Clinical trial results:
Adjuvant Chemotherapy in Treating Women Who Have Undergone Resection for Relapsed Breast Cancer; Chemotherapy as Adjuvant for Locally Recurrent Breast Cancer (CALOR).

Summary

EudraCT number	2005-001484-64
Trial protocol	BE
Global end of trial date	22 August 2016

Results information

Result version number	v1 (current)
This version publication date	17 March 2021
First version publication date	17 March 2021

Trial information

Trial identification

Sponsor protocol code	IBCSG 27-02 CALOR

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00074152
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	IBCSG
Sponsor organisation address	Effingerstrasse 40, Bern, Switzerland, 3008
Public contact	IBCSG Coordinating Center, International Breast Cancer Study Group (IBCSG), +41 313899391, regulatoryoffice@ibcsg.org
Scientific contact	IBCSG Coordinating Center, International Breast Cancer Study Group (IBCSG), +41 313899391, regulatoryoffice@ibcsg.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	08 September 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	22 August 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The objective of this long-term follow-up update is to evaluate the efficacy of adjuvant chemotherapy after local
treatment of a first loco-regional recurrence of breast cancer at a median follow-up of nine years, including analyses according to ER status of the ILRR, recognizing that the ERpositive subgroup in particular requires longer follow-up than previously available.

Protection of trial subjects:

Participating institutions' ethics committees or Institutional Review Boards approved the trial according to local laws and regulations. All patients gave written informed consent, and the trial was performed in compliance with the Helsinki Declaration. The Data and Safety Monitoring Committee reviewed accrual and safety data semi-annually throughout the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	22 August 2003
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	Hungary: 33
Country: Number of subjects enrolled	Australia: 2
Country: Number of subjects enrolled	Switzerland: 16
Country: Number of subjects enrolled	Spain: 20
Country: Number of subjects enrolled	United States: 42
Country: Number of subjects enrolled	South Africa: 5
Country: Number of subjects enrolled	Peru: 1
Country: Number of subjects enrolled	Netherlands: 12
Country: Number of subjects enrolled	Canada: 31
Worldwide total number of subjects	162
EEA total number of subjects	65

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)	131
From 65 to 84 years	31
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

IBCSG and GEICAM (Spain) began enrolling in collaboration with Breast International Group (BIG) in 2003, and NSABP (US/Canada) began in 2005, and BOOG (Netherlands) in 2006 (through BIG). BIG centers enrolled 89 patients, and NSABP enrolled 73. There were 55 centers from nine countries participating in the trial.

Pre-assignment

Screening details:

This trial used a web-based randomization system. Each Participating Group determined how its Participating Centers will access the randomization system, either through a Group Randomization Center, or directly from the Participating Center.

Period 1

Period 1 title	Overall study (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 I

Arm description:

Observation (+/- Radiation). Patients receive radiotherapy* within 6 months after surgery.

Radiation therapy: Given within 6 months after surger

Arm type	Observation

No investigational medicinal product assigned in this arm

Arm title	Arm II

Arm description:

Chemotherapy (+/- Radiation). Within 10 weeks after surgery, patients receive at least 3 courses of an adjuvant chemotherapy regimen as determined by the investigator. Patients may receive radiotherapy within 6 months after surgery and after the completion of chemotherapy OR integrated with chemotherapy.

Chemotherapy: Given within 10 weeks after surgery.

Arm type	Experimental
Investigational medicinal product name	Chemotherapy
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

If the patient was randomized to receive chemotherapy, choice of chemotherapy, dose adjustments, and supportive therapies was left to the discretion of the investigators. The
protocol recommended at least two cytotoxic drugs for three to six months. Chemotherapy was to start within four weeks of randomization and within 16 weeks of resection of
locoregional recurrence.

Number of subjects in period 1	Arm I	Arm II
Started	77	85
Completed	22	52
Not completed	55	33
Death	21	9
Lack of efficacy	34	24

Baseline characteristics

Reporting groups	
Reporting group title	Arm I

Reporting group description:

Observation (+/- Radiation). Patients receive radiotherapy* within 6 months after surgery.

Radiation therapy: Given within 6 months after surger

Reporting group title	Arm II

Reporting group description:

Chemotherapy (+/- Radiation). Within 10 weeks after surgery, patients receive at least 3 courses of an adjuvant chemotherapy regimen as determined by the investigator. Patients may receive radiotherapy within 6 months after surgery and after the completion of chemotherapy OR integrated with chemotherapy.

Chemotherapy: Given within 10 weeks after surgery.

Reporting group values	Arm I	Arm II	Total
Number of subjects	77	85	162
Age categorical Units: Subjects			
<=18	0	0	0
18 - 65	60	71	131
>=65	17	14	31
Gender categorical Units: Subjects			
Female	77	85	162
Male	0	0	0
Region of Enrollment Units: Subjects			
United States	19	23	42
Hungary	17	16	33
Canada	15	16	31
Spain	9	11	20
Peru	1	0	1
Australia	1	1	2
South Africa	3	2	5
Netherlands	6	6	12
Switzerland	6	10	16
Surgery for primary tumor Units: Subjects			
Mastectomy	31	33	64
Breast conserving	46	52	98
Estrogen receptor (ER) status of the isolated local or regional recurrence Units: Subjects			
Positive	48	56	104
Negative	29	29	58
Progesterone receptor (PgR) status of the isolated local or regional recurrence Units: Subjects			

Positive	35	44	79
Negative	40	39	79
Not available	2	2	4
Location of isolated loco-regional recurrence Units: Subjects			
Breast	41	47	88
Mx scar/chest wall	26	27	53
Regional lymph nodes	10	11	21
Menopausal Status at isolated loco-regional recurrence Units: Subjects			
pre	14	20	34
post	63	65	128
Estrogen receptor (ER) status of primary tumor Units: Subjects			
negative	20	27	47
positive	47	49	96
unknown	10	9	19
Time from primary surgery to isolated loco-regional recurrence (ILRR) surgery Units: Years			
median	6.2	5.0	
full range (min-max)	2.9 to 11.3	2.9 to 9.5	-

End points

End points reporting groups

Reporting group title	Arm I

Reporting group description:

Observation (+/- Radiation). Patients receive radiotherapy* within 6 months after surgery.

Radiation therapy: Given within 6 months after surger

Reporting group title	Arm II

Reporting group description:

Chemotherapy (+/- Radiation). Within 10 weeks after surgery, patients receive at least 3 courses of an adjuvant chemotherapy regimen as determined by the investigator. Patients may receive radiotherapy within 6 months after surgery and after the completion of chemotherapy OR integrated with chemotherapy.

Chemotherapy: Given within 10 weeks after surgery.

Primary: Disease-free Survival

End point title	Disease-free Survival

End point description:

End point type	Primary

End point timeframe:

5 years after randomization

End point values	Arm I	Arm II		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	77	85		
Units: Percentage of participants				
number (confidence interval 95%)	57 (44 to 67)	69 (56 to 79)		

Statistical analyses

Statistical analysis title	Statistical analysis primary endpoint
Comparison groups	Arm I v Arm II
Number of subjects included in analysis	162
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.083
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.66

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.4
upper limit	1.06

Secondary: Overall Survival

End point title	Overall Survival

End point description:

End point type	Secondary

End point timeframe:

5 years after randomization

End point values	Arm I	Arm II		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	77	85		
Units: Percentage of participants				
number (confidence interval 95%)	76 (63 to 85)	88 (77 to 94)		

Statistical analyses

No statistical analyses for this end point

Secondary: Sites of First Failures

End point title	Sites of First Failures

End point description:

Tumor recurrence in the breast, lymph nodes or other areas of the body including bone, lung, liver, central nervous system, bone marrow.

End point type	Secondary

End point timeframe:

5 years after randomization

End point values	Arm I	Arm II		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	77	85		
Units: Participants				
number (not applicable)				
Failures	34	24		
Deaths	21	9		

Local or Regional	9	6		
Distant	22	15		
Soft Tissue	2	0		
Bone	5	8		
Viscera	15	7		
Contralateral Breast	1	1		
Second (non-breat) Malignancy	0	1		
Death without prior Cancer Event	0	1		
Death, cause unknown	2	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

From date patient provided informed consent until 4 weeks after study treatment completion, beyond 4 weeks after stopping study treatment any death or serious adverse event considered possibly related to previous study treatment (approximately 10 years)

Assessment type	Systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	3.0

Reporting groups

Reporting group title	Arm I

Reporting group description:

Observation (+/- Radiation). Patients receive radiotherapy* within 6 months after surgery.

Radiation therapy: Given within 6 months after surgery

Reporting group title	Arm II

Reporting group description:

Chemotherapy (+/- Radiation). Within 10 weeks after surgery, patients receive at least 3 courses of an adjuvant chemotherapy regimen as determined by the investigator. Patients may receive radiotherapy within 6 months after surgery and after the completion of chemotherapy OR integrated with chemotherapy.

Chemotherapy: Given within 10 weeks after surgery.

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: AEs were not an endpoint of the CALOR trial. Because the chemotherapy regimens were not consistent, and the no chemotherapy group was considered at no risk for toxicities, the CALOR trial did not collect AEs in the form of a routine checklist. Serious Adverse Events (SAEs) were collected on an event-driven basis in accordance with regulatory requirements.

Serious adverse events	Arm I	Arm II	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 77 (0.00%)	12 / 85 (14.12%)	
number of deaths (all causes)	27	18	
number of deaths resulting from adverse events			
Cardiac disorders			
Left ventricular dysfunction			
subjects affected / exposed	0 / 77 (0.00%)	1 / 85 (1.18%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac ischemia			
subjects affected / exposed	0 / 77 (0.00%)	2 / 85 (2.35%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			

Motor neuropathy			
subjects affected / exposed	0 / 77 (0.00%)	1 / 85 (1.18%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	0 / 77 (0.00%)	1 / 85 (1.18%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastrointestinal pain			
subjects affected / exposed	0 / 77 (0.00%)	1 / 85 (1.18%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	0 / 77 (0.00%)	1 / 85 (1.18%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Endometrial mucosa thickening			
subjects affected / exposed	0 / 77 (0.00%)	1 / 85 (1.18%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Febrile neutropenia			
subjects affected / exposed	0 / 77 (0.00%)	3 / 85 (3.53%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary/upper respiratory infection			
subjects affected / exposed	0 / 77 (0.00%)	1 / 85 (1.18%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			

subjects affected / exposed	0 / 77 (0.00%)	1 / 85 (1.18%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Arm I	Arm II	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 77 (0.00%)	0 / 85 (0.00%)	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 December 2004	To allow the use of adjuvant trastuzumab if declared prior to randomization, clarify the use of radiation therapy, and add NSABP as a collaborating group.
18 December 2006	18 December 2006. To facilitate patient accrual by broadening inclusion criteria and treatment requirements regarding timing and type of surgery and radiotherapy timing and dose.
13 November 2008	To revise the sample size to 265 patients and allow the use of lapatinib and other HER2-directed therapies. Remove quality-of-life assessments.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported