophosphamide, methotrexate, fluorouracil (CMF)	21	18	39
Other	1	0	1
No previous (neo) adjuvant chemotherapy	96	107	203
Previous (neo)adjuvant endocrine therapy Units: Subjects			

Antiestrogens	58	64	122
Aromatase inhibitor	13	8	21
Both	24	28	52
No previous (neo)adjuvant endocrine therap	89	90	179
Stage of disease at study entry Units: Subjects			
Locally advanced	6	5	11
Metastatic	178	185	363
Number of metastatic sites Units: Subjects			
Single	67	80	147
Multiple	117	110	227
Bone disease Units: Subjects			
Present	118	124	242
Not present	66	66	132
Visceral disease Units: Subjects			
Present	88	90	178
Not present	96	100	196
Measurable disease Units: Subjects			
Measurable	146	142	288
Non Measurable	38	48	86

End points

End points reporting groups

Reporting group title	Arm A: Endocrine Therapy (ET)
Reporting group description:	
Endocrine Therapy consisting of either letrozole (2.5mg per day) or fulvestrant (250 mg every 4 weeks). The patients received the assigned treatment until the progression of the disease, unacceptable toxicity or withdrawal of the consent.	
Reporting group title	Arm B: ET with Bevacizumab (ET-B)
Reporting group description:	
Endocrine treatment consisted on either letrozole [2.5mg per day] or fulvestrant [250 mg every 4 weeks] plus bevacizumab 15mg/kg i.v. on day 1 every 3 weeks. The patients received the assigned treatment until the progression of the disease, unacceptable toxicity or withdrawal of the consent.	

Primary: Progression-free Survival (PFS)

End point title	Progression-free Survival (PFS)
End point description:	
PFS was defined as the time elapsed from randomization until the date in which the progression of the disease or the death for any reason (whichever occurs first) is documented.	
End point type	Primary
End point timeframe:	
Up to 2 years	

End point values	Arm A: Endocrine Therapy (ET)	Arm B: ET with Bevacizumab (ET-B)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	184	190		
Units: Events	135	128		

Attachments (see zip file)	PFS KM/2006-11 PFS.docx

Statistical analyses

Statistical analysis title	Kaplan–Meier, log rank test and Cox's HR
Comparison groups	Arm B: ET with Bevacizumab (ET-B) v Arm A: Endocrine Therapy (ET)
Number of subjects included in analysis	374
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.126
Method	Logrank
Parameter estimate	Cox proportional hazard

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.65
upper limit	1.06
Variability estimate	Standard deviation

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

OS was defined as the time elapsed since randomization, until the time in which death occurs for any reason. The patients lost in the follow-up will be censured at the date of the last follow-up.

End point type	Secondary

End point timeframe:

Up to 2 years

End point values	Arm A: Endocrine Therapy (ET)	Arm B: ET with Bevacizumab (ET-B)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	184	190		
Units: Events	46	47		

Attachments (see zip file)	OS KM/2006-11 OS KM.docx

Statistical analyses

Statistical analysis title	Kaplan–Meier, log rank test and Cox's HR
Comparison groups	Arm A: Endocrine Therapy (ET) v Arm B: ET with Bevacizumab (ET-B)
Number of subjects included in analysis	374
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.158
Method	Logrank
Parameter estimate	Cox proportional hazard
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.58
upper limit	1.32
Variability estimate	Standard deviation

Secondary: Time to Treatment Failure (TTF)

End point title	Time to Treatment Failure (TTF)

End point description:

TTF was defined as the time elapsed since randomization until the date the treatment is discontinued for any reason (progression disease, treatment toxicity or death).

End point type	Secondary

End point timeframe:

Up to 2 years

End point values	Arm A: Endocrine Therapy (ET)	Arm B: ET with Bevacizumab (ET-B)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	184	190		
Units: Events	135	142		

Attachments (see zip file)	TTF/2066-11 TTF.docx

Statistical analyses

No statistical analyses for this end point

Secondary: Overall response rate (ORR)

End point title	Overall response rate (ORR)

End point description:

ORR to treatment is reflected by a frequency table containing the data of the best overall response (Complete Response, Partial Response,Stable Disease or Progressive Disease) experienced for each patient during treatment (recorded from the start of the treatment until disease progression) per arm.

End point type	Secondary

End point timeframe:

2 years

End point values	Arm A: Endocrine Therapy (ET)	Arm B: ET with Bevacizumab (ET-B)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	146[1]	142[2]		
Units: Participants	32	58		

Notes:

[1] - Only patients with measurable lesions were taken into account

[2] - Only patients with measurable lesions were taken into account

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The adverse events were recorded throughout the study. The events that are not related with the study medication were followed up for 30 days and the related ones until their resolution or stabilization.

Adverse event reporting additional description:

The selected target adverse events, regardless of their causality, will be followed up until their resolution or stabilization, as specified in the protocol.

Assessment type	Systematic

Dictionary used

Dictionary name	CTCAE-NCI
Dictionary version	3.0

Reporting groups

Reporting group title	Arm A: Endocrine Therapy (ET)

Reporting group description:

Endocrine Therapy consisting of either letrozole (2.5mg per day) or fulvestrant (250 mg every 4 weeks). The patients received the assigned treatment until the progression of the disease, unacceptable toxicity or withdrawal of the consent.

Reporting group title	Arm B: ET with Bevacizumab (ET-B)

Reporting group description:

Endocrine treatment consisted on either letrozole [2.5mg per day] or fulvestrant [250 mg every 4 weeks] plus bevacizumab 15mg/kg i.v. on day 1 every 3 weeks. The patients received the assigned treatment until the progression of the disease, unacceptable toxicity or withdrawal of the consent.

Serious adverse events	Arm A: Endocrine Therapy (ET)	Arm B: ET with Bevacizumab (ET-B)	
Total subjects affected by serious adverse events			
subjects affected / exposed	21 / 184 (11.41%)	64 / 190 (33.68%)	
number of deaths (all causes)	0	8	
number of deaths resulting from adverse events	0	1	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasm			
subjects affected / exposed	0 / 184 (0.00%)	1 / 190 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 18	
deaths causally related to treatment / all	0 / 0	0 / 0	
Promyelocytic leukemia			
subjects affected / exposed	0 / 184 (0.00%)	1 / 190 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypertension			

subjects affected / exposed	0 / 184 (0.00%)	6 / 190 (3.16%)	
occurrences causally related to treatment / all	0 / 0	5 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombosis lower left leg			
subjects affected / exposed	1 / 184 (0.54%)	0 / 190 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Pain in back			
subjects affected / exposed	1 / 184 (0.54%)	0 / 190 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Ulceration of Mama			
subjects affected / exposed	0 / 184 (0.00%)	1 / 190 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Social circumstances			
Sudden death			
subjects affected / exposed	0 / 184 (0.00%)	1 / 190 (0.53%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Unknown death			
subjects affected / exposed	0 / 184 (0.00%)	1 / 190 (0.53%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory, thoracic and mediastinal disorders			
Aspiration pneumonia			
subjects affected / exposed	1 / 184 (0.54%)	0 / 190 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			

subjects affected / exposed	2 / 184 (1.09%)	0 / 190 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	0 / 184 (0.00%)	1 / 190 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	2 / 184 (1.09%)	0 / 190 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 184 (0.00%)	1 / 190 (0.53%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	1 / 184 (0.54%)	5 / 190 (2.63%)	
occurrences causally related to treatment / all	0 / 1	3 / 5	
deaths causally related to treatment / all	0 / 0	0 / 1	
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 184 (0.00%)	1 / 190 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Hypochondrium pain by transaminase values increased			
subjects affected / exposed	0 / 184 (0.00%)	1 / 190 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Benzodiacepine intoxication			

subjects affected / exposed	1 / 184 (0.54%)	0 / 190 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fracture oleacranon			
subjects affected / exposed	0 / 184 (0.00%)	1 / 190 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Overdose bevacizumab			
subjects affected / exposed	0 / 184 (0.00%)	2 / 190 (1.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Right iliac fracture			
subjects affected / exposed	1 / 184 (0.54%)	0 / 190 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound healing complication			
subjects affected / exposed	0 / 184 (0.00%)	1 / 190 (0.53%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	0 / 184 (0.00%)	1 / 190 (0.53%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac infarction			
subjects affected / exposed	0 / 184 (0.00%)	1 / 190 (0.53%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Heart failure			
subjects affected / exposed	0 / 184 (0.00%)	1 / 190 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Infarction			

subjects affected / exposed	0 / 184 (0.00%)	1 / 190 (0.53%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Nervous system disorders			
Cerebellum infarction			
subjects affected / exposed	0 / 184 (0.00%)	1 / 190 (0.53%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
CNS cerebrovascular ischemia			
subjects affected / exposed	0 / 184 (0.00%)	1 / 190 (0.53%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headhache			
subjects affected / exposed	0 / 184 (0.00%)	1 / 190 (0.53%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemihyperaesthesia right			
subjects affected / exposed	0 / 184 (0.00%)	1 / 190 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic insult			
subjects affected / exposed	0 / 184 (0.00%)	1 / 190 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope vasovagal			
subjects affected / exposed	0 / 184 (0.00%)	1 / 190 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Lymphangitis			
subjects affected / exposed	0 / 184 (0.00%)	1 / 190 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			

Acute pancreatitis			
subjects affected / exposed	0 / 184 (0.00%)	1 / 190 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal fistula			
subjects affected / exposed	0 / 184 (0.00%)	1 / 190 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	1 / 184 (0.54%)	0 / 190 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	0 / 184 (0.00%)	2 / 190 (1.05%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	0 / 184 (0.00%)	1 / 190 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemorrhoids			
subjects affected / exposed	0 / 184 (0.00%)	1 / 190 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia surgery			
subjects affected / exposed	1 / 184 (0.54%)	0 / 190 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal perforation			
subjects affected / exposed	0 / 184 (0.00%)	1 / 190 (0.53%)	
occurrences causally related to treatment / all	0 / 0	1 / 15	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucositis			

subjects affected / exposed	1 / 184 (0.54%)	0 / 190 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	0 / 184 (0.00%)	1 / 190 (0.53%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parodontitis			
subjects affected / exposed	0 / 184 (0.00%)	1 / 190 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subileus			
subjects affected / exposed	0 / 184 (0.00%)	1 / 190 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 184 (0.00%)	2 / 190 (1.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Biliary colic			
subjects affected / exposed	1 / 184 (0.54%)	0 / 190 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	0 / 184 (0.00%)	1 / 190 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	0 / 184 (0.00%)	1 / 190 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Descompensated liver disease			

subjects affected / exposed	0 / 184 (0.00%)	1 / 190 (0.53%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Liver disease			
subjects affected / exposed	0 / 184 (0.00%)	1 / 190 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Nephritis			
subjects affected / exposed	1 / 184 (0.54%)	0 / 190 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Proteinuria			
subjects affected / exposed	0 / 184 (0.00%)	4 / 190 (2.11%)	
occurrences causally related to treatment / all	0 / 0	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Severe renal failure			
subjects affected / exposed	0 / 184 (0.00%)	1 / 190 (0.53%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary obstruction			
subjects affected / exposed	1 / 184 (0.54%)	0 / 190 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Aseptic necrosis of jaw			
subjects affected / exposed	0 / 184 (0.00%)	1 / 190 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaw osteonecrosis			
subjects affected / exposed	1 / 184 (0.54%)	2 / 190 (1.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Osteochemonecrosis			
subjects affected / exposed	0 / 184 (0.00%)	1 / 190 (0.53%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain left lower extremity			
subjects affected / exposed	0 / 184 (0.00%)	1 / 190 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abscess right breast			
subjects affected / exposed	1 / 184 (0.54%)	0 / 190 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	0 / 184 (0.00%)	1 / 190 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas right arm			
subjects affected / exposed	1 / 184 (0.54%)	0 / 190 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas left arm			
subjects affected / exposed	1 / 184 (0.54%)	0 / 190 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	0 / 184 (0.00%)	1 / 190 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyperkalaemia			
subjects affected / exposed	0 / 184 (0.00%)	1 / 190 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Arm A: Endocrine Therapy (ET)	Arm B: ET with Bevacizumab (ET-B)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	184 / 184 (100.00%)	190 / 190 (100.00%)	
Investigations			
Lymphopenia			
subjects affected / exposed	38 / 184 (20.65%)	57 / 190 (30.00%)	
occurrences (all)	38	57	
Platelet count			
subjects affected / exposed	21 / 184 (11.41%)	42 / 190 (22.11%)	
occurrences (all)	21	42	
White blood cell decreased			
subjects affected / exposed	22 / 184 (11.96%)	48 / 190 (25.26%)	
occurrences (all)	22	48	
Neutrophil count decreased			
subjects affected / exposed	11 / 184 (5.98%)	22 / 190 (11.58%)	
occurrences (all)	11	22	
Alanine aminotransferase increased			
subjects affected / exposed	56 / 184 (30.43%)	82 / 190 (43.16%)	
occurrences (all)	56	82	
Aspartate aminotransferase increased			
subjects affected / exposed	51 / 184 (27.72%)	98 / 190 (51.58%)	
occurrences (all)	51	98	
Alkaline phosphatase increased			
subjects affected / exposed	22 / 184 (11.96%)	48 / 190 (25.26%)	
occurrences (all)	22	48	
Blood bilirubin increased			
subjects affected / exposed	9 / 184 (4.89%)	24 / 190 (12.63%)	
occurrences (all)	9	24	
Creatinine increased			

subjects affected / exposed	18 / 184 (9.78%)	38 / 190 (20.00%)	
occurrences (all)	18	38	
Vascular disorders			
Haemorrhage			
subjects affected / exposed	3 / 184 (1.63%)	36 / 190 (18.95%)	
occurrences (all)	3	36	
Hot flashes			
subjects affected / exposed	33 / 184 (17.93%)	32 / 190 (16.84%)	
occurrences (all)	33	32	
Hypertension			
subjects affected / exposed	36 / 184 (19.57%)	145 / 190 (76.32%)	
occurrences (all)	36	145	
Thrombosis			
subjects affected / exposed	1 / 184 (0.54%)	8 / 190 (4.21%)	
occurrences (all)	1	8	
Nervous system disorders			
Sensory Neuropathy			
subjects affected / exposed	11 / 184 (5.98%)	17 / 190 (8.95%)	
occurrences (all)	11	17	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	52 / 184 (28.26%)	105 / 190 (55.26%)	
occurrences (all)	52	105	
Fever without Neutropenia			
subjects affected / exposed	6 / 184 (3.26%)	18 / 190 (9.47%)	
occurrences (all)	6	18	
Pain			
subjects affected / exposed	94 / 184 (51.09%)	144 / 190 (75.79%)	
occurrences (all)	94	144	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	179 / 184 (97.28%)	189 / 190 (99.47%)	
occurrences (all)	179	189	
Immune system disorders			
Allergic Reaction			

subjects affected / exposed	4 / 184 (2.17%)	5 / 190 (2.63%)	
occurrences (all)	4	5	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	10 / 184 (5.43%)	28 / 190 (14.74%)	
occurrences (all)	10	28	
Mucositis/Stomatitis			
subjects affected / exposed	5 / 184 (2.72%)	16 / 190 (8.42%)	
occurrences (all)	5	16	
Nausea			
subjects affected / exposed	20 / 184 (10.87%)	38 / 190 (20.00%)	
occurrences (all)	20	38	
Vomiting			
subjects affected / exposed	7 / 184 (3.80%)	25 / 190 (13.16%)	
occurrences (all)	7	25	
Reproductive system and breast disorders			
Vaginal discharge			
subjects affected / exposed	1 / 184 (0.54%)	4 / 190 (2.11%)	
occurrences (all)	1	4	
Hepatobiliary disorders			
Liver Dysfunction			
subjects affected / exposed	0 / 184 (0.00%)	10 / 190 (5.26%)	
occurrences (all)	0	10	
Elevated liver enzyme (ALT and/or AST)			
subjects affected / exposed	72 / 184 (39.13%)	115 / 190 (60.53%)	
occurrences (all)	72	115	
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	5 / 184 (2.72%)	77 / 190 (40.53%)	
occurrences (all)	5	77	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 December 2007	The calendar, the expected date of completion, the inclusion and exclusion criteria of the trial were changed, reducing the number of stratification and updating the list of Participating Sites. Collaboration in the study of the German Breast Group (GBG –German Breast Group) that will be sponsor of the study in German sites is also included in this modification.
20 August 2008	Creation of an Independent Data Monitoring Committee. Statistical Clarifications. Correction of previous errata: Proteinuria algorithm. Update of participating sites.
14 July 2009	A new drug, Fulvestrant, that belongs to the same type of endocrine treatment has been incorporated. Now patients who were previously treated with aromatase inhibitor can be recruited. As a result of this change, the study title has been modified. The 12-month washing period is eliminated in the inclusion criterion # 12 in the case of having previously received aromatase inhibitor, since in this amendment the option is given to start treatment in combination or as a single agent with fulvestrant, not being necessary this temporary margin. Corrections have been made, corrected errata and terms have been modified or clarified throughout the protocol, as well as the update of the participating sites and staff of the study involved. In the informed consent of the study, the main adverse events known from the use of fulvestrant are included, as well as those already indicated of letrozole.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/25691671

http://www.ncbi.nlm.nih.gov/pubmed/31276981