



Clinical trial results:

Phase II, open label, neoadjuvant study of Bevacizumab in patients with inflammatory or locally advanced breast cancer

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2006-003291-35 |
| Trial protocol | IT |
| Global end of trial date | 28 July 2015 |

Results information

| | |
|--------------------------------|---|
| Result version number | v2 (current) |
| This version publication date | 17 February 2017 |
| First version publication date | 16 November 2016 |
| Version creation reason | <ul style="list-style-type: none">• Correction of full data set Update to align with ClinicalTrials.gov registry posting. |

Trial information

Trial identification

| | |
|-----------------------|----------|
| Sponsor protocol code | ML 19884 |
|-----------------------|----------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT00559845 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | F. Hoffmann-La Roche AG |
| Sponsor organisation address | Grenzacherstrasse 124, Basel, Switzerland, CH-4070 |
| Public contact | F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.com |
| Scientific contact | F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.com |

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 | 28 July 2015 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 28 July 2015 |
| Global end of trial reached? | Yes |
| Global end of trial date | 28 July 2015 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To determine the rate of pathological complete responses (pCR) defined as absence of invasive neoplastic cells at microscopic examination of the tumor remnants after surgery following primary systemic therapy.

Protection of trial subjects:

All study subjects were required to read and sign an informed consent form.

Background therapy: -

Evidence for comparator: -

| | |
|---|------------------|
| Actual start date of recruitment | 18 February 2008 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Efficacy, Safety |
| Long term follow-up duration | 5 Years |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-----------|
| Country: Number of subjects enrolled | Italy: 56 |
| Worldwide total number of subjects | 56 |
| EEA total number of subjects | 56 |

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) | 52 |
| From 65 to 84 years | 4 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

56 subjects were enrolled in 8 centers in Italy.

Period 1

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

Arms

| | |
|-----------|-------------|
| Arm title | Bevacizumab |
|-----------|-------------|

Arm description:

5-fluorouracil, epidoxorubicin and cyclophosphamide (FEC), followed by paclitaxel, given concomitantly with bevacizumab for approximately 3-12 months.

| | |
|--|------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | 5-fluorouracil |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Intravenous bolus use |

Dosage and administration details:

600 milligrams per metre squared (mg/m²) as an intravenous (i.v.) bolus over ≤15 minutes every 3 weeks for 4 cycles.

| | |
|--|-----------------------|
| Investigational medicinal product name | Epidoxorubicin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

90 mg/m² as an i.v. infusion over 1 hour every 3 weeks for 4 cycles.

| | |
|--|-----------------------|
| Investigational medicinal product name | Cyclophosphamide |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

600 mg/m² as an i.v. infusion over 1 hour every 3 weeks for 4 cycles.

| | |
|--|-----------------------|
| Investigational medicinal product name | Paclitaxel |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravascular use |

Dosage and administration details:

80 mg/m² i.v. over 1 hour weekly for 12 weeks.

| | |
|--|---------------------------------------|
| Investigational medicinal product name | Bevacizumab |
| Investigational medicinal product code | |
| Other name | Avastin® |
| Pharmaceutical forms | Concentrate for emulsion for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

10 milligrams per kilogram (mg/kg) i.v. every 2 weeks for 6 cycles.

| Number of subjects in period 1 | Bevacizumab |
|---|-------------|
| Started | 56 |
| Completed | 49 |
| Not completed | 7 |
| Did not attend cycle 6 hospital visit | 1 |
| Disease progression | 1 |
| Adverse event | 3 |
| Premature surgery-investigator decision | 1 |
| Withdrew consent | 1 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|-------------|
| Reporting group title | Bevacizumab |
|-----------------------|-------------|

Reporting group description:

5-fluorouracil, epidoxorubicin and cyclophosphamide (FEC), followed by paclitaxel, given concomitantly with bevacizumab for approximately 3-12 months.

| Reporting group values | Bevacizumab | Total | |
|---|---------------|-------|--|
| Number of subjects | 56 | 56 | |
| Age categorical Units: Subjects | | | |
| Age continuous Units: years arithmetic mean standard deviation | 50 ± 9.279 | - | |
| Gender categorical Units: Subjects | | | |
| Female | 56 | 56 | |
| Male | 0 | 0 | |

End points

End points reporting groups

| | |
|--|-------------|
| Reporting group title | Bevacizumab |
| Reporting group description: 5-fluorouracil, epirubicin and cyclophosphamide (FEC), followed by paclitaxel, given concomitantly with bevacizumab for approximately 3-12 months. | |

Primary: Percentage of Subjects With Pathological Complete Response Following Principle Investigator Review

| | |
|---|---|
| End point title | Percentage of Subjects With Pathological Complete Response Following Principle Investigator Review ^[1] |
| End point description: Pathological complete response was defined as absence of invasive neoplastic cells at microscopic examination of the tumor remnants after surgery following primary systemic therapy. Intention-to-Treat (ITT) population, defined as all subjects that were included in the trial and underwent surgery. | |
| End point type | Primary |
| End point timeframe: Up to 7.5 years | |
| 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: Only descriptive data was planned to be reported. | |

| End point values | Bevacizumab | | | |
|-------------------------------|-----------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 56 | | | |
| Units: percentage of subjects | | | | |
| number (not applicable) | 23.2 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Objective Response Rate

| | |
|--|-------------------------|
| End point title | Objective Response Rate |
| End point description: Objective response rate was defined as the percentage of subjects with a Complete Response (CR) or Partial Response (PR) as defined by the Response Evaluation Criteria in Solid Tumors (RECIST). CR was defined as the disappearance of all target lesions; PR was defined as a 30% decrease in sum of longest diameter of target lesions. ITT population, defined as all subjects that were included in the trial and underwent surgery. | |
| End point type | Secondary |
| End point timeframe: Up to 7.5 years | |

| | | | | |
|-------------------------------|-----------------|--|--|--|
| End point values | Bevacizumab | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 56 | | | |
| Units: percentage of subjects | | | | |
| number (not applicable) | 59 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Breast-Conserving Surgery

| | |
|--|---|
| End point title | Percentage of Subjects With Breast-Conserving Surgery |
| End point description: Categories breast-conserving procedure, and breast-conserving procedure plus axillary dissection are presented. ITT population, defined as all subjects that were included in the trial and underwent surgery. | |
| End point type | Secondary |
| End point timeframe: Up to 7.5 years | |

| | | | | |
|---------------------------------|-----------------|--|--|--|
| End point values | Bevacizumab | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 56 | | | |
| Units: percentage of subjects | | | | |
| number (not applicable) | | | | |
| Breast-conserving | 17 | | | |
| Breast-conserving plus axillary | 13.2 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Disease-Free Interval at Specified Time Points

| | |
|---|--|
| End point title | Percentage of Subjects With Disease-Free Interval at Specified Time Points |
| End point description: Disease-free interval was defined as the time from enrollment until recurrence of tumor or death from any cause, and was estimated using the Kaplan-Meier method. The percentage of subjects without events at Months 12, 24, 36, 48, and 60 is presented. ITT population, defined as all subjects that were included in the trial and underwent surgery. | |
| End point type | Secondary |

End point timeframe:
Months 12, 24, 36, 48, and 60

| | | | | |
|----------------------------------|---------------------|--|--|--|
| End point values | Bevacizumab | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 53 ^[2] | | | |
| Units: percentage of subjects | | | | |
| number (confidence interval 95%) | | | | |
| 12 Months | 92.2 (85.1 to 99.8) | | | |
| 24 Months | 84.3 (74.9 to 94.9) | | | |
| 36 Months | 80.4 (70.2 to 92.1) | | | |
| 48 Months | 76.5 (65.7 to 89.1) | | | |
| 60 Months | 76.5 (65.7 to 89.1) | | | |

Notes:

[2] - Number of subjects analyzed signifies those subjects who were evaluable for the endpoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival

| | |
|--|------------------|
| End point title | Overall Survival |
| End point description: | |
| Overall survival was defined as the time from enrollment of subject to death from any cause. | |
| End point type | Secondary |
| End point timeframe: | |
| Up to 7.5 years | |

| | | | | |
|-------------------------------|------------------|--|--|--|
| End point values | Bevacizumab | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 0 ^[3] | | | |
| Units: months | | | | |
| median (full range (min-max)) | (to) | | | |

Notes:

[3] - Data for the outcome measure was not collected.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Experiencing Any Adverse Event

| | |
|--|---|
| End point title | Percentage of Subjects Experiencing Any Adverse Event |
| End point description: | |
| An adverse event was defined as any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. Safety population, defined as all subjects who received at least one infusion of Bevacizumab. | |
| End point type | Secondary |
| End point timeframe: | |
| Up to 7.5 years | |

| | | | | |
|-------------------------------|-----------------|--|--|--|
| End point values | Bevacizumab | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 56 | | | |
| Units: percentage of subjects | | | | |
| number (not applicable) | 100 | | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 7.5 years

Adverse event reporting additional description:

Safety population, defined as all subjects who received at least one infusion of Bevacizumab.

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 13.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|-------------|
| Reporting group title | Bevacizumab |
|-----------------------|-------------|

Reporting group description:

5-fluorouracil, epidoxorubicin and cyclophosphamide (FEC), followed by paclitaxel, given concomitantly with bevacizumab for approximately 3-12 months.

| Serious adverse events | Bevacizumab | | |
|---|-----------------|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 8 / 54 (14.81%) | | |
| number of deaths (all causes) | 0 | | |
| number of deaths resulting from adverse events | 0 | | |
| Investigations | | | |
| Cardiac imaging procedure abnormal | | | |
| subjects affected / exposed | 1 / 54 (1.85%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Malignant melanoma in situ | | | |
| subjects affected / exposed | 1 / 54 (1.85%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Injury, poisoning and procedural complications | | | |
| Postoperative wound complication | | | |
| subjects affected / exposed | 1 / 54 (1.85%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Blood and lymphatic system disorders | | | |

| | | | |
|---|----------------|--|--|
| Anaemia | | | |
| subjects affected / exposed | 1 / 54 (1.85%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Febrile neutropenia | | | |
| subjects affected / exposed | 1 / 54 (1.85%) | | |
| occurrences causally related to treatment / all | 4 / 6 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Eye disorders | | | |
| Retinopathy hypertensive | | | |
| subjects affected / exposed | 1 / 54 (1.85%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Dyspnoea | | | |
| subjects affected / exposed | 1 / 54 (1.85%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Psychiatric disorders | | | |
| Suicide attempt | | | |
| subjects affected / exposed | 1 / 54 (1.85%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| Febrile infection | | | |
| subjects affected / exposed | 1 / 54 (1.85%) | | |
| 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 | Bevacizumab | | |
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 54 / 54 (100.00%) | | |

| | | | |
|--|------------------------|--|--|
| Investigations | | | |
| Alanine aminotransferase increased subjects affected / exposed occurrences (all) | 6 / 54 (11.11%) 8 | | |
| Ast increased subjects affected / exposed occurrences (all) | 3 / 54 (5.56%) 4 | | |
| Vascular disorders | | | |
| Hypertension subjects affected / exposed occurrences (all) | 13 / 54 (24.07%) 15 | | |
| Phlebitis subjects affected / exposed occurrences (all) | 4 / 54 (7.41%) 4 | | |
| Surgical and medical procedures | | | |
| Astringent therapy subjects affected / exposed occurrences (all) | 3 / 54 (5.56%) 3 | | |
| Nervous system disorders | | | |
| Paraesthesia subjects affected / exposed occurrences (all) | 27 / 54 (50.00%) 37 | | |
| Headache subjects affected / exposed occurrences (all) | 10 / 54 (18.52%) 16 | | |
| Dysgeusia subjects affected / exposed occurrences (all) | 5 / 54 (9.26%) 6 | | |
| Syncope subjects affected / exposed occurrences (all) | 3 / 54 (5.56%) 3 | | |
| Blood and lymphatic system disorders | | | |
| Neutropenia subjects affected / exposed occurrences (all) | 22 / 54 (40.74%) 50 | | |
| Leukopenia | | | |

| | | | |
|--|------------------------|--|--|
| subjects affected / exposed occurrences (all) | 15 / 54 (27.78%) 26 | | |
| Anaemia subjects affected / exposed occurrences (all) | 12 / 54 (22.22%) 15 | | |
| General disorders and administration site conditions | | | |
| Asthenia subjects affected / exposed occurrences (all) | 30 / 54 (55.56%) 83 | | |
| Mucosal inflammation subjects affected / exposed occurrences (all) | 18 / 54 (33.33%) 41 | | |
| Pyrexia subjects affected / exposed occurrences (all) | 15 / 54 (27.78%) 27 | | |
| Oedema subjects affected / exposed occurrences (all) | 3 / 54 (5.56%) 3 | | |
| Pain subjects affected / exposed occurrences (all) | 3 / 54 (5.56%) 4 | | |
| Eye disorders | | | |
| Conjunctivitis subjects affected / exposed occurrences (all) | 9 / 54 (16.67%) 17 | | |
| Gastrointestinal disorders | | | |
| Nausea subjects affected / exposed occurrences (all) | 38 / 54 (70.37%) 66 | | |
| Diarrhea subjects affected / exposed occurrences (all) | 17 / 54 (31.48%) 27 | | |
| Vomiting subjects affected / exposed occurrences (all) | 17 / 54 (31.48%) 28 | | |
| Constipation | | | |

| | | | |
|---|------------------|--|--|
| subjects affected / exposed | 11 / 54 (20.37%) | | |
| occurrences (all) | 16 | | |
| Stomatitis | | | |
| subjects affected / exposed | 11 / 54 (20.37%) | | |
| occurrences (all) | 14 | | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 7 / 54 (12.96%) | | |
| occurrences (all) | 8 | | |
| Dyspepsia | | | |
| subjects affected / exposed | 6 / 54 (11.11%) | | |
| occurrences (all) | 7 | | |
| Haemorrhoids | | | |
| subjects affected / exposed | 4 / 54 (7.41%) | | |
| occurrences (all) | 4 | | |
| Abdominal pain | | | |
| subjects affected / exposed | 3 / 54 (5.56%) | | |
| occurrences (all) | 3 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Epistaxis | | | |
| subjects affected / exposed | 33 / 54 (61.11%) | | |
| occurrences (all) | 47 | | |
| Cough | | | |
| subjects affected / exposed | 4 / 54 (7.41%) | | |
| occurrences (all) | 4 | | |
| Dyspnoea | | | |
| subjects affected / exposed | 3 / 54 (5.56%) | | |
| occurrences (all) | 6 | | |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 3 / 54 (5.56%) | | |
| occurrences (all) | 3 | | |
| Skin and subcutaneous tissue disorders | | | |
| Alopecia | | | |
| subjects affected / exposed | 36 / 54 (66.67%) | | |
| occurrences (all) | 36 | | |
| Nail disorder | | | |

| | | | |
|---|---|--|--|
| <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Rash</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Pruritus</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Erythema</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>10 / 54 (18.52%)</p> <p>10</p> <p>8 / 54 (14.81%)</p> <p>11</p> <p>4 / 54 (7.41%)</p> <p>5</p> <p>3 / 54 (5.56%)</p> <p>3</p> | | |
| <p>Psychiatric disorders</p> <p>Anxiety</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>4 / 54 (7.41%)</p> <p>4</p> | | |
| <p>Musculoskeletal and connective tissue disorders</p> <p>Myalgia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Bone Pain</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Arthralgia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Pain in extremity</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>18 / 54 (33.33%)</p> <p>35</p> <p>13 / 54 (24.07%)</p> <p>24</p> <p>3 / 54 (5.56%)</p> <p>7</p> <p>3 / 54 (5.56%)</p> <p>3</p> | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|---|
| 20 November 2009 | <ol style="list-style-type: none">1. Better define and specify the objectives of the study2. Update the duration of the study according to the new definition of "Long-Term Follow-up" for a maximum of 5 years3. Update the examinations to be performed during the "Long-Term Follow-up" according to the clinical practice |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported