



## 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   |
| <b>Arm title</b>             | Arm I |

Arm description:

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

Radiation therapy: Given within 6 months after surgery

|   |             |
|---|-------------|
| Arm type  | Observation |
| No investigational medicinal product assigned in this arm |             |
| <b>Arm title</b>  | 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.

| <b>Number of subjects in period 1</b> | 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 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.

| 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<br>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<br>Units: Subjects                     |             |            |     |
| pre   | 14          | 20         | 34  |
| post  | 63          | 65         | 128 |
| Estrogen receptor (ER) status of primary tumor<br>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<br>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:<br>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:<br>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:<br>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-breast) 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<sup>[1]</sup>

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 %

| <b>Non-serious adverse events</b>                     | 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:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported