Clinical trial results:
PHASE IV.III, MULTICENTER, OPEN, RANDOMIZED TREATMENT STUDY TO EVALUATE THE EFFICACY OF MAINTENANCE THERAPY WITH CAPECITABINE (X) AFTER STANDARD ADJUVANT CHEMOTHERAPY IN PATIENTS WITH OPERABLE, HORMONE RECEPTOR AND HER2neu NEGATIVE BREAST CANCER

Summary

EudraCT number	2005-002838-36
Trial protocol	ES
Global end of trial date	17 February 2017

Results information

Result version number	v1
This version publication date	22 March 2020
First version publication date	22 March 2020

Trial information

Trial identification

Sponsor protocol code	CIBOMA/2004-01

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00130533
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
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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	17 February 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	17 February 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Principal objective: Compare 5-year disease-free survival after maintenance therapy with 8 cycles of capecitabine (X) compared to observation, in patients with operable, hormone receptor and HER2neu negative breast cancer who have received standard adjuvant chemotherapy

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:

Early triple negative breast cancer (TNBC) can be cured with local-regional therapy plus adjuvant chemotherapy (usually anthracycline and/or taxane-based combinations). However, in spite of these therapies, a proportion of patients eventually relapses and dies. A recent analysis of data from the National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) reported a 3-year relapse rate of around 8%, 15% and 40% for stages I, II and III TNBC patients, respectively.
Therefore, new adjuvant options are necessary to improve the prognosis of this breast cancer subtype. Capecitabine is an oral prodrug of 5-fluorouracil approved for the treatment of metastatic breast cancer in patients with prior progression after anthracyclines and taxanes and, therefore, is partially non-crossresistant with these two class of agents. Based on this concept, we carried out a trial in which capecitabine was sequentially added to standard (neo)adjuvant chemotherapy in operable TNBC, in order to explore the ability of the drug to reduce the rate of relapse and increase the survival of this disease.

Evidence for comparator: -

Actual start date of recruitment	26 October 2006
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	Brazil: 139
Country: Number of subjects enrolled	Mexico: 113
Country: Number of subjects enrolled	Chile: 42
Country: Number of subjects enrolled	Peru: 19
Country: Number of subjects enrolled	Ecuador: 18
Country: Number of subjects enrolled	Colombia: 9
Country: Number of subjects enrolled	Venezuela, Bolivarian Republic of: 4
Country: Number of subjects enrolled	Spain: 532

Worldwide total number of subjects	876
EEA total number of subjects	532

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)	768
From 65 to 84 years	108
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Between October 2006 and September 2011, 876 patients were recruited, across 80 institutions in 8 countries (Spain, Brazil, Chile, Colombia, Ecuador, Mexico, Peru and Venezuela)

Pre-assignment

Screening details:

Between October 2006 and September 2011, 876 patients were recruited, across 80 institutions in 8 countries (Spain, Brazil, Chile, Colombia, Ecuador, Mexico, Peru, and Venezuela)

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	Xeloda (capecitabine)

Arm description:

1000 mgrs/m2 twice a day, tablets, 8 cycles

Arm type	Experimental
Investigational medicinal product name	Capecitabine
Investigational medicinal product code	
Other name	Xeloda
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

1000 mgrs/m2 twice a day, tablets, 8 cycles

Arm title	Observation

Arm description:

Observation. No intervention.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 1	Xeloda (capecitabine)	Observation
Started	448	428
Completed	337	398
Not completed	111	30
Consent withdrawn by subject	33	6
Second Primary Malignancy	-	1
Interruption of treatment > 3 weeks	11	-
Adverse event, non-fatal	34	1
Death	4	2

Not specified	12	5
Disease relapse	9	13
Lost to follow-up	1	1
Sponsor´s decision	2	-
Protocol deviation	5	1

Baseline characteristics

Reporting groups	
Reporting group title	Xeloda (capecitabine)
Reporting group description:	
1000 mgrs/m2 twice a day, tablets, 8 cycles	
Reporting group title	Observation
Reporting group description:	
Observation. No intervention.	

Reporting group values	Xeloda (capecitabine)	Observation	Total
Number of subjects	448	428	876
Age categorical Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			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)			0
From 65-84 years			0
85 years and over			0
Age continuous Units: years			
median	50	49	
full range (min-max)	20 to 79	23 to 82	-
Gender categorical Units: Subjects			
Female	448	428	876
Male	0	0	0
Race Units: Subjects			
Caucasian	313	309	622
Hispanic	107	97	204
Black	16	11	27
Other	12	11	23
Karnofsky Index Performance			
Karnofsky Scale allows patients to be classified as to their functional impairment. The lower the Karnofsky score, the worse the survival for most serious illnesses 100: Normal, no complaints 90: Minor signs or disease symptoms 80: Normal activity with effort 70: Care for self. Unable to carry on normal activity 60: Requires occasional assistance 50: Requires considerable assistance and frequent medical care 40: Disabled. Requires special care and assistance 30: Severly disabled 20: Very sick. Active supportive treatment necessary 10: Moribund			

0: Dead			
Units: Subjects			
80	8	17	25
90	57	67	124
100	383	344	727
Menopausal status at diagnosis Units: Subjects			
Premenopausal	136	140	276
Postmenopausal	312	288	600
Histologic type Units: Subjects			
Invasive ductal carcinoma	395	369	764
Invasive lobular carcinoma	9	10	19
Other	44	49	93
Histologic grade			
Cancer cells are given a Grade (G) when they are removed from the breast and checked under a microscope. The G is based on how much the cancer cells look like normal cells. • G1 or well differentiated (score 3, 4, or 5): cells are slower-growing, and look more like normal breast tissue. • G2 or moderately differentiated (score 6, 7): cells are growing at a speed of and look like cells somewhere between G1 and 3. • G3 or poorly differentiated (score 8, 9): cells look very different from normal and will probably grow and spread faster.			
Units: Subjects			
Grade 1	15	12	27
Grade 2	82	81	163
Grade 3	323	299	622
Unknown	28	36	64
Phenotype by immunohistochemistry			
Basal phenotype: Basal-like tumors receive this name because their genetic expression profile is similar to that of a normal basal epithelial cell. These similarities include the absence of expression of the estrogen receptor and other genes related with this and the human epidermal growth factor receptor 2 (HER2) receptor. They also share with the basal epithelial cells overexpression of cytokeratins 5/6 and 17, epidermal growth factor receptor (EGFR) and genes associated with proliferation. p53 mutations in thyrosine are also basal cell characteristics.			
Units: Subjects			
Basal	329	318	647
Non-basal	119	110	229
Stage at diagnosis			
Measure Description: According to American Joint Committee on Cancer (AJCC) 2002: • Stage (S) I: tumour <2 centimetres (cm) • S II: S IIA: cancer spread to movable ipsilateral axillary (MIA) Lymph Nodes (LN). tumor <2 cm and spread to MIA LN tumor >2 cm but >5 cm S IIB: tumor >2 cm but <5 cm and spread to MIA LN tumor >5 cm • S III: S IIIA: cancer spread to ipsilateral axillary LN fixed or matted S IIIB: tumor spread to the chest wall or caused swelling or ulceration of the breast or is diagnosed as inflammatory breast cancer. S IIIC: metastases in ipsilateral infraclavicular LN.			
Units: Subjects			
Stage I	62	74	136
Stage II	270	271	541
Stage III	106	80	186
Unknown	10	3	13
Nodal status Units: Subjects			

Negative	244	242	486
1-3 positive nodes	121	124	245
≥4 positive nodes	77	61	138
Missing data	6	1	7
Type of prior Chemotherapy Units: Subjects			
Adjuvant only	353	352	705
Neoadjuvant only	70	64	134
Neoadjuvant + Adjuvant	19	11	30
Missing data	6	1	7
Chemotherapy regimens Units: Subjects			
Anthracyclines without Taxanes	147	138	285
Anthracyclines and Taxanes	301	290	591
Breast surgery Units: Subjects			
Conservative	237	242	479
Mastectomy	205	185	390
Missing data	6	1	7
Axillary surgery Units: Subjects			
Lymphadenectomy	321	280	601
Sentinel lymph node biopsy	99	122	221
Lymphadenectomy + Sentinel lymph node biopsy	28	26	54
Radiation therapy Units: Subjects			
Yes	352	346	698
No	91	81	172
Unknown	5	1	6

End points

End points reporting groups	
Reporting group title	Xeloda (capecitabine)
Reporting group description:	
1000 mgrs/m2 twice a day, tablets, 8 cycles	
Reporting group title	Observation
Reporting group description:	
Observation. No intervention.	

Primary: Disease Free Survival (DFS)	
End point title	Disease Free Survival (DFS)
End point description:	
DFS was measured from the date of randomization assignment in the intent to treat (ITT) population to loco-regional or distant recurrence, second primary malignancy or death date, whichever occurred first.	
End point type	Primary
End point timeframe:	
5 years	

End point values	Xeloda (capecitabine)	Observation		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	448	428		
Units: Survival probability	105	120		

Statistical analyses

Statistical analysis title	Cox's proportional Hazard Ratio
Comparison groups	Xeloda (capecitabine) v Observation
Number of subjects included in analysis	876
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.136
Method	Regression, Cox
Parameter estimate	Cox proportional hazard
Point estimate	0.82
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.63
upper limit	1.06
Variability estimate	Standard deviation

Secondary: Overall Survival (OS)	
End point title	Overall Survival (OS)
End point description: OS event is defined as the death from any cause.	
End point type	Secondary
End point timeframe: 5 years	

End point values	Xeloda (capecitabine)	Observation		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	448	428		
Units: Deaths	71	73		

Statistical analyses

Statistical analysis title	Cox's proportional Hazard Ratio
Comparison groups	Xeloda (capecitabine) v Observation
Number of subjects included in analysis	876
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.623
Method	Regression, Cox
Parameter estimate	Cox proportional hazard
Point estimate	0.92
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.66
upper limit	1.28
Variability estimate	Standard deviation

Secondary: Disease Free Survival (DFS) by Basal Phenotype	
End point title	Disease Free Survival (DFS) by Basal Phenotype
End point description:	
End point type	Secondary
End point timeframe: 5 years	

End point values	Xeloda (capecitabine)	Observation		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	329	318		
Units: Events	84	86		

Statistical analyses

Statistical analysis title	Cox's Hazard Ratio
Comparison groups	Xeloda (capecitabine) v Observation
Number of subjects included in analysis	647
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.6955
Method	Regression, Cox
Parameter estimate	Cox proportional hazard
Point estimate	0.94
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.7
upper limit	1.27
Variability estimate	Standard deviation

Secondary: Disease Free Survival (DFS) by Non-Basal Phenotype

End point title	Disease Free Survival (DFS) by Non-Basal Phenotype

End point description:

End point type	Secondary

End point timeframe:

5 years

End point values	Xeloda (capecitabine)	Observation		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	119	110		
Units: Events	21	34		

Statistical analyses

Statistical analysis title	Cox's proportional Hazard Ratio
Comparison groups	Xeloda (capecitabine) v Observation
Number of subjects included in analysis	229
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.0221
Method	Regression, Cox
Parameter estimate	Cox proportional hazard
Point estimate	0.53
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.31
upper limit	0.91
Variability estimate	Standard deviation

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events (AEs) and Serious Adverse Events (SAEs) were recorded from the date informed consent was signed, during treatment period, and for up 30 days after the end of treatment.

Assessment type	Systematic

Dictionary used

Dictionary name	NCI-CTC
Dictionary version	3.0

Reporting groups

Reporting group title	Xeloda (capecitabine)
Reporting group description: -	
Reporting group title	Observation

Reporting group description: -

Serious adverse events	Xeloda (capecitabine)	Observation	
Total subjects affected by serious adverse events			
subjects affected / exposed	23 / 436 (5.28%)	6 / 425 (1.41%)	
number of deaths (all causes)	73	73	
number of deaths resulting from adverse events	5	2	
Vascular disorders			
Thrombosis/thrombus/embolism: venous thrombosis			
subjects affected / exposed	1 / 436 (0.23%)	0 / 425 (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			
Axillar node disection			
subjects affected / exposed	1 / 436 (0.23%)	0 / 425 (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			
Diarrhea + Vomiting + Septic shock			
subjects affected / exposed	1 / 436 (0.23%)	0 / 425 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Gastroenteritis and renal insuficience			

subjects affected / exposed	1 / 436 (0.23%)	0 / 425 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thoracic pain			
subjects affected / exposed	0 / 436 (0.00%)	1 / 425 (0.24%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thorax and left arm pain			
subjects affected / exposed	1 / 436 (0.23%)	0 / 425 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy			
subjects affected / exposed	0 / 436 (0.00%)	1 / 425 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Supraventricular arrhythmia NOS			
subjects affected / exposed	1 / 436 (0.23%)	0 / 425 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary vasospam			
subjects affected / exposed	1 / 436 (0.23%)	0 / 425 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Heart failure			
subjects affected / exposed	0 / 436 (0.00%)	1 / 425 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac ischemia/infarction			
subjects affected / exposed	1 / 436 (0.23%)	1 / 425 (0.24%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Nervous system disorders			

CNS cerebrovascular ischemia			
subjects affected / exposed	2 / 436 (0.46%)	0 / 425 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Worsening of depressive syndrome			
subjects affected / exposed	1 / 436 (0.23%)	0 / 425 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Blood and lymphatic system disorders			
Neutropenia + Leucopenia			
subjects affected / exposed	1 / 436 (0.23%)	0 / 425 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Dehydration			
subjects affected / exposed	1 / 436 (0.23%)	0 / 425 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhea			
subjects affected / exposed	4 / 436 (0.92%)	0 / 425 (0.00%)	
occurrences causally related to treatment / all	4 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ulcer gastric			
subjects affected / exposed	1 / 436 (0.23%)	0 / 425 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucositis Oral cavity and Pharynx			
subjects affected / exposed	1 / 436 (0.23%)	0 / 425 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Pancreatitis			

subjects affected / exposed	2 / 436 (0.46%)	0 / 425 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Rash: hand-foot skin reaction			
subjects affected / exposed	1 / 436 (0.23%)	0 / 425 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Right renal colic			
subjects affected / exposed	1 / 436 (0.23%)	0 / 425 (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			
Showed lumbar column fracture(L4)			
subjects affected / exposed	0 / 436 (0.00%)	1 / 425 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 436 (0.23%)	1 / 425 (0.24%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Febrile neutropenia			
subjects affected / exposed	1 / 436 (0.23%)	0 / 425 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection with normal ANC (Urinary)			
subjects affected / exposed	1 / 436 (0.23%)	0 / 425 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
hyperbilirrubinemia			

subjects affected / exposed	1 / 436 (0.23%)	0 / 425 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	

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

Non-serious adverse events	Xeloda (capecitabine)	Observation	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	416 / 436 (95.41%)	271 / 425 (63.76%)	
Cardiac disorders			
Any Cardiac event			
subjects affected / exposed	5 / 436 (1.15%)	4 / 425 (0.94%)	
occurrences (all)	5	4	
Nervous system disorders			
NEUROPATHY: SENSORY			
subjects affected / exposed	66 / 436 (15.14%)	25 / 425 (5.88%)	
occurrences (all)	66	25	
General disorders and administration site conditions			
Abdominal pain, general			
subjects affected / exposed	27 / 436 (6.19%)	1 / 425 (0.24%)	
occurrences (all)	27	1	
Fatigue			
subjects affected / exposed	172 / 436 (39.45%)	48 / 425 (11.29%)	
occurrences (all)	172	48	
PAIN: MUSCULOSKELETAL: JOINT			
subjects affected / exposed	54 / 436 (12.39%)	29 / 425 (6.82%)	
occurrences (all)	54	29	
PAIN: MUSCULOSKELETAL: MUSCLE			
subjects affected / exposed	39 / 436 (8.94%)	9 / 425 (2.12%)	
occurrences (all)	39	9	
PAIN: NEUROLOGY: HEAD/HEADACHE			
subjects affected / exposed	43 / 436 (9.86%)	7 / 425 (1.65%)	
occurrences (all)	43	7	
Blood and lymphatic system disorders			

Hemoglobin			
subjects affected / exposed	107 / 436 (24.54%)	27 / 425 (6.35%)	
occurrences (all)	107	27	
Hyperbilirubinemia			
subjects affected / exposed	52 / 436 (11.93%)	2 / 425 (0.47%)	
occurrences (all)	52	2	
Leucocytes (total WBC)			
subjects affected / exposed	136 / 436 (31.19%)	58 / 425 (13.65%)	
occurrences (all)	136	58	
Lymphopenia			
subjects affected / exposed	63 / 436 (14.45%)	33 / 425 (7.76%)	
occurrences (all)	63	33	
Neutrophils/ Granulocytes			
subjects affected / exposed	125 / 436 (28.67%)	46 / 425 (10.82%)	
occurrences (all)	125	46	
Thrombocytopenia			
subjects affected / exposed	22 / 436 (5.05%)	8 / 425 (1.88%)	
occurrences (all)	22	8	
Gastrointestinal disorders			
Diarrhea			
subjects affected / exposed	154 / 436 (35.32%)	6 / 425 (1.41%)	
occurrences (all)	154	6	
HEARTBURN/DYSPEPSIA			
subjects affected / exposed	53 / 436 (12.16%)	5 / 425 (1.18%)	
occurrences (all)	53	5	
Nausea			
subjects affected / exposed	103 / 436 (23.62%)	6 / 425 (1.41%)	
occurrences (all)	103	6	
Vomiting			
subjects affected / exposed	45 / 436 (10.32%)	2 / 425 (0.47%)	
occurrences (all)	45	2	
Reproductive system and breast disorders			
Irregular menses			
subjects affected / exposed	69 / 436 (15.83%)	67 / 425 (15.76%)	
occurrences (all)	69	67	
Skin and subcutaneous tissue disorders			

Hand and foot syndrome			
subjects affected / exposed	306 / 436 (70.18%)	3 / 425 (0.71%)	
occurrences (all)	306	3	
NAIL CHANGES			
subjects affected / exposed	42 / 436 (9.63%)	3 / 425 (0.71%)	
occurrences (all)	42	3	
Metabolism and nutrition disorders			
ALKALINE PHOSPHATASE			
subjects affected / exposed	63 / 436 (14.45%)	30 / 425 (7.06%)	
occurrences (all)	63	30	
ALT, SGPT			
subjects affected / exposed	85 / 436 (19.50%)	28 / 425 (6.59%)	
occurrences (all)	85	28	
AST, SGOT			
subjects affected / exposed	83 / 436 (19.04%)	23 / 425 (5.41%)	
occurrences (all)	83	23	
CHOLESTEROL, SERUM-HIGH			
subjects affected / exposed	34 / 436 (7.80%)	35 / 425 (8.24%)	
occurrences (all)	34	35	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 June 2007	This protocol amendment included the following changes: To allow the inclusion of patients treated with previous neoadjuvant chemotherapy. On that date, the clinical trials published did not show inferior results with neoadjuvant treatment compared to the adjuvant one. In addition, a meta-analysis showed that the comparison of both therapies did not have differences in terms of DFS and OS. In regards to it, to consider the absence of a biological reason justifying different efficacy results of the same regimen administered before or after the breast surgery was thought to be critical. All these considerations were taken into account to allow the inclusion of this subgroup of patients on the study. To allow the administration of 4 cycles of adriamycin and cyclophosphamide (AC) as chemotherapy for patients without axillary lymph node involvement. At that moment of time, in some countries of Latin America participating on the study, the treatment of this type of patients (considered to have an intermediate risk) included 6 cycles of CMF (cyclophosphamide, methotrexate, 5-fluorouracil) regimen or 4 cycles of AC regimen as per local clinical guidelines. With this consideration, patients without axillary lymph node involvement were allowed to be enrolled on the study. Grammatical mistakes were corrected, some administrative data were updated and there was an increase in the number of study sites with 2 new sites (Hospital General Yagüe in Burgos and Hospital Infanta Luisa in Seville, both in Spain).
16 September 2009	This protocol amendment was made to re-calculate the sample size of the study based on the results of the FinXX trial presented by Joensuu H. et al, at San Antonio Breast Cancer Symposium in 2008. The Finnish group showed the initial results from a clinical trial in adjuvant setting that evaluated the addition of capecitabine to the combination chemotherapy with epirubicin, cyclophosphamide and docetaxel. These results showed a statistically significant difference in terms of DFS and distant DFS in favor of the addition of capecitabine. The Hazard Ratio was of 0.66 showing an advantage of 34%. Patient population on this study included patients with positive or negative regional lymph node involvement, and tumor size > 2 cm. An estimated comparative analysis of the risk of recurrence indicated that patients on CIBOMA study had a higher risk of recurrence. Additionally, an exploratory subgroup analysis already presented at San Antonio Breast Cancer Symposium in 2008, showed that patients with HER2-negative tumors (not all of them triple negative), had a relevant benefit with the addition of capecitabine. We thought that at least a good proportion of patients on CIBOMA study could have better outcomes with the addition of adjuvant capecitabine. Our initial proposal estimated a benefit of 25% with the addition of capecitabine compared to observation; this required the inclusion of approximately 1,324 patients. When adjusting the potential benefit expected to 30% with a drop-out rate of 5%, the number of patients necessary to reach a possible positive result of the study was of 876. These data were obtained from the database of the “El Alamo” project (Project “The Alamo III”. ISBN: 84-938762-5-9. Legal deposit: M-36626-2013). One thousand six hundred and twenty-seven (1,627) in total were considered during the years from 1990 to 1997. The population was formed of patients with operable breast cancer, with surgery, positive nodes, and negative hormone receptors, or ne

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/31804894