

**Clinical trial results:**

Estudio aleatorizado de quimioterapia adyuvante individualizada según los niveles de ARNm de BRCA1 en pacientes con cáncer de pulmón no microcítico (estadios II-IIIa)

Phase III, Open, Multicenter and Randomized Study of Customized Adjuvant Chemotherapy Based on BRCA1 mRNA Levels in Completely Resected Stages II-IIIa Non-Small-Cell Lung Cancer Patients

Summary

EudraCT number	2007-000067-15
Trial protocol	ES
Global end of trial date	01 June 2018

Results information

Result version number	v1 (current)
This version publication date	09 September 2020
First version publication date	09 September 2020
Summary attachment (see zip file)	GECP_SCAT_final report_summary (GECP-SCAT_CSR_final report summary_20Aug2020.pdf)

Trial information**Trial identification**

Sponsor protocol code	GECP-SCAT
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00478699
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Grupo Español de Cáncer de Pulmón
Sponsor organisation address	Avenida Meridiana 358, 6ª planta, Barcelona, Spain, 08027
Public contact	Eva Pereira Álvarez, Grupo Español de Cáncer de Pulmón, +34 934302006, epereira@gecp.org
Scientific contact	Mariano Provencio,, Grupo Español de Cáncer de Pulmón, +34 934302006, epereira@gecp.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	11 June 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 July 2015
Global end of trial reached?	Yes
Global end of trial date	01 June 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Evaluar y comparar la supervivencia global entre el grupo de quimioterapia adyuvante estándar no individualizada y los 3 grupos de quimioterapia individualizada.

Evaluate and compare overall survival between the group of Non-individualized standard adjuvant chemotherapy and the 3 subgroups individualized chemotherapy

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were followed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	02 July 2007
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: 456
Worldwide total number of subjects	456
EEA total number of subjects	456

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)	200
From 65 to 84 years	256
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The recruitment was 500 patients in 47 centers between June 2007 and May 2013.

Pre-assignment

Screening details:

Finally 456 patients were finally selected for final analysis were randomly assigned 101 to a control treatment and 355 to an experimental treatment.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Control Arm

Arm description:

Docetaxel 75 mg / m², and cisplatin 75 mg / m², both on day 1, every 21 days. Total cycles: 4.

Arm type	Active comparator
Investigational medicinal product name	Docetaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Docetaxel 75 mg / m², on day 1, every 21 days. Total cycles: 4.

Docetaxel presentation: 20 and 80 mg vials

Route of administration: Intravenous.

Therapeutic Group L01C3

A maximum of two dose reductions per patient of each of the chemotherapy agents will be allowed.

Investigational medicinal product name	Cisplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Dose Cisplatin 75 mg / m², both on day 1, every 21 days. Total cycles: Four.

Cisplatin presentation: 10, 25, 50 and 100 mg vials

Route of administration: intravenous

Therapeutic group: L01E1

A maximum of two dose reductions per patient of each of the chemotherapy agents will be allowed.

Arm title	Experimental Arm
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Arm description:

Experimental group (B), according to the BRAC1 levels of the tumor tissue, one of the following treatments will be assigned:

o Low expression of BRCA1 gemcitabine 1250 mg / m², days 1 and 8, and cisplatin 75 mg / m², day 1. Cycles every 21 days. Total cycles: 4

o Intermediate expression levels of BRCA1 docetaxel 75 mg / m², and cisplatin 75 mg / m², both administered on day 1, every 21 days. Total cycles: 4.

o High expression levels of BRCA1 docetaxel 75 mg / m², day 1. Cycles every 21 days. Total cycles: 4.

Arm type	Experimental
Investigational medicinal product name	Docetaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Intermediate expression levels of BRCA1 and High expression levels of BRCA1 docetaxel 75 mg / m², administered on day 1, every 21 days. Total cycles: 4.

Docetaxel presentation: 20 and 80 mg vials

Route of administration: Intravenous.

Therapeutic Group L01C3

A maximum of two dose reductions per patient of each of the chemotherapy agents will be allowed.

Investigational medicinal product name	Cisplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Dose Cisplatin

Low expression of BRCA1 and Intermediate expression levels of BRCA1 :75 mg / m², both on day 1, every 21 days. Total cycles: Four.

Cisplatin presentation: 10, 25, 50 and 100 mg vials

Route of administration: intravenous

Therapeutic group: L01E1

A maximum of two dose reductions per patient of each of the chemotherapy agents will be allowed.

Investigational medicinal product name	Gemcitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Low expression of BRCA1 gemcitabine 1250 mg / m², days 1 and 8. Cycles every 21 days. Total cycles: 4

Gemcitabine, hydrochloride 1 g, and 200 mg vials

Route of administration: intravenous

Therapeutic group: L01B2

Number of subjects in period 1	Control Arm	Experimental Arm
Started	101	355
Completed	101	355

Baseline characteristics

Reporting groups

Reporting group title	Control Arm
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Reporting group description:

Docetaxel 75 mg / m², and cisplatin 75 mg / m², both on day 1, every 21 days. Total cycles: 4.

Reporting group title	Experimental Arm
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Reporting group description:

Experimental group (B), according to the BRCA1 levels of the tumor tissue, one of the following treatments will be assigned:

o Low expression of BRCA1 gemcitabine 1250 mg / m², days 1 and 8, and cisplatin 75 mg / m², day 1. Cycles every 21 days. Total cycles: 4

o Intermediate expression levels of BRCA1 docetaxel 75 mg / m², and cisplatin 75 mg / m², both administered on day 1, every 21 days. Total cycles: 4.

o High expression levels of BRCA1 docetaxel 75 mg / m², day 1. Cycles every 21 days. Total cycles: 4.

Reporting group values	Control Arm	Experimental Arm	Total
Number of subjects	101	355	456
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	63	61	
full range (min-max)	57 to 68	56 to 68	-
Gender categorical Units: Subjects			
Female	22	74	96
Male	79	281	360
Smoking habit Units: Subjects			
Former smoker	62	221	283
Smoker	28	102	130
Never smoker	11	32	43
Treatment according to BRCA1 level Units: Subjects			
Control: Docetaxel and Cisplatin	101	0	101

Experimental: BRCA1 Low: Gemcitabine / Cisplatin	0	155	155
Experimental BRCA1 medium: Docetaxel / Cisplatin	0	99	99
Experimental BRCA1 High: Docetaxel	0	101	101
Histology Units: Subjects			
Adenocarcinomas	47	175	222
Squamous	46	155	201
Other	8	25	33
Staging T Units: Subjects			
T1	22	68	90
T2	64	230	294
T3	15	57	72
Staging N Units: Subjects			
N1	62	215	277
N2	39	140	179
Stage Units: Subjects			
IIA	14	38	52
IIB	37	142	179
IIIA	50	175	225
Treatment compliance Units: Subjects			
Completed	84	307	391
Not completed	17	48	65

End points

End points reporting groups

Reporting group title	Control Arm
Reporting group description: Docetaxel 75 mg / m ² , and cisplatin 75 mg / m ² , both on day 1, every 21 days. Total cycles: 4.	
Reporting group title	Experimental Arm
Reporting group description: Experimental group (B), according to the BRCA1 levels of the tumor tissue, one of the following treatments will be assigned: o Low expression of BRCA1 gemcitabine 1250 mg / m ² , days 1 and 8, and cisplatin 75 mg / m ² , day 1. Cycles every 21 days. Total cycles: 4 o Intermediate expression levels of BRCA1 docetaxel 75 mg / m ² , and cisplatin 75 mg / m ² , both administered on day 1, every 21 days. Total cycles: 4. o High expression levels of BRCA1 docetaxel 75 mg / m ² , day 1. Cycles every 21 days. Total cycles: 4.	

Primary: Overall survival

End point title	Overall survival
End point description: To assess and compare the overall survival between the non-individualized standard adjuvant chemotherapy group and the 3 individualized chemotherapy subgroups.	
End point type	Primary
End point timeframe: Overall survival: it will be measured from the date of inclusion to the date of death from any cause.	

End point values	Control Arm	Experimental Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	101	355		
Units: Month				
median (confidence interval 95%)				
Control	57.4 (1.8 to 111.9)	0 (0 to 0)		
Experimental Low BRCA1: Gemcitabine / Cisplatin	0 (0 to 0)	52.8 (1.9 to 104.1)		
Experimental Medium BRCA1: Docetaxel / Cisplatin	0 (0 to 0)	49.8 (2 to 120.4)		
Experimental High BRCA1: Docetaxel	0 (0 to 0)	51.8 (2.4 to 112.8)		

Statistical analyses

Statistical analysis title	Statistical analysis 1
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Statistical analysis description:

The estimated median survival of the patients included in the study is 79.3 months (95% CI 63.5-95.1 months).

Comparison groups	Control Arm v Experimental Arm
Number of subjects included in analysis	456
Analysis specification	Pre-specified
Analysis type	superiority ^[1]
P-value	= 0.73 ^[2]
Method	long-rank
Parameter estimate	Mean difference (final values)
Point estimate	52.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.8
upper limit	120.4

Notes:

[1] - No significant differences were observed between the overall survival of the patients assigned to the control group compared to the experimental group (p-value: 0.730).

[2] - No significant differences were observed between the overall survival of the patients assigned to the control group compared to the experimental group (p-value: 0.730).

Statistical analysis title	Statistical analysis 2
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Statistical analysis description:

Very significant differences are observed in the overall survival of 280 patients under 65 years of age compared to 176 patients 65 years of age or older at the time of resection (p-value <0.001). The estimated median is 106.4 months for those under 65 years of age and 56.2 months for patients 65 years of age or older.

Comparison groups	Experimental Arm v Control Arm
Number of subjects included in analysis	456
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[3]
Method	long-rank
Parameter estimate	Mean difference (final values)
Point estimate	106.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	56.2
upper limit	106.4

Notes:

[3] - Very significant differences are observed in the overall survival of 280 patients under 65 years of age compared to 176 patients 65 years of age or older at the time of resection (p-value <0.001).

Statistical analysis title	Statistical analysis 3
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Statistical analysis description:

Regarding the overall survival of the patients based on their lymph node involvement, significant differences (p-value: 0.001) were observed in favor of patients with N1 lymph node involvement. (52.0 months for N2 patients and 120.4 for N1 patients)

Comparison groups	Control Arm v Experimental Arm
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Number of subjects included in analysis	456
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001 [4]
Method	long-rank
Parameter estimate	Mean difference (final values)
Point estimate	120.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	52
upper limit	120.4

Notes:

[4] - Regarding the overall survival of the patients based on their lymph node involvement, significant differences (p-value: 0.001) were observed

Secondary: Disease free survival

End point title	Disease free survival
End point description: To assess the disease-free survival of both treatment groups.	
End point type	Secondary
End point timeframe: Disease-free survival: will be calculated from the date of surgery until there is some clinical evidence of disease progression or the date of death due to the disease.	

End point values	Control Arm	Experimental Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	101	355		
Units: Months				
median (confidence interval 80%)				
Control arm	38.7 (18.6 to 58.8)	0 (0 to 0)		
Experimental arm	0 (0 to 0)	32.7 (24.1 to 41.2)		

Statistical analyses

Statistical analysis title	Statistical analysis 1
Statistical analysis description: The comparison of Disease free survival for patients treated in the control group with respect to those treated in the experimental group is made.	
Comparison groups	Control Arm v Experimental Arm

Number of subjects included in analysis	456
Analysis specification	Pre-specified
Analysis type	superiority ^[5]
P-value	= 0.753 ^[6]
Method	Iong-Rank
Parameter estimate	Median difference (final values)
Point estimate	79.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	63.5
upper limit	95.1

Notes:

[5] - Regarding progression-free survival for both the control group and the experimental group, no significant differences were observed between the two when applying the long-rank test (p-value = 0.753).

[6] - Regarding progression-free survival for both the control group and the experimental group, no significant differences were observed.

Statistical analysis title	Statistical analysis 2
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Statistical analysis description:

Very significant differences are observed (p-value: 0.025), as on disease free survival depending on the age of the patients (<65 or > 65). The estimated median to progression is 38.7 months for those under 65 and 27.0 months for those over 65.

Comparison groups	Control Arm v Experimental Arm
Number of subjects included in analysis	456
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.025 ^[7]
Method	long-rank
Parameter estimate	Median difference (final values)
Point estimate	38.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	28
upper limit	38.7

Notes:

[7] - Very significant differences are observed (p-value: 0.025), as on disease free survival depending on the age of the patients (<65 or > 65).

Statistical analysis title	Statistical analys 3
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Statistical analysis description:

Also for lymph node involvement, significant differences (p-value: 0.009) were observed with a median progression-free survival of 42.7 months for N1 patients vs 26.2 months for N2 patients.

Comparison groups	Control Arm v Experimental Arm
Number of subjects included in analysis	456
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.009
Method	long-rank
Parameter estimate	Median difference (final values)
Point estimate	42.7

Confidence interval

level	95 %
sides	2-sided
lower limit	26.2
upper limit	42.7

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Any adverse event or breakdown occurring during the course of the study.

Adverse event reporting additional description:

The severity of AE will be determined using CTCAE version 3.0.

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	10.0
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Reporting groups

Reporting group title	Subjects per protocol
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Reporting group description: -

Serious adverse events	Subjects per protocol		
Total subjects affected by serious adverse events			
subjects affected / exposed	52 / 456 (11.40%)		
number of deaths (all causes)	11		
number of deaths resulting from adverse events	4		
Vascular disorders			
Pulmonary thromboembolism			
subjects affected / exposed	2 / 456 (0.44%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	1 / 1		
Thrombolysis			
subjects affected / exposed	1 / 456 (0.22%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Tachycardia			
subjects affected / exposed	1 / 456 (0.22%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Acute myocardial infarction			

subjects affected / exposed	1 / 456 (0.22%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	35 / 456 (7.68%)		
occurrences causally related to treatment / all	35 / 35		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Anorexy			
subjects affected / exposed	2 / 456 (0.44%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Sudden death			
subjects affected / exposed	1 / 456 (0.22%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Gastrointestinal disorders			
Diarrhea			
subjects affected / exposed	9 / 456 (1.97%)		
occurrences causally related to treatment / all	9 / 9		
deaths causally related to treatment / all	0 / 0		
Vomits			
subjects affected / exposed	3 / 456 (0.66%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		
Mucositis			
subjects affected / exposed	4 / 456 (0.88%)		
occurrences causally related to treatment / all	4 / 4		
deaths causally related to treatment / all	1 / 1		
Respiratory, thoracic and mediastinal disorders			
Respiratory infection			

subjects affected / exposed	6 / 456 (1.32%)		
occurrences causally related to treatment / all	6 / 6		
deaths causally related to treatment / all	0 / 0		
Respiratory arrest			
subjects affected / exposed	1 / 456 (0.22%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Palmoplantar disease			
subjects affected / exposed	1 / 456 (0.22%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Renal and urinary disorders			
Acute kidney failure			
subjects affected / exposed	1 / 456 (0.22%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Subjects per protocol		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	425 / 456 (93.20%)		
Vascular disorders			
Phlebitis			
subjects affected / exposed	11 / 456 (2.41%)		
occurrences (all)	11		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	283 / 456 (62.06%)		
occurrences (all)	283		
Fever			
subjects affected / exposed	20 / 456 (4.39%)		
occurrences (all)	20		
Abdominal pain			

subjects affected / exposed occurrences (all)	11 / 456 (2.41%) 11		
Immune system disorders Allergic reaction subjects affected / exposed occurrences (all)	15 / 456 (3.29%) 15		
Respiratory, thoracic and mediastinal disorders Dyspnoea subjects affected / exposed occurrences (all)	25 / 456 (5.48%) 25		
Cardiac disorders Cardiac Arrhythmia subjects affected / exposed occurrences (all)	2 / 456 (0.44%) 2		
Nervous system disorders Sensitivity in sensory processing subjects affected / exposed occurrences (all)	48 / 456 (10.53%) 48		
Blood and lymphatic system disorders Hemoglobin subjects affected / exposed occurrences (all) Leukocytes subjects affected / exposed occurrences (all) Neutrophils subjects affected / exposed occurrences (all) Platelets subjects affected / exposed occurrences (all) Epistaxis subjects affected / exposed occurrences (all) Edema	220 / 456 (48.25%) 220 80 / 456 (17.54%) 80 138 / 456 (30.26%) 138 50 / 456 (10.96%) 50 5 / 456 (1.10%) 5		

subjects affected / exposed occurrences (all)	12 / 456 (2.63%) 12		
Ear and labyrinth disorders Tinnitus subjects affected / exposed occurrences (all)	8 / 456 (1.75%) 8		
Eye disorders Conjunctivitis subjects affected / exposed occurrences (all)	3 / 456 (0.66%) 3		
Gastrointestinal disorders Anorexy subjects affected / exposed occurrences (all) Constipation subjects affected / exposed occurrences (all) Diarrhea subjects affected / exposed occurrences (all) Mucositis subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all) Epigastralgia subjects affected / exposed occurrences (all)	63 / 456 (13.82%) 63 57 / 456 (12.50%) 57 125 / 456 (27.41%) 125 93 / 456 (20.39%) 93 182 / 456 (39.91%) 182 126 / 456 (27.63%) 126 13 / 456 (2.85%) 13		
Skin and subcutaneous tissue disorders Alopecia subjects affected / exposed occurrences (all) Rash	142 / 456 (31.14%) 142		

subjects affected / exposed occurrences (all)	25 / 456 (5.48%) 25		
Musculoskeletal and connective tissue disorders Myalgia subjects affected / exposed occurrences (all)	17 / 456 (3.73%) 17		
Infections and infestations Infection subjects affected / exposed occurrences (all)	51 / 456 (11.18%) 51		
Metabolism and nutrition disorders GGT alteration subjects affected / exposed occurrences (all) Creatinine alteration subjects affected / exposed occurrences (all) GPT/ GOT alterations subjects affected / exposed occurrences (all) LDH alteration subjects affected / exposed occurrences (all)	42 / 456 (9.21%) 42 33 / 456 (7.24%) 33 37 / 456 (8.11%) 37 29 / 456 (6.36%) 29		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 September 2007	Modification of the criteria that are considered specific for the clinical situation of non-small cell lung cancer with complete surgical resection.
16 March 2009	Change of quartiles by tertiles in the determination of the expression of BRCA1.
09 February 2012	Allowing to use Carboplatin as a substitute for Cisplatin due to side effects or poor tolerance in a previous cycle, if the Principal Investigator of any of the participating sites deems it appropriate.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported