Clinical trial results:
A phase II trial of BKM120 (a PI3K inhibitor) in patients with triple negative metastatic breast cancer

Summary

EudraCT number	2011-006083-45
Trial protocol	ES
Global end of trial date	30 September 2015

Results information

Result version number	v1 (current)
This version publication date	27 April 2022
First version publication date	27 April 2022

Trial information

Trial identification

Sponsor protocol code	CBKM120ZES02T/SOLTI-1103

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01629615
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	SOLTI
Sponsor organisation address	C/ Balmes 89 3-7, Barcelona, Spain, 08008
Public contact	Investigación Clínica, SOLTI, +34 933436302, regsolti@gruposolti.org
Scientific contact	Investigación Clínica, SOLTI, +34 933436302, regsolti@gruposolti.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	30 September 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 September 2015
Global end of trial reached?	Yes
Global end of trial date	30 September 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine clinical activity of BKM120 in patients with metastatic triple negative breast cancer that have developed disease progression after standard chemotherapy in the adjuvant or metastatic setting.

Protection of trial subjects:

All patients were screened for inclusion and exclusion criteria within 2 weeks prior to the first dose of BKM120. Screening includes obtaining written informed consent, a physical exam, demography, medical history/current medical conditions, current concomitant medications/therapies, disease history and extent of disease, and prior anticancer therapies. Additionally, the following assessments were performed: Physical examination, weight and height; Vital signs including sitting blood pressure/pulse and heart rate, respiratory rate and temperature; ECOG performance status; ECG; Safety laboratory assessments: chemistry, hematology and urinalysis; Pregnancy test; Neuro-psychiatric assessment (self-rating mood questionnaire); - Baseline TAC or MRI;Baseline tumour tissue collection for biomarker assessments.
Patients continued on treatment with BKM120 until the patient experiences unacceptable toxicity that recludes any further treatment, disease progression, and/or treatment was discontinued at the discretion of the investigator or by patient refusal. A treatment cycle was arbitrarily defined as 28 days for the purposes of scheduling procedures and evaluations.
On Day 1 and 15 of each cycle, the following assessments were performed: Complete physical examination; ECOG performance status; Vital signs; Body weight; Collection of any AEs and SAEs, with assignment of the appropriate AE grade according to NCI CTCAE v.4.0; Documentation of concomitant medications; Laboratory tests (haematology tests (with differential, reticulocytes, and platelets count), coagulation panel (including INR and APTT), and comprehensive chemistry panel (sodium, potassium, chloride, creatinine, calcium, BUN,
albumin, AST, ALT, AP, LDH, and total bilirubin);fasting plasma glucose); ECG.
Additionally, Neuro-psychiatric assessment (self-rating mood questionnaire) was done
on day 15 and every 2 weeks.
Response assessment at the end of C2 and every 2 cycles.

Background therapy: -
Evidence for comparator: -

Actual start date of recruitment	26 June 2012
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: 23
Country: Number of subjects enrolled	United States: 27
Worldwide total number of subjects	50
EEA total number of subjects	23

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)	50
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study was conducted at 5 study centers: 1 in US and 4 in Spain

Pre-assignment

Screening details:

Histologically confirmed metastatic triple negative breast cancer (Stage IV disease). Available tumor block which is ER-negative, PR-negative and HER2 negative. Subjects must have received at least two prior chemotherapy regimens in metastatic setting and have not received previous treatment with PI3K inhibitors.

Period 1

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

Arms

Arm title	Cohort 1 (unselected)

Arm description:

Stage 1 included up to 50 patients with TN disease. A total of 32 patients were screened at Spanish sites. A total number of 50 patients were enrolled for the first stage of the study, in Spain and USA.

Arm type	Single-arm
Investigational medicinal product name	BKM 120
Investigational medicinal product code	AN2025 BKM120 PI3K_Inhibitor_BKM120
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

The investigational study drug used in this trial was BKM120, supplied as 10-mg and 50-mg hard gelatine capsules. The dose of 100 mg/day was identified as the maximum tolerated dose (MTD) in the
phase I study [BKM120X2101]. BKM120 was administered on a continuous once daily dosing schedule at a dose of 100 mg (p.o). The patient was dosed on a flat scale of 100mg/day and the dose of the drug wasn’t adjusted to body weight or body surface area.

Number of subjects in period 1	Cohort 1 (unselected)
Started	50
Interim analysis	29 [1]
Completed	41
Not completed	9
Consent withdrawn by subject	1
Physician decision	1
Adverse event, non-fatal	7

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: After the enrollment of the first 29 evaluable subjects in Stage 1, an interim analysis of safety and efficacy was performed by a Steering Committee. The study pre-specified threshold to continue enrollment was at least one patient with clinical benefit in the first 29 patients. Therefore, we have met the pre-specified protocol to proceed to the next stage of accrual.

Baseline characteristics

Reporting groups

Reporting group title	Stage I

Reporting group description: -

Reporting group values	Stage I	Total	
Number of subjects	50	50	
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	53		
full range (min-max)	29 to 79	-	
Gender categorical Units: Subjects			
Female	50	50	
Male	0	0	
Race Units: Subjects			
White	46	46	
Black	1	1	
Asian	1	1	
Other	2	2	
Ethnicity Units: Subjects			
Hispanic or Latino	12	12	
Non-Hispanic	37	37	
Unknown	1	1	
ECOG PS at Baseline Units: Subjects			
Zero	32	32	
One	18	18	
Two	0	0	
Stage at Initial Diagnosis Units: Subjects			
One	4	4	
Two	20	20	

Three	20	20	
Four	5	5	
Unknown	1	1	
Receptor Status - Primary tumor Units: Subjects			
ER and/or PR positive, HER2-negative	7	7	
ER and/or PR positive, HER2-positive	1	1	
ER and PR negative, HER2-negative	38	38	
ER and PR negative, HER2-positive	1	1	
Not done/unknown	3	3	
Receptor Status - Metastatic/recurrent tumor Units: Subjects			
ER and/or PR positive, HER2-negative	0	0	
ER and/or PR positive, HER2-positive	1	1	
ER and PR negative, HER2-negative	40	40	
ER and PR negative, HER2-positive	1	1	
Not done/unknown	8	8	
Lines of chemotherapy for Metastasis or Recurrence Units: Subjects			
None	7	7	
1 line	18	18	
2 lines	9	9	
3 or more lines	16	16	
Adjuvant or neoadjuvant hormonal therapy Units: Subjects			
Yes	7	7	
No	43	43	
Adjuvant or neoadjuvant chemotherapy Units: Subjects			
Yes	44	44	
No	6	6	
Adjuvant or neoadjuvant anthracycline Units: Subjects			
Yes	36	36	
No	14	14	
Adjuvant or neoadjuvant taxane Units: Subjects			
Yes	42	42	
No	8	8	
Prior metastatic chemotherapy - Anthracycline Units: Subjects			
YES	4	4	
NO	46	46	
Prior metastatic chemotherapy - Taxane Units: Subjects			
YES	14	14	

NO	36	36	
Prior metastatic chemotherapy - Platinum Units: Subjects			
YES	18	18	
NO	32	32	
Prior metastatic chemotherapy - Capecitabine Units: Subjects			
YES	23	23	
NO	27	27	
Prior metastatic chemotherapy - Eribulin Units: Subjects			
YES	8	8	
NO	42	42	
Prior metastatic chemotherapy - Other Units: Subjects			
YES	26	26	
NO	24	24	
Sites of disease at trial initiation - CNS Units: Subjects			
YES	2	2	
NO	48	48	
Sites of disease at trial initiation - Lung or pleural effusion Units: Subjects			
YES	13	13	
NO	37	37	
Sites of disease at trial initiation - Liver Units: Subjects			
YES	5	5	
NO	45	45	
Sites of disease at trial initiation - Bone Units: Subjects			
YES	8	8	
NO	42	42	
Sites of disease at trial initiation - Breast or chest wall Units: Subjects			
YES	15	15	
NO	35	35	
Sites of disease at trial initiation - Lymph nodes Units: Subjects			
YES	20	20	
NO	30	30	
Sites of disease at trial initiation - Soft tissue Units: Subjects			
YES	2	2	
NO	48	48	
Sites of disease at trial initiation - Other Units: Subjects			

YES	4	4	
NO	46	46	

Lines of chemotherapy for Metastasis or Recurrence			
Units: Number of lines			
median	1.5		
full range (min-max)	0 to 7	-	

End points

End points reporting groups

Reporting group title	Cohort 1 (unselected)

Reporting group description:

Stage 1 included up to 50 patients with TN disease. A total of 32 patients were screened at Spanish sites. A total number of 50 patients were enrolled for the first stage of the study, in Spain and USA.

Subject analysis set title	Efficacy endpoint
Subject analysis set type	Per protocol

Subject analysis set description:

All recruited population that receives the study treatment. This population was the primary population for all efficacy parameters. Fifty women were enrolled between June 2012 and September 2014 across 4 sites in
Spain and 1 site in USA, with a median follow-up of 13.8 months.
Evaluable patients for tumor response were all treated patients with at least one baseline tumor assessment and one post-baseline assessment, and also all treated patients with early disease progression (PD) before first planned tumor assessment.

Subject analysis set title	Safety population
Subject analysis set type	Safety analysis

Subject analysis set description:

A subset of randomized patients who received at least one cycle of treatment. This population was used for the safety analysis.

Primary: Rate of clinical benefit

End point title	Rate of clinical benefit[1]

End point description:

The primary efficacy endpoint was rate of clinical benefit (CR+PR+SD≥4 months) per RECISTS 1.1. At interim analysis, 4 (13%) patients had stable disease. 37 patients were evaluable for best response; 12 patients were taken off treatment before the first restaging evaluation due to clinical progression, and one patient was taken off treatment due to toxicity.
No patient had confirmed CR or PR. Six patients (12%) experienced stable disease > 4 months, and met the study pre-defined primary endpoint of clinical benefit. The rate of clinical benefit was 12% (95% CI 5.6-23.8%).

End point type	Primary

End point timeframe:

The baseline evaluation performed within 28 days prior to enrollment. During treatment, every 2 cycles and in 7 days from the planned date. At the end of the study it is recommended f it has not been done in the previous 21 days.

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: In addition to the following primary efficacy analysis on the response rates, we will also conduct additional analysis on TTP using Kaplan-Meier estimates both overall and for each biomarker subtype. Cox proportional hazards models will be fit for the TTP with biomarker subtype as an independent variable adjusting for potential baseline predictive biomarkers.
Binary response endpoint will be analyzed using logistic regression with subgroup indicator (clinical/radiological/molecular status)

End point values	Cohort 1 (unselected)			
Subject group type	Reporting group			
Number of subjects analysed	50			
Units: Best Response by RECIST 1.1				
Confirmed CR	0			
Confirmed PR	0			
SD >/= 4 months	6			

SD < 4 months	11			
Progressive disease	20			
Non-evaluable	13			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression free survival (PFS)

End point title	Progression free survival (PFS)

End point description:

End point type	Secondary

End point timeframe:

from date of study enrollment until disease progression or death from any cause, whichever came first. If no PFS events were observed, patients' PFS times were censored at the date of their last assessments

End point values	Cohort 1 (unselected)			
Subject group type	Reporting group			
Number of subjects analysed	37			
Units: Months				
median (confidence interval 95%)	1.8 (1.6 to 2.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival (OS)

End point title	Overall survival (OS)

End point description:

End point type	Secondary

End point timeframe:

OS was defined as time from date of study enrollment until death from any cause. For patients alive, their OS times were censored at the date of last known alive.

End point values	Cohort 1 (unselected)			
Subject group type	Reporting group			
Number of subjects analysed	37			
Units: Months				
median (confidence interval 95%)	11.2 (6.2 to 25)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events (AEs) were assessed according to the National Cancer Institute CTCAE version 4.0. Safety assessments, including fasting plasma glucose, were conducted every 2 weeks for the first 2 cycles

Adverse event reporting additional description:

Two different mood questionnaires (PHQ-9 and GAD-7) must be completed at each assessment visit to the clinic, as well as at the end-of-treatment visit.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.1

Reporting groups

Reporting group title	Cohort 1

Reporting group description: -

Serious adverse events	Cohort 1		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 50 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

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

Non-serious adverse events	Cohort 1		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	50 / 50 (100.00%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour pain			
subjects affected / exposed	3 / 50 (6.00%)		
occurrences (all)	3		
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Lymphoedema			

subjects affected / exposed	2 / 50 (4.00%)		
occurrences (all)	2		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	29 / 50 (58.00%)		
occurrences (all)	29		
Pyrexia			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
General disorders and administration site conditions - Other, specify			
subjects affected / exposed	3 / 50 (6.00%)		
occurrences (all)	3		
Localised oedema			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Non-cardiac chest pain			
subjects affected / exposed	3 / 50 (6.00%)		
occurrences (all)	3		
Pain			
subjects affected / exposed	6 / 50 (12.00%)		
occurrences (all)	6		
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Immune system disorders - Other, specify			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Reproductive system and breast disorders			
Breast pain			
subjects affected / exposed	3 / 50 (6.00%)		
occurrences (all)	3		
Respiratory, thoracic and mediastinal disorders			

Cough			
subjects affected / exposed	6 / 50 (12.00%)		
occurrences (all)	6		
Dyspnoea			
subjects affected / exposed	5 / 50 (10.00%)		
occurrences (all)	5		
Pulmonary hypertension			
subjects affected / exposed	2 / 50 (4.00%)		
occurrences (all)	2		
Dysphonia			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders - Other, specify			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	9 / 50 (18.00%)		
occurrences (all)	9		
Depression			
subjects affected / exposed	9 / 50 (18.00%)		
occurrences (all)	9		
Libido increased			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Insomnia			
subjects affected / exposed	6 / 50 (12.00%)		
occurrences (all)	6		
Psychiatric disorders - Other, specify			
subjects affected / exposed	7 / 50 (14.00%)		
occurrences (all)	7		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	10 / 50 (20.00%)		
occurrences (all)	10		
Blood alkaline phosphatase increased			

subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Aspartate aminotransferase increased			
subjects affected / exposed	8 / 50 (16.00%)		
occurrences (all)	8		
Investigations - Other, specify			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Weight decreased			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Fracture			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Nervous system disorders			
Dizziness			
subjects affected / exposed	2 / 50 (4.00%)		
occurrences (all)	2		
Dysgeusia			
subjects affected / exposed	2 / 50 (4.00%)		
occurrences (all)	2		
Headache			
subjects affected / exposed	3 / 50 (6.00%)		
occurrences (all)	3		
Nervous system disorders - Other, specify			
subjects affected / exposed	2 / 50 (4.00%)		
occurrences (all)	2		
Peripheral motor neuropathy			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Peripheral sensory neuropathy			
subjects affected / exposed	3 / 50 (6.00%)		
occurrences (all)	3		
Somnolence			

subjects affected / exposed	2 / 50 (4.00%)		
occurrences (all)	2		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Febrile neutropenia			
subjects affected / exposed	2 / 50 (4.00%)		
occurrences (all)	2		
Lymph node pain			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Blood and lymphatic system disorders - Other, specify			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Ear and labyrinth disorders			
Ear and labyrinth disorders - Other, specify			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Eye disorders			
Eye disorders - Other, specify			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Lacrimation increased			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Gastrointestinal disorders			
Gastrointestinal disorders - Other, specify			
subjects affected / exposed	6 / 50 (12.00%)		
occurrences (all)	6		
Stomatitis			
subjects affected / exposed	5 / 50 (10.00%)		
occurrences (all)	5		
Nausea			

subjects affected / exposed	17 / 50 (34.00%)		
occurrences (all)	17		
Rectal haemorrhage			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Vomiting			
subjects affected / exposed	2 / 50 (4.00%)		
occurrences (all)	2		
Abdominal distension			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Constipation			
subjects affected / exposed	6 / 50 (12.00%)		
occurrences (all)	6		
Diarrhoea			
subjects affected / exposed	9 / 50 (18.00%)		
occurrences (all)	9		
Dyspepsia			
subjects affected / exposed	2 / 50 (4.00%)		
occurrences (all)	2		
Hepatobiliary disorders			
Hepatic failure			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Dry skin			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Erythema multiforme			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Photosensitivity reaction			

subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Pruritus			
subjects affected / exposed	3 / 50 (6.00%)		
occurrences (all)	3		
Dermatitis acneiform			
subjects affected / exposed	6 / 50 (12.00%)		
occurrences (all)	6		
Rash maculo-papular			
subjects affected / exposed	4 / 50 (8.00%)		
occurrences (all)	4		
Skin and subcutaneous tissue disorders - Other, specify			
subjects affected / exposed	2 / 50 (4.00%)		
occurrences (all)	2		
Renal and urinary disorders			
Bladder spasm			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Cystitis noninfective			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Haematuria			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	3 / 50 (6.00%)		
occurrences (all)	3		
Musculoskeletal and connective tissue disorder - Other, specify			
subjects affected / exposed	2 / 50 (4.00%)		
occurrences (all)	2		

Myalgia			
subjects affected / exposed	2 / 50 (4.00%)		
occurrences (all)	2		
Neck pain			
subjects affected / exposed	2 / 50 (4.00%)		
occurrences (all)	2		
Pain in extremity			
subjects affected / exposed	2 / 50 (4.00%)		
occurrences (all)	2		
Infections and infestations			
Infections and infestations - Other, specify			
subjects affected / exposed	2 / 50 (4.00%)		
occurrences (all)	2		
Rash pustular			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Upper respiratory tract infection			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Urinary tract infection			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Alkalosis			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Decreased appetite			
subjects affected / exposed	15 / 50 (30.00%)		
occurrences (all)	15		
Hyperglycaemia			
subjects affected / exposed	16 / 50 (32.00%)		
occurrences (all)	16		
Hypomagnesaemia			
subjects affected / exposed	2 / 50 (4.00%)		
occurrences (all)	2		
Hyponatraemia			

subjects affected / exposed occurrences (all)	1 / 50 (2.00%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 June 2012	To update the sponsor contact details; To amend inconsistencies detected in the previous protocol version and clarify some procedures related with sample obtention and clinical assessments. Changes regarding the patient diary.
27 March 2013	To clarify the inclusion criteria concerning Potassium, Calcium, Magnesium, Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) values. To modify the exclusion criteria; To amend inconsistencies detected in the previous protocol version and clarify some procedures related with sample obtention and clinical assessments; To update the adverse events in line with the current version of Investigator's Brochure; To prolong the interval of treatment interruption for adverse events resolution from 21 to 28 days before discontinuing a patient from the study. To update the hyperglycemia grade 2 management guides.
25 October 2013	- Update trial monitor contact information and name of SOLTI - Modify in part the definition of the primary endpoint - Reduce the number of chemotherapy lines received by the study population.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported