



Clinical trial results:

Phase II of randomized study of the continuous versus standard capecitabine treatment in patients with metastatic breast cancer

Summary

EudraCT number	2004-002759-15
Trial protocol	ES
Global end of trial date	30 December 2014

Results information

Result version number	v1 (current)
This version publication date	13 May 2020
First version publication date	13 May 2020

Trial information

Trial identification

Sponsor protocol code	XEL-CONT-VS ESTANDAR
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00418028
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Dr. Miguel Martín. GEICAM (Spanish Breast Cancer Research Group Foundation).
Sponsor organisation address	Av. de los Pirineos, 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	03 December 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 December 2014
Global end of trial reached?	Yes
Global end of trial date	30 December 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess non-inferiority in terms of time to progression within one year of capecitabine treatment group in continuous administration versus capecitabine treatment group in standard administration.

Protection of trial subjects:

Each patient was monitored on a regular basis in order to detect potential adverse events. Before each cycle administration was evaluated white cell count, neutrophils/granulocytes, hemoglobin and platelet count, total bilirubin, GOT/GPT, alkaline phosphatase total protein, clearance of creatinine (calculated), serum creatinine and also physical examination and functional status (ECOG).

Background therapy:

The approved capecitabine regimen in monotherapy in metastatic breast cancer is 1,250 mg/m² twice daily, two weeks on one week off. Dose modifications are often required due to appearance of severe hand-foot syndrome. We tested a continuous regimen with lower daily dose but similar cumulative dose trying to reduce the severity of adverse events maintaining the efficacy

Evidence for comparator: -

Actual start date of recruitment	25 November 2004
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	Spain: 192
Worldwide total number of subjects	192
EEA total number of subjects	192

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)	118

From 65 to 84 years	73
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

Between November 2004 and August 2010, 195 patients were randomly assigned to Cint (97) and Ccont (98) in 13 GEICAM sites in Spain. Three patients never received treatment, leaving 192 for ITT analysis (95 Cint; 97 Ccont); 5 patients in each treatment arm had major protocol violations, leaving 182 PP evaluable patients.

Pre-assignment

Screening details:

To be eligible, patients had to be over age 18, have confirmed histological adenocarcinoma of the breast that was metastatic or inoperable locally advanced and negative for HER2/neu overexpression. Patients were excluded if they had prior severe reactions or hypersensitivity to fluoropyrimidines.

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, Cint

Arm description:

Capecitabine doses of 1250 mg/m² orally twice-daily (morning and evening which is the equivalent to one 2500mg/m² dose) during 14 days, in 3 week cycles with a resting period of 7 days.

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

Dosage and administration details:

Capecitabine 1250 mg/m² orally twice-daily (morning and evening which is the equivalent to one 2500mg/m² dose) during 14 days, in 3 week cycles with a resting period of 7 days.

Arm title	Arm B, Ccont
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Arm description:

Capecitabine at doses of 800 mg/m² twice daily continuously, without rest periods, over the entire 21-day cycle.

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

Dosage and administration details:

Capecitabine 1250 mg/m² orally twice-daily (morning and evening which is the equivalent to one 2500mg/m² dose) during 14 days, in 3 week cycles with a resting period of 7 days.

Number of subjects in period 1	Arm A, Cint	Arm B, Ccont
Started	95	97
Completed	90	92
Not completed	5	5
Protocol deviation	5	5

Baseline characteristics

Reporting groups

Reporting group title	Arm A, Cint
Reporting group description:	
Capecitabine doses of 1250 mg/m ² orally twice-daily (morning and evening which is the equivalent to one 2500mg/m ² dose) during 14 days, in 3 week cycles with a resting period of 7 days.	
Reporting group title	Arm B, Ccont
Reporting group description:	
Capecitabine at doses of 800 mg/m ² twice daily continuously, without rest periods, over the entire 21-day cycle.	

Reporting group values	Arm A, Cint	Arm B, Ccont	Total
Number of subjects	95	97	192
Age categorical			
Units: Subjects			
Adults (18-64 years)	54	64	118
From 65-84 years	40	33	73
85 years and over	1	0	1
Age continuous			
Units: years			
median	61	59	
full range (min-max)	34 to 87	29 to 81	-
Gender categorical			
Units: Subjects			
Female	95	97	192
Male	0	0	0
Menopausal status			
Units: Subjects			
Premenopausal	32	37	69
Postmenopausal	62	60	122
No data	1	0	1
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	41	44	85
ECOG 1	21	27	48
ECOG 2	3	0	3
Missing	30	26	56
Hormone receptor status			
Units: Subjects			
Positive	75	76	151
Negative	18	16	34
Unknown	2	5	7

Type of metastases			
Units: Subjects			
Visceral	72	78	150
Non-visceral	23	19	42
Metastatic sites			
Units: Subjects			
1 site	41	50	91
2 sites	27	25	52
≥3 sites	26	22	48
Missing	1	0	1

End points

End points reporting groups

Reporting group title	Arm A, Cint
Reporting group description:	
Capecitabine doses of 1250 mg/m ² orally twice-daily (morning and evening which is the equivalent to one 2500mg/m ² dose) during 14 days, in 3 week cycles with a resting period of 7 days.	
Reporting group title	Arm B, Ccont
Reporting group description:	
Capecitabine at doses of 800 mg/m ² twice daily continuously, without rest periods, over the entire 21-day cycle.	

Primary: Time to Progression (TTP) after 1 year

End point title	Time to Progression (TTP) after 1 year
End point description:	
Time to Progression (TTP) is defined as the time (in months) from the moment the patient starts the study treatment to the date of progressive disease. That is, a patient has an event is she progresses or dies due to progressive disease. For this analysis we are including all patients belonging to the PP Population (182 patients: 90 under treatment A and 92 under treatment B).	
End point type	Primary
End point timeframe:	
After 1 year from the treatment start day.	

End point values	Arm A, Cint	Arm B, Ccont		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	73	82		
Units: Events	53	62		

Statistical analyses

Statistical analysis title	Non-Inferiority
Comparison groups	Arm A, Cint v Arm B, Ccont
Number of subjects included in analysis	155
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Risk difference (RD)
Point estimate	-3.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-16.83
upper limit	10.82
Variability estimate	Standard deviation

Secondary: Time to Progression (TTP)

End point title	Time to Progression (TTP)
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End point description:

Time to Progression (TTP) is defined as the time (in months) from the moment the patient starts the study treatment to the date of an Event. Event was defined as Progressive Disease (PD) or Death due to PD, whichever happens first. Progression is defined using Response Evaluation Criteria In Solid Tumors Criteria (RECIST v1.0).

If a patient did not progress or dies due to PD during the treatment but she receives an antitumoral treatment, after the end of the study treatment, it is censored.

If the patient does neither progress nor dies due to PD, and she does not receive an antitumoral treatment, after the end of the study treatment, it is censored.

End point type	Secondary
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End point timeframe:

Through the study treatment, an average of 5 months.

End point values	Arm A, Cint	Arm B, Ccont		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	90	92		
Units: Months				
median (confidence interval 95%)	8.68 (6.55 to 11.18)	6.84 (6.02 to 8.06)		

Statistical analyses

Statistical analysis title	Non-Inferiority
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Statistical analysis description:

If we assume that the non-inferiority level is up to 15% lower (equivalent to a median progression-free time of 3 months), for a one-sided error $\alpha=0.05$, and 80% power, are necessary 88 patients per group. Considering an dropout rate of around 10%, the number of patients would be 98 per group.

Comparison groups	Arm A, Cint v Arm B, Ccont
Number of subjects included in analysis	182
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.0996
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.313
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.948
upper limit	1.817

Secondary: Overall Response Rate

End point title	Overall Response Rate
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End point description:

Overall Response Rate (complete response plus partial responses) was evaluated using the Response Evaluation Criteria In Solid Tumors Criteria (RECIST v1.0), every 3 cycles of chemotherapy (each cycle last 3 weeks) and at the end of treatment (at 21 weeks from the start of treatment).

End point type	Secondary
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End point timeframe:

Through the study treatment, an average of 5 months.

End point values	Arm A, Cint	Arm B, Ccont		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	90	92		
Units: Participants	76	68		

Statistical analyses

No statistical analyses for this end point

Secondary: Response Duration (RD)

End point title	Response Duration (RD)
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End point description:

Response duration is computed for all patients with Partial Response or Complete Response, during the treatment period, as the time from the moment the Partial or Complete Response is reported to the date the patient Progresses or Dies, whichever happens first.

A patient is censored if she does not progress or die. In these cases Response duration is computed as the time from the moment the Partial or Complete Response is reported to the last contact date.

End point type	Secondary
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End point timeframe:

Time from the moment the Partial or Complete Response is reported to the date the patient Progresses or Dies, whichever happens first, assessed up to 72 weeks.

End point values	Arm A, Cint	Arm B, Ccont		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30	29		
Units: Months				
median (confidence interval 95%)	10.07 (7.96 to 16.71)	7.01 (4.11 to 12.43)		

Statistical analyses

Statistical analysis title	Superiority
Comparison groups	Arm A, Cint v Arm B, Ccont
Number of subjects included in analysis	59
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4934
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.22
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.68
upper limit	2.1

Secondary: Time to treatment failure (TTF)

End point title	Time to treatment failure (TTF)
End point description:	
Time to treatment failure (TTF) is defined as the time (in months) from the moment the patient starts the study treatment to the end of treatment date (due to death, progressive disease, adverse events, patient's decision or investigator criteria. If a patient did not end the treatment, it is censored. The censoring date is the date of the last dose received.	
End point type	Secondary
End point timeframe:	
Time (in months) from the moment the patient starts the study treatment to the end of treatment date (due to death, progressive disease, adverse events, patient's decision or investigator criteria, assessed up to 72 months.	

End point values	Arm A, Cint	Arm B, Ccont		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	90	92		
Units: Months				
median (confidence interval 95%)	5.41 (4.34 to 8.03)	5.87 (3.55 to 7.14)		

Statistical analyses

Statistical analysis title	Superiority
Comparison groups	Arm A, Cint v Arm B, Ccont

Number of subjects included in analysis	182
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4686
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.115
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.83
upper limit	1.49

Secondary: Progression Free Survival (PFS)

End point title	Progression Free Survival (PFS)
End point description:	
<p>Progresion Free Survival (PFS) is defined as the time (in months) from the moment the patient starts the study treatment to the date of progressive disease. That is, a patient has an event is she progresses or dies for any reason.</p> <p>If a patient did not progresses or dies during the treatment but she receives an antitumoral treatment, after the end of the study treatment, it is censored. The censoring date is the first follow up date when she receives the antitumoral treatment. In this case, the time from the moment the patient starts the study treatment to the start date of the antitumoral treatment is computed as the time to progression.</p> <p>If the patient does neither progresses nor dies, and she does not receive an antitumoral treatment, after the end of the study treatment, it is censored. In this case, the time from the moment the patient starts the study treatment to the last date of contact is computed as the time to progression.</p>	
End point type	Secondary
End point timeframe:	
Time from the moment the patient starts the study treatment to the date of progressive disease assessed up to 84 months.	

End point values	Arm A, Cint	Arm B, Ccont		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	90	92		
Units: Months				
median (confidence interval 95%)	8.55 (5.92 to 10.26)	6.84 (6.02 to 8.06)		

Statistical analyses

Statistical analysis title	Superiority
Comparison groups	Arm A, Cint v Arm B, Ccont

Number of subjects included in analysis	182
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1901
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.2379
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.8985
upper limit	1.7054

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)
End point description:	
An event is defined as death. A patient is censored if she does not die. The censoring date is last contact date.	
End point type	Secondary
End point timeframe:	
Time to survival is the number of months from the study treatment start date to the date of death, assessed up to 100 months.	

End point values	Arm A, Cint	Arm B, Ccont		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	90	92		
Units: Months				
median (confidence interval 95%)	28.55 (23.85 to 34.21)	23.29 (18.16 to 32.27)		

Statistical analyses

Statistical analysis title	Superiority
Comparison groups	Arm A, Cint v Arm B, Ccont
Number of subjects included in analysis	182
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8014
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.9589

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.6908
upper limit	1.3309

Secondary: Clinical Benefit Rate (CBR)

End point title	Clinical Benefit Rate (CBR)
End point description:	
A patient experiences a Clinical Benefit if the following is satisfied: The patient has Complete response (CR), Partial Response (PR) or Stable Disease (SD) and it continues during more than 3 months. The time has been calculated as the months from "CR" "PR" or "SD" (the first one) until the first of the following dates: progression date, new treatment during follow-up date or last contact date.	
End point type	Secondary
End point timeframe:	
Months from CR, PR or SD (the first one) until Progression date, new treatment or last contact date.	

End point values	Arm A, Cint	Arm B, Ccont		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	82	88		
Units: Events	54	54		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival (PFS) rate per year

End point title	Progression Free Survival (PFS) rate per year
End point description:	
Progression Free Survival rate per year is defined as percentage of survival each year.	
End point type	Secondary
End point timeframe:	
One year	

End point values	Arm A, Cint	Arm B, Ccont		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	90	92		
Units: percentage				
12 months	31	26		
24 months	12	8		

36 months	9	7		
48 months	5	3		
60 months	5	3		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

During the study treatment (Metastatic Breast Cancer patients), up to 30 weeks approximately.

Assessment type	Systematic
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Dictionary used

Dictionary name	NCI-CTCAE
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Dictionary version	3
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Reporting groups

Reporting group title	Arm A, Cint
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Reporting group description:

Capecitabine doses of 1250 mg/m² orally twice-daily (morning and evening which is the equivalent to one 2500mg/m² dose) during 14 days, in 3 week cycles with a resting period of 7 days.

Reporting group title	Arm B, Ccont
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Reporting group description:

Capecitabine at doses of 800 mg/m² twice daily continuously, without rest periods, over the entire 21-day cycle.

Serious adverse events	Arm A, Cint	Arm B, Ccont	
Total subjects affected by serious adverse events			
subjects affected / exposed	28 / 95 (29.47%)	21 / 97 (21.65%)	
number of deaths (all causes)	81	72	
number of deaths resulting from adverse events	1	1	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant neoplasm progression			
subjects affected / exposed	1 / 95 (1.05%)	0 / 97 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Vascular disorders			
Thrombosis/thrombus/embolism			
subjects affected / exposed	0 / 95 (0.00%)	2 / 97 (2.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Disease progression			
subjects affected / exposed	1 / 95 (1.05%)	2 / 97 (2.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 2	

Pain			
subjects affected / exposed	1 / 95 (1.05%)	1 / 97 (1.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	3 / 95 (3.16%)	4 / 97 (4.12%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 2	0 / 1	
Pleural effusion (non-malignant)			
subjects affected / exposed	1 / 95 (1.05%)	1 / 97 (1.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Calcium, serum-high (hypercalcemia)			
subjects affected / exposed	0 / 95 (0.00%)	1 / 97 (1.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac General			
subjects affected / exposed	1 / 95 (1.05%)	1 / 97 (1.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Ventricular arrhythmia			
subjects affected / exposed	0 / 95 (0.00%)	1 / 97 (1.03%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vasovagal episode			
subjects affected / exposed	1 / 95 (1.05%)	0 / 97 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial effusion (non-malignant)			

subjects affected / exposed	0 / 95 (0.00%)	1 / 97 (1.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Neurology			
subjects affected / exposed	2 / 95 (2.11%)	0 / 97 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	1 / 95 (1.05%)	1 / 97 (1.03%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalopathy			
subjects affected / exposed	0 / 95 (0.00%)	1 / 97 (1.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Blood and lymphatic system disorders			
Neutrophils/granulocytes (ANC/AGC)			
subjects affected / exposed	1 / 95 (1.05%)	1 / 97 (1.03%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Phlebotymphatic cording			
subjects affected / exposed	1 / 95 (1.05%)	0 / 97 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	6 / 95 (6.32%)	0 / 97 (0.00%)	
occurrences causally related to treatment / all	6 / 6	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obstruction			
subjects affected / exposed	1 / 95 (1.05%)	0 / 97 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	

Mucositis/stomatitis			
subjects affected / exposed	1 / 95 (1.05%)	0 / 97 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	1 / 95 (1.05%)	0 / 97 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal			
subjects affected / exposed	1 / 95 (1.05%)	0 / 97 (0.00%)	
occurrences causally related to treatment / all	0 / 1	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	0 / 95 (0.00%)	1 / 97 (1.03%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	0 / 95 (0.00%)	1 / 97 (1.03%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Fracture			
subjects affected / exposed	2 / 95 (2.11%)	0 / 97 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Febrile neutropenia			
subjects affected / exposed	2 / 95 (2.11%)	2 / 97 (2.06%)	
occurrences causally related to treatment / all	2 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection with unknown ANC			

subjects affected / exposed	3 / 95 (3.16%)	4 / 97 (4.12%)	
occurrences causally related to treatment / all	0 / 4	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Arm A, Cint	Arm B, Ccont	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	94 / 95 (98.95%)	95 / 97 (97.94%)	
Investigations			
Neutrophils/granulocytes (ANC/AGC) Grade 3-4			
subjects affected / exposed	9 / 95 (9.47%)	2 / 97 (2.06%)	
occurrences (all)	9	2	
Nervous system disorders			
Neuropathy: sensory Grade 1-2			
subjects affected / exposed	6 / 95 (6.32%)	7 / 97 (7.22%)	
occurrences (all)	6	7	
Dizziness Grade 1-2			
subjects affected / exposed	5 / 95 (5.26%)	2 / 97 (2.06%)	
occurrences (all)	5	2	
Blood and lymphatic system disorders			
Hemoglobin Grade 1-2			
subjects affected / exposed	33 / 95 (34.74%)	20 / 97 (20.62%)	
occurrences (all)	33	20	
Neutrophils/granulocytes (ANC/AGC) Grade 1-2			
subjects affected / exposed	18 / 95 (18.95%)	9 / 97 (9.28%)	
occurrences (all)	18	9	
Platelets Grade 1-2			
subjects affected / exposed	9 / 95 (9.47%)	4 / 97 (4.12%)	
occurrences (all)	9	4	
Leukocytes (total WBC) Grade 1-2			
subjects affected / exposed	6 / 95 (6.32%)	5 / 97 (5.15%)	
occurrences (all)	6	5	
General disorders and administration site conditions			

Fatigue (asthenia, lethargy, malaise) Grade 1-2			
subjects affected / exposed	43 / 95 (45.26%)	36 / 97 (37.11%)	
occurrences (all)	43	36	
Fatigue (asthenia, lethargy, malaise) Grade 3-4			
subjects affected / exposed	14 / 95 (14.74%)	6 / 97 (6.19%)	
occurrences (all)	14	6	
Weight loss Grade 1-2			
subjects affected / exposed	6 / 95 (6.32%)	4 / 97 (4.12%)	
occurrences (all)	6	4	
Pain Grade 1-2			
subjects affected / exposed	25 / 95 (26.32%)	13 / 97 (13.40%)	
occurrences (all)	25	13	
Gastrointestinal disorders			
Diarrhea Grade 1-2			
subjects affected / exposed	28 / 95 (29.47%)	24 / 97 (24.74%)	
occurrences (all)	28	24	
Diarrhea Grade 3-4			
subjects affected / exposed	19 / 95 (20.00%)	6 / 97 (6.19%)	
occurrences (all)	19	6	
Mucositis/stomatitis (functional/symptomatic) Grade 1-2			
subjects affected / exposed	25 / 95 (26.32%)	26 / 97 (26.80%)	
occurrences (all)	25	26	
Mucositis/stomatitis (functional/symptomatic) Grade 3-4			
subjects affected / exposed	11 / 95 (11.58%)	2 / 97 (2.06%)	
occurrences (all)	11	2	
Nausea Grade 1-2			
subjects affected / exposed	25 / 95 (26.32%)	17 / 97 (17.53%)	
occurrences (all)	25	17	
Vomiting Grade 1-2			
subjects affected / exposed	19 / 95 (20.00%)	14 / 97 (14.43%)	
occurrences (all)	19	14	
Anorexia Grade 1-2			
subjects affected / exposed	20 / 95 (21.05%)	2 / 97 (2.06%)	
occurrences (all)	20	2	

Constipation Grade 1-2 subjects affected / exposed occurrences (all)	9 / 95 (9.47%) 9	8 / 97 (8.25%) 8	
Dysphagia (difficulty swallowing) Grade 1-2 subjects affected / exposed occurrences (all)	6 / 95 (6.32%) 6	4 / 97 (4.12%) 4	
Heartburn/dyspepsia Grade 1-2 subjects affected / exposed occurrences (all)	6 / 95 (6.32%) 6	2 / 97 (2.06%) 2	
Distension/bloating Grade 1-2 subjects affected / exposed occurrences (all)	5 / 95 (5.26%) 5	1 / 97 (1.03%) 1	
Respiratory, thoracic and mediastinal disorders Dyspnea (shortness of breath) Grade 1-2 subjects affected / exposed occurrences (all)	3 / 95 (3.16%) 3	5 / 97 (5.15%) 5	
Skin and subcutaneous tissue disorders Rash: hand-foot skin reaction Grade 1-2 subjects affected / exposed occurrences (all)	35 / 95 (36.84%) 35	38 / 97 (39.18%) 38	
Rash: hand-foot skin reaction Grade 3-4 subjects affected / exposed occurrences (all)	39 / 95 (41.05%) 39	41 / 97 (42.27%) 41	
Nail changes Grade 1-2 subjects affected / exposed occurrences (all)	10 / 95 (10.53%) 10	11 / 97 (11.34%) 11	
Hair loss/alopecia (scalp or body) Grade 1-2 subjects affected / exposed occurrences (all)	3 / 95 (3.16%) 3	8 / 97 (8.25%) 8	
Infections and infestations Infection with unknown ANC Grade 1-2 subjects affected / exposed occurrences (all)	11 / 95 (11.58%) 11	10 / 97 (10.31%) 10	
Metabolism and nutrition disorders			

ALT, SGPT (serum glutamic pyruvic transaminase) Grade 1-2			
subjects affected / exposed	19 / 95 (20.00%)	16 / 97 (16.49%)	
occurrences (all)	19	16	
AST, SGOT (serum glutamic oxaloacetic transaminase) Grade 1-2			
subjects affected / exposed	22 / 95 (23.16%)	14 / 97 (14.43%)	
occurrences (all)	22	14	
Bilirubin (hyperbilirubinemia) Grade 1-2			
subjects affected / exposed	12 / 95 (12.63%)	14 / 97 (14.43%)	
occurrences (all)	12	14	
GGT (gamma-Glutamyl transpeptidase) Grade 1-2			
subjects affected / exposed	9 / 95 (9.47%)	8 / 97 (8.25%)	
occurrences (all)	9	8	
Alkaline phosphatase Grade 1-2			
subjects affected / exposed	6 / 95 (6.32%)	5 / 97 (5.15%)	
occurrences (all)	6	5	
Glucose, serum-high (hyperglycemia) Grade 1-2			
subjects affected / exposed	5 / 95 (5.26%)	1 / 97 (1.03%)	
occurrences (all)	5	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 October 2007	<ul style="list-style-type: none">- Reorder the primary and secondary objectives of the study.- Modify the sample size calculation according to the new main valuation variable.- Extend the recruitment period to include sufficient number of patients according to the new sample size.- Modify the evaluation methods according to these objectives.- Rework the statistical analysis section
26 May 2008	<ul style="list-style-type: none">- To clarify some of the inclusion and exclusion criteria. The suggested changes do not substantially change the population under test.- Expand the use of bisphosphonates and corticosteroids in patients with bone metastases.- Update the toxicity coding system from the NCI v 2.0 system to NCI 3.0.- To add a new secondary objective: to evaluate the relationship between enzyme polymorphisms related to the metabolism of Capecitabine, and its toxicity and efficacy.- Addition of two new sites- Clarify some aspects of the protocol that may give rise to erroneous interpretations; such as, for example, the section referring to the Xeloda dose reduction guidelines in the event of the adverse effect of Palmar-plantar erythrodysesthesia syndrome.
26 February 2010	Increase sample size: The primary objective was based on obtaining 88 evaluable patients per group, total 176, not including any prediction of losses. Based on the fact that the usual percentage of losses in metastatic studies is approximately 10%, it is intended to increase the number of expected subjects to 196 recruited patients to finally obtain the 176 evaluable patients.
23 September 2011	<ul style="list-style-type: none">- Incorporation of a Secondary Objective: The magnitude of the progression-free survival rate at one year is a reasonably important objective, given its behavior as a predictor of overall survival in patients with breast cancer.- Modification in the definitions of Population and Efficacy: The variables of time to an event or survival times are widely used variables in the field of cancer treatment, however, some scientific publications show discrepancies in the definitions of these variables in different clinical trials which can lead to difficulties in interpreting their results and comparability between trials. The objective of this amendment is to standardize the terminology according to the definitions contemplated by the regulatory agencies.

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/25601966>