



## Clinical trial results:

### A Randomized Phase III Clinical Study of Bevacizumab Plus Capecitabine vs. Bevacizumab Alone as Maintenance Therapy in Patients with HER2-Negative Metastatic Breast Cancer That Has Not Progressed During First-Line Docetaxel Plus Bevacizumab Therapy Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2008-006872-31 |
| Trial protocol           | ES FR IT       |
| Global end of trial date | 14 June 2014   |

#### Results information

|                                |                |
|--------------------------------|----------------|
| Result version number          | v1 (current)   |
| This version publication date  | 14 July 2016   |
| First version publication date | 06 August 2015 |

#### Trial information

##### Trial identification

|                       |         |
|-----------------------|---------|
| Sponsor protocol code | MO22223 |
|-----------------------|---------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT00929240 |
| 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               | Roche Trial Information Hotline, F. Hoffmann-La Roche AG, 41 616878333, global.trial_information@roche.com |
| Scientific contact           | Roche Trial Information Hotline, 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                       | 14 June 2014 |
| Is this the analysis of the primary completion data? | No           |
| Global end of trial reached?                         | Yes          |
| Global end of trial date                             | 14 June 2014 |
| Was the trial ended prematurely?                     | No           |

Notes:

## General information about the trial

Main objective of the trial:

To evaluate whether maintenance therapy with bevacizumab plus capecitabine, compared to bevacizumab alone, can further increase Progression-Free Survival (PFS) in patients showing objective response or stable disease following initial therapy with bevacizumab plus (+) docetaxel.

Protection of trial subjects:

The study was conducted in accordance with the principles of the "Declaration of Helsinki" and Good Clinical Practice (GCP) according to the regulations and procedures described in the following sections of the protocol.

Background therapy: -

Evidence for comparator: -

|                                                           |              |
|-----------------------------------------------------------|--------------|
| Actual start date of recruitment                          | 16 July 2009 |
| 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 | Poland: 9     |
| Country: Number of subjects enrolled | Spain: 31     |
| Country: Number of subjects enrolled | France: 54    |
| Country: Number of subjects enrolled | Italy: 30     |
| Country: Number of subjects enrolled | Brazil: 40    |
| Country: Number of subjects enrolled | China: 25     |
| Country: Number of subjects enrolled | Egypt: 13     |
| Country: Number of subjects enrolled | India: 48     |
| Country: Number of subjects enrolled | Turkey: 25    |
| Country: Number of subjects enrolled | Hong Kong: 12 |
| Worldwide total number of subjects   | 287           |
| EEA total number of subjects         | 124           |

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)                     | 238 |
| From 65 to 84 years                      | 49  |
| 85 years and over                        | 0   |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

Screening was performed from Day -28 to Day 1 (Baseline).

### Period 1

|                              |                         |
|------------------------------|-------------------------|
| Period 1 title               | Initial Treatment Phase |
| Is this the baseline period? | Yes                     |
| Allocation method            | Randomised - controlled |
| Blinding used                | Not blinded             |

### Arms

|                  |                                                         |
|------------------|---------------------------------------------------------|
| <b>Arm title</b> | Initial Treatment Phase: Bevacizumab Plus (+) Docetaxel |
|------------------|---------------------------------------------------------|

Arm description:

During the Initial Phase all participants received bevacizumab 15 milligrams per kilogram (mg/kg) intravenously (IV) on Day 1 of each 3 week cycle for a minimum of 3 cycles and a maximum of 6 cycles or until disease progression, unacceptable toxicity or participant request for withdrawal, whichever occurred first. Participants also received docetaxel, a recommended dose of 100 milligrams per square meter (mg/m<sup>2</sup>) IV administered on Day 1 of each cycle. Doses of 75 to 100 mg/m<sup>2</sup> of docetaxel could be administered at investigator's discretion. At the end of the Initial Treatment Phase, participants with an objective response (partial response [PR] or complete response [CR]) or stable disease (SD) following 3-6 cycles of bevacizumab + docetaxel were randomized to receive maintenance therapy with either bevacizumab alone or bevacizumab + capecitabine.

|                                        |                       |
|----------------------------------------|-----------------------|
| Arm type                               | Experimental          |
| Investigational medicinal product name | Bevacizumab           |
| Investigational medicinal product code |                       |
| Other name                             |                       |
| Pharmaceutical forms                   | Solution for infusion |
| Routes of administration               | Intravenous use       |

Dosage and administration details:

During the Initial Phase all participants received bevacizumab 15 mg/kg IV on Day 1 of each 3 week cycle for a minimum of 3 cycles and a maximum of 6 cycles or until disease progression, unacceptable toxicity or participant request for withdrawal, whichever occurred first.

|                                        |                                                       |
|----------------------------------------|-------------------------------------------------------|
| Investigational medicinal product name | Docetaxel                                             |
| Investigational medicinal product code |                                                       |
| Other name                             |                                                       |
| Pharmaceutical forms                   | Solution for injection/infusion in pre-filled syringe |
| Routes of administration               | Intravenous use                                       |

Dosage and administration details:

Participants received docetaxel, a recommended dose of 100 mg/m<sup>2</sup> IV administered on Day 1 of each cycle. Doses of 75 to 100 mg/m<sup>2</sup> of docetaxel could be administered at investigator's discretion for a minimum of 3 cycles and a maximum of 6 cycles.

| Number of subjects in period 1         | Initial Treatment Phase: Bevacizumab Plus (+) Docetaxel |
|----------------------------------------|---------------------------------------------------------|
| Started                                | 287                                                     |
| Completed                              | 185                                                     |
| Not completed                          | 102                                                     |
| Adverse event, serious fatal           | 2                                                       |
| Consent withdrawn by subject           | 13                                                      |
| Physician decision                     | 4                                                       |
| Disease progression                    | 41                                                      |
| Adverse event, non-fatal               | 31                                                      |
| Health authority/Study termination     | 3                                                       |
| Participants who received no treatment | 3                                                       |
| Protocol deviation                     | 5                                                       |

## Period 2

|                              |                         |
|------------------------------|-------------------------|
| Period 2 title               | Maintenance Phase       |
| Is this the baseline period? | No                      |
| Allocation method            | Randomised - controlled |
| Blinding used                | Not blinded             |

## Arms

|                              |                                |
|------------------------------|--------------------------------|
| Are arms mutually exclusive? | Yes                            |
| <b>Arm title</b>             | Maintenance Phase: Bevacizumab |

### Arm description:

During the Initial Phase all participants received bevacizumab 15 mg/kg IV on Day 1 of each 3 week cycle for a minimum of 3 cycles and a maximum of 6 cycles or until disease progression, unacceptable toxicity or participant request for withdrawal, whichever occurred first along with docetaxel, a recommended dose of 100 mg/m<sup>2</sup> IV administered on Day 1 of each cycle. Doses of 75 to 100 mg/m<sup>2</sup> of docetaxel could be administered at investigator's discretion. At the end of the Initial Phase, participants with an objective response (PR or CR) or SD received 15 mg/kg bevacizumab IV on Day 1 of each 3 week cycle until disease progression, unacceptable toxicity, participant request for withdrawal or end of study, whichever occurred first.

|                                        |                       |
|----------------------------------------|-----------------------|
| Arm type                               | Active comparator     |
| Investigational medicinal product name | Bevacizumab           |
| Investigational medicinal product code |                       |
| Other name                             |                       |
| Pharmaceutical forms                   | Solution for infusion |
| Routes of administration               | Intravenous use       |

### Dosage and administration details:

During the Initial Phase all participants received bevacizumab 15 mg/kg IV on Day 1 of each 3 week cycle for a minimum of 3 cycles and a maximum of 6 cycles or until disease progression, unacceptable toxicity or participant request for withdrawal, whichever occurred first.

|                                        |                       |
|----------------------------------------|-----------------------|
| Investigational medicinal product name | Docetaxel             |
| Investigational medicinal product code |                       |
| Other name                             |                       |
| Pharmaceutical forms                   | Solution for infusion |

|                          |                 |
|--------------------------|-----------------|
| Routes of administration | Intravenous use |
|--------------------------|-----------------|

Dosage and administration details:

Participants received docetaxel, a recommended dose of 100 mg/m<sup>2</sup> IV administered on Day 1 of each cycle. Doses of 75 to 100 mg/m<sup>2</sup> of docetaxel could be administered at investigator's discretion.

|                  |                                               |
|------------------|-----------------------------------------------|
| <b>Arm title</b> | Maintenance Phase: Bevacizumab + Capecitabine |
|------------------|-----------------------------------------------|

Arm description:

During the Initial Phase participants received bevacizumab 15 mg/kg IV on Day 1 of each 3 week cycle for a minimum of 3 cycles and a maximum of 6 cycles or until disease progression, unacceptable toxicity or withdrawal, whichever occurred first, along with docetaxel, a recommended dose of 100 mg/m<sup>2</sup> IV administered on Day 1 of each cycle. Doses of 75 to 100 mg/m<sup>2</sup> of docetaxel could be administered at investigator's discretion. At the end of the Initial Phase, participants with an objective response were randomized to receive bevacizumab 15 mg/kg IV on Day 1 of each 3-week cycle plus capecitabine 1000 mg/m<sup>2</sup> twice daily on Days 1 to 14 of each 3 week cycle until disease progression, unacceptable toxicity, request for withdrawal or end of study, whichever occurred first. If one of the drugs was discontinued before disease progression, treatment was continued with the second drug until disease progression, unacceptable toxicity, withdrawal or end of study, whichever occurred first.

|                                        |                       |
|----------------------------------------|-----------------------|
| Arm type                               | Experimental          |
| Investigational medicinal product name | Bevacizumab           |
| Investigational medicinal product code |                       |
| Other name                             |                       |
| Pharmaceutical forms                   | Solution for infusion |
| Routes of administration               | Intravenous use       |

Dosage and administration details:

During the Initial Phase all participants received bevacizumab 15 milligrams per kilogram (mg/kg) intravenously (IV) on Day 1 of each 3 week cycle for a minimum of 3 cycles and a maximum of 6 cycles or until disease progression, unacceptable toxicity or participant request for withdrawal, whichever occurred first.

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

Dosage and administration details:

Participants received docetaxel, a recommended dose of 100 mg/m<sup>2</sup> IV administered on Day 1 of each cycle. Doses of 75 to 100 mg/m<sup>2</sup> of docetaxel could be administered at investigator's discretion.

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

Dosage and administration details:

Participants received capecitabine 1000 mg/m<sup>2</sup> twice daily on Days 1 to 14 of each 3 week cycle until disease progression, unacceptable toxicity, request for withdrawal or end of study, whichever occurred first.

| Number of subjects in period 2            | Maintenance Phase:<br>Bevacizumab | Maintenance Phase:<br>Bevacizumab +<br>Capecitabine |
|-------------------------------------------|-----------------------------------|-----------------------------------------------------|
|                                           |                                   |                                                     |
| Started                                   | 94                                | 91                                                  |
| Completed                                 | 0                                 | 0                                                   |
| Not completed                             | 94                                | 91                                                  |
| Consent withdrawn by subject              | 2                                 | 6                                                   |
| Physician decision                        | 2                                 | 1                                                   |
| Disease progression                       | 73                                | 60                                                  |
| Adverse event, non-fatal                  | 9                                 | 12                                                  |
| Health authority/Study termination        | 1                                 | 2                                                   |
| Treatment ongoing at study<br>termination | -                                 | 10                                                  |
| Change of treatment                       | 4                                 | -                                                   |
| Participant not treated                   | 2                                 | -                                                   |
| Protocol deviation                        | 1                                 | -                                                   |

## Baseline characteristics

### Reporting groups

|                       |                         |
|-----------------------|-------------------------|
| Reporting group title | Initial Treatment Phase |
|-----------------------|-------------------------|

Reporting group description:

During the Initial Phase all participants received bevacizumab 15 mg/kg IV on Day 1 of each 3 week cycle for a minimum of 3 cycles and a maximum of 6 cycles or until disease progression, unacceptable toxicity or participant request for withdrawal, whichever occurred first. Participants also received docetaxel, a recommended dose of 100 mg/m<sup>2</sup> IV administered on Day 1 of each cycle. Doses of 75 to 100 mg/m<sup>2</sup> of docetaxel could be administered at investigator's discretion. At the end of the Initial Treatment Phase, participants with an objective response (PR or CR) or SD following 3-6 cycles of bevacizumab + docetaxel were randomized to receive maintenance therapy with either bevacizumab alone or bevacizumab + capecitabine.

| Reporting group values                                                  | Initial Treatment Phase | Total |  |
|-------------------------------------------------------------------------|-------------------------|-------|--|
| Number of subjects                                                      | 287                     | 287   |  |
| Age categorical<br>Units: Subjects                                      |                         |       |  |
| Age continuous<br>Units: years<br>arithmetic mean<br>standard deviation | 52.5<br>± 11.8          | -     |  |
| Gender categorical<br>Units: Subjects                                   |                         |       |  |
| Female                                                                  | 287                     | 287   |  |
| Male                                                                    | 0                       | 0     |  |



## End points

### End points reporting groups

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                         |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------|
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | Initial Treatment Phase: Bevacizumab Plus (+) Docetaxel |
| Reporting group description:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                                         |
| During the Initial Phase all participants received bevacizumab 15 milligrams per kilogram (mg/kg) intravenously (IV) on Day 1 of each 3 week cycle for a minimum of 3 cycles and a maximum of 6 cycles or until disease progression, unacceptable toxicity or participant request for withdrawal, whichever occurred first. Participants also received docetaxel, a recommended dose of 100 milligrams per square meter (mg/m <sup>2</sup> ) IV administered on Day 1 of each cycle. Doses of 75 to 100 mg/m <sup>2</sup> of docetaxel could be administered at investigator's discretion. At the end of the Initial Treatment Phase, participants with an objective response (partial response [PR] or complete response [CR]) or stable disease (SD) following 3-6 cycles of bevacizumab + docetaxel were randomized to receive maintenance therapy with either bevacizumab alone or bevacizumab + capecitabine.                                                                                                                                                  |                                                         |
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | Maintenance Phase: Bevacizumab                          |
| Reporting group description:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                                         |
| During the Initial Phase all participants received bevacizumab 15 mg/kg IV on Day 1 of each 3 week cycle for a minimum of 3 cycles and a maximum of 6 cycles or until disease progression, unacceptable toxicity or participant request for withdrawal, whichever occurred first along with docetaxel, a recommended dose of 100 mg/m <sup>2</sup> IV administered on Day 1 of each cycle. Doses of 75 to 100 mg/m <sup>2</sup> of docetaxel could be administered at investigator's discretion. At the end of the Initial Phase, participants with an objective response (PR or CR) or SD received 15 mg/kg bevacizumab IV on Day 1 of each 3 week cycle until disease progression, unacceptable toxicity, participant request for withdrawal or end of study, whichever occurred first.                                                                                                                                                                                                                                                                           |                                                         |
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | Maintenance Phase: Bevacizumab + Capecitabine           |
| Reporting group description:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                                         |
| During the Initial Phase participants received bevacizumab 15 mg/kg IV on Day 1 of each 3 week cycle for a minimum of 3 cycles and a maximum of 6 cycles or until disease progression, unacceptable toxicity or withdrawal, whichever occurred first, along with docetaxel, a recommended dose of 100 mg/m <sup>2</sup> IV administered on Day 1 of each cycle. Doses of 75 to 100 mg/m <sup>2</sup> of docetaxel could be administered at investigator's discretion. At the end of the Initial Phase, participants with an objective response were randomized to receive bevacizumab 15 mg/kg IV on Day 1 of each 3-week cycle plus capecitabine 1000 mg/m <sup>2</sup> twice daily on Days 1 to 14 of each 3 week cycle until disease progression, unacceptable toxicity, request for withdrawal or end of study, whichever occurred first. If one of the drugs was discontinued before disease progression, treatment was continued with the second drug until disease progression, unacceptable toxicity, withdrawal or end of study, whichever occurred first. |                                                         |

### Primary: Percentage of Participants With Disease Progression or Death (Maintenance Phase Data Cutoff October 4, 2013)

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                             |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Percentage of Participants With Disease Progression or Death (Maintenance Phase Data Cutoff October 4, 2013) <sup>[1]</sup> |
| End point description:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                             |
| Progression Free Survival (PFS) was defined as the time from first study drug dosing (during the maintenance treatment phase) to the first documented disease progression or death, whichever occurred first. Progression was based on tumor assessment made by the investigators according to the Response Evaluation Criteria In Solid Tumors (RECIST). Progressive Disease (PD) was defined as a 20 percent (%) or greater increase in the sum of the Longest Diameter (LD) of the target lesions taking as reference the smallest sum LD recorded or appearance of new lesions. |                                                                                                                             |
| End point type                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | Primary                                                                                                                     |
| End point timeframe:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                             |
| Randomization, at the end of every third cycle (every 9 weeks) until the end of maintenance phase and every 3 months until disease progression or death until data cutoff on October 4, 2013, up to 4 year                                                                                                                                                                                                                                                                                                                                                                          |                                                                                                                             |
| 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: Statistical analysis was performed for Progression free survival which is defined as survival without disease progression or death.                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                                                             |

| End point values                  | Maintenance Phase: Bevacizumab | Maintenance Phase: Bevacizumab + Capecitabine |  |  |
|-----------------------------------|--------------------------------|-----------------------------------------------|--|--|
| Subject group type                | Reporting group                | Reporting group                               |  |  |
| Number of subjects analysed       | 94                             | 91                                            |  |  |
| Units: percentage of participants |                                |                                               |  |  |
| number (not applicable)           | 88.3                           | 75.8                                          |  |  |

## Statistical analyses

No statistical analyses for this end point

## Primary: Progression Free Survival (Maintenance Phase Data Cutoff October 4, 2013)

|                 |                                                                           |
|-----------------|---------------------------------------------------------------------------|
| End point title | Progression Free Survival (Maintenance Phase Data Cutoff October 4, 2013) |
|-----------------|---------------------------------------------------------------------------|

End point description:

PFS was defined as time from first study drug during the maintenance treatment phase dosing to first documented disease progression or death, whichever occurred first. Time to progression was defined as time from randomization to first documented disease progression defined per RECIST 1.0 criteria. Participants without an event at data cut-off or who were withdrawn from study without documented progression were censored at date of last tumor assessment when participant was known to be progression free. Participants who took other non-protocol anti-cancer drugs while being on study medication, and who were still event free were censored on date of first dose of anti-cancer drug. Participants without post-randomization tumor assessments but alive were censored at the time of randomization. Participants without post-randomization assessments, who died after randomization were considered to have the PFS event at date of death. Kaplan-Meier estimation was used for median time to PFS.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Randomization, at the end of every third cycle (every 9 weeks) until the end of maintenance phase and every 3 months until disease progression or death until data cutoff on October 4, 2013, up to 4 years

| End point values                 | Maintenance Phase: Bevacizumab | Maintenance Phase: Bevacizumab + Capecitabine |  |  |
|----------------------------------|--------------------------------|-----------------------------------------------|--|--|
| Subject group type               | Reporting group                | Reporting group                               |  |  |
| Number of subjects analysed      | 94                             | 91                                            |  |  |
| Units: months                    |                                |                                               |  |  |
| median (confidence interval 95%) | 4.3 (3.9 to 6.8)               | 11.9 (9.8 to 15.4)                            |  |  |

## Statistical analyses

|                            |                        |
|----------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 1 |
|----------------------------|------------------------|

Statistical analysis description:

Stratified by estrogen receptor (ER) status, visceral metastasis (yes/no), response to initial phase, and lactate dehydrogenase (LDH) level.

|                                         |                                                                                |
|-----------------------------------------|--------------------------------------------------------------------------------|
| Comparison groups                       | Maintenance Phase: Bevacizumab v Maintenance Phase: Bevacizumab + Capecitabine |
| Number of subjects included in analysis | 185                                                                            |
| Analysis specification                  | Pre-specified                                                                  |
| Analysis type                           | other                                                                          |
| P-value                                 | < 0.0001                                                                       |
| Method                                  | Logrank                                                                        |
| Parameter estimate                      | Hazard ratio (HR)                                                              |
| Point estimate                          | 0.383                                                                          |
| Confidence interval                     |                                                                                |
| level                                   | 95 %                                                                           |
| sides                                   | 2-sided                                                                        |
| lower limit                             | 0.266                                                                          |
| upper limit                             | 0.551                                                                          |

### Secondary: Percentage of Participants With Best Overall Confirmed Objective Response of CR or PR Per RECIST 1.0 (Maintenance Phase Data Cutoff October 4, 2013)

|                 |                                                                                                                                                      |
|-----------------|------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Percentage of Participants With Best Overall Confirmed Objective Response of CR or PR Per RECIST 1.0 (Maintenance Phase Data Cutoff October 4, 2013) |
|-----------------|------------------------------------------------------------------------------------------------------------------------------------------------------|

#### End point description:

Objective Response was determined by the investigator using modified RECIST criteria, Version 1.0. An objective response was a complete or partial overall confirmed response as determined by investigators. CR was defined as complete disappearance of all target and non-target lesions and no new lesions. PR was defined as greater than or equal to ( $\geq$ ) 30 % decrease in the sum of appropriate diameters of all target measurable lesions, no progress in the non-measurable disease, and no new lesions. PD was defined as 20% increase in the sum of the longest diameter of target lesions and SD was defined as small changes that do not meet above criteria. Pearson-Clopper one-sample method was used for confidence intervals (CIs).

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

#### End point timeframe:

Randomization, at the end of every third cycle (every 9 weeks) until the end of maintenance phase and every 3 months until disease progression or death until data cutoff on October 4, 2013, up to 4 years

| End point values                  | Maintenance Phase: Bevacizumab | Maintenance Phase: Bevacizumab + Capecitabine |  |  |
|-----------------------------------|--------------------------------|-----------------------------------------------|--|--|
| Subject group type                | Reporting group                | Reporting group                               |  |  |
| Number of subjects analysed       | 94                             | 91                                            |  |  |
| Units: percentage of participants |                                |                                               |  |  |
| number (confidence interval 95%)  | 76.6 (66.7 to 84.7)            | 85.7 (76.8 to 92.2)                           |  |  |

### Statistical analyses

|                                         |                                                                                   |
|-----------------------------------------|-----------------------------------------------------------------------------------|
| <b>Statistical analysis title</b>       | Statistical Analysis 1                                                            |
| Comparison groups                       | Maintenance Phase: Bevacizumab + Capecitabine v<br>Maintenance Phase: Bevacizumab |
| Number of subjects included in analysis | 185                                                                               |
| Analysis specification                  | Pre-specified                                                                     |
| Analysis type                           | other                                                                             |
| P-value                                 | = 0.113                                                                           |
| Method                                  | Chi-squared                                                                       |
| Parameter estimate                      | Mean difference (final values)                                                    |
| Point estimate                          | 9.1                                                                               |
| Confidence interval                     |                                                                                   |
| level                                   | 95 %                                                                              |
| sides                                   | 2-sided                                                                           |
| lower limit                             | -2.1                                                                              |
| upper limit                             | 20.3                                                                              |

### Secondary: Percentage of Participants With Clinical Benefit (CR, PR and SD) Per RECIST 1.0 (Data Cutoff October 4, 2013)

|                 |                                                                                                               |
|-----------------|---------------------------------------------------------------------------------------------------------------|
| End point title | Percentage of Participants With Clinical Benefit (CR, PR and SD) Per RECIST 1.0 (Data Cutoff October 4, 2013) |
|-----------------|---------------------------------------------------------------------------------------------------------------|

End point description:

CR was defined as complete disappearance of all target and non-target lesions and no new lesions. PR was defined as  $\geq 30\%$  decrease in the sum of appropriate diameters of all target measurable lesions, no progress in the non-measurable disease, and no new lesions. SD was defined as small changes that do not meet above criteria with Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Randomization, at the end of every third cycle (every 9 weeks) until the end of maintenance phase and every 3 months until disease progression or death until data cutoff on October 4, 2013, up to 4 years

|                                   |                                |                                               |  |  |
|-----------------------------------|--------------------------------|-----------------------------------------------|--|--|
| <b>End point values</b>           | Maintenance Phase: Bevacizumab | Maintenance Phase: Bevacizumab + Capecitabine |  |  |
| Subject group type                | Reporting group                | Reporting group                               |  |  |
| Number of subjects analysed       | 94                             | 91                                            |  |  |
| Units: percentage of participants |                                |                                               |  |  |
| number (confidence interval 95%)  | 97.9 (92.5 to 99.7)            | 98.9 (94 to 100)                              |  |  |

### Statistical analyses

|                                   |                                                                                |
|-----------------------------------|--------------------------------------------------------------------------------|
| <b>Statistical analysis title</b> | Statistical Analysis 1                                                         |
| Comparison groups                 | Maintenance Phase: Bevacizumab v Maintenance Phase: Bevacizumab + Capecitabine |

|                                         |                                |
|-----------------------------------------|--------------------------------|
| Number of subjects included in analysis | 185                            |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | other                          |
| P-value                                 | = 0.58                         |
| Method                                  | Chi-squared                    |
| Parameter estimate                      | Mean difference (final values) |
| Point estimate                          | 1                              |
| Confidence interval                     |                                |
| level                                   | 95 %                           |
| sides                                   | 2-sided                        |
| lower limit                             | -2.6                           |
| upper limit                             | 4.6                            |

### Secondary: Percentage of Participants Who Died (Maintenance Phase Data Cutoff October 4, 2013)

|                 |                                                                                     |
|-----------------|-------------------------------------------------------------------------------------|
| End point title | Percentage of Participants Who Died (Maintenance Phase Data Cutoff October 4, 2013) |
|-----------------|-------------------------------------------------------------------------------------|

End point description:

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Randomization, at the end of every third cycle (every 9 weeks) until the end of maintenance phase and every 3 months until disease progression or death until data cutoff on October 4, 2013, up to 4 years

| End point values                  | Maintenance Phase:<br>Bevacizumab | Maintenance Phase:<br>Bevacizumab +<br>Capecitabine |  |  |
|-----------------------------------|-----------------------------------|-----------------------------------------------------|--|--|
| Subject group type                | Reporting group                   | Reporting group                                     |  |  |
| Number of subjects analysed       | 94                                | 91                                                  |  |  |
| Units: percentage of participants |                                   |                                                     |  |  |
| number (not applicable)           | 56.4                              | 36.3                                                |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Overall Survival (Maintenance Phase Data Cutoff October 4, 2013)

|                 |                                                                  |
|-----------------|------------------------------------------------------------------|
| End point title | Overall Survival (Maintenance Phase Data Cutoff October 4, 2013) |
|-----------------|------------------------------------------------------------------|

End point description:

Duration of Overall Survival (OS) was defined as the time from randomization to death of any cause. The OS data for participants for whom no death was captured in the clinical database were censored at the last time they were known to be alive. Kaplan Meier estimation was used to determine OS. A value of 999 represents that the upper limit of the confidence interval was inestimable.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Randomization, at the end of every third cycle (every 9 weeks) until the end of maintenance phase and every 3 months until disease progression or death until data cutoff on October 4, 2013, up to 4 years

| <b>End point values</b>          | Maintenance Phase: Bevacizumab | Maintenance Phase: Bevacizumab + Capecitabine |  |  |
|----------------------------------|--------------------------------|-----------------------------------------------|--|--|
| Subject group type               | Reporting group                | Reporting group                               |  |  |
| Number of subjects analysed      | 94                             | 91                                            |  |  |
| Units: Months                    |                                |                                               |  |  |
| median (confidence interval 95%) | 23.7 (18.5 to 31.7)            | 39 (32.3 to 999)                              |  |  |

### Statistical analyses

| <b>Statistical analysis title</b>       | Statistical Analysis 1                                                         |
|-----------------------------------------|--------------------------------------------------------------------------------|
| Comparison groups                       | Maintenance Phase: Bevacizumab + Capecitabine v Maintenance Phase: Bevacizumab |
| Number of subjects included in analysis | 185                                                                            |
| Analysis specification                  | Pre-specified                                                                  |
| Analysis type                           | other                                                                          |
| P-value                                 | < 0.0003 [2]                                                                   |
| Method                                  | Logrank                                                                        |
| Parameter estimate                      | Hazard ratio (HR)                                                              |
| Point estimate                          | 0.425                                                                          |
| Confidence interval                     |                                                                                |
| level                                   | 95 %                                                                           |
| sides                                   | 2-sided                                                                        |
| lower limit                             | 0.263                                                                          |
| upper limit                             | 0.685                                                                          |

Notes:

[2] - Stratified by ER status, visceral metastasis (yes/no), response to initial phase, and LDH level.

| <b>Statistical analysis title</b>       | Statistical Analysis 2                                                         |
|-----------------------------------------|--------------------------------------------------------------------------------|
| Comparison groups                       | Maintenance Phase: Bevacizumab v Maintenance Phase: Bevacizumab + Capecitabine |
| Number of subjects included in analysis | 185                                                                            |
| Analysis specification                  | Pre-specified                                                                  |
| Analysis type                           | other                                                                          |
| P-value                                 | = 0.002 [3]                                                                    |
| Method                                  | Logrank                                                                        |
| Parameter estimate                      | Hazard ratio (HR)                                                              |
| Point estimate                          | 0.516                                                                          |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | 0.334   |
| upper limit         | 0.798   |

Notes:

[3] - Unstratified analysis

### Secondary: Percentage of Participants Expected to Be Alive After 1 and 2 Years on Treatment (Maintenance Phase Data Cutoff October 4, 2013)

|                 |                                                                                                                                  |
|-----------------|----------------------------------------------------------------------------------------------------------------------------------|
| End point title | Percentage of Participants Expected to Be Alive After 1 and 2 Years on Treatment (Maintenance Phase Data Cutoff October 4, 2013) |
|-----------------|----------------------------------------------------------------------------------------------------------------------------------|

End point description:

Probability of being alive after 1 and 2 years on treatment with 95% CIs was calculated using Kaplan Meier approach with LOGLOG transformation.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Years 1 and 2

| End point values                  | Maintenance Phase: Bevacizumab | Maintenance Phase: Bevacizumab + Capecitabine |  |  |
|-----------------------------------|--------------------------------|-----------------------------------------------|--|--|
| Subject group type                | Reporting group                | Reporting group                               |  |  |
| Number of subjects analysed       | 94                             | 91                                            |  |  |
| Units: percentage of participants |                                |                                               |  |  |
| number (confidence interval 95%)  |                                |                                               |  |  |
| 1 Year                            | 71.6 (61.1 to 79.7)            | 90.4 (81.8 to 95.1)                           |  |  |
| 2 Years                           | 49.4 (38.5 to 59.3)            | 69 (57.6 to 77.9)                             |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage Of Participants With PD or Death Due to PD (Maintenance Phase Data Cutoff October 4, 2013)

|                 |                                                                                                       |
|-----------------|-------------------------------------------------------------------------------------------------------|
| End point title | Percentage Of Participants With PD or Death Due to PD (Maintenance Phase Data Cutoff October 4, 2013) |
|-----------------|-------------------------------------------------------------------------------------------------------|

End point description:

PD was defined per RECIST version 1.0 as 20% increase in the sum of the longest diameter of target lesions.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Randomization, at the end of every third cycle (every 9 weeks) until the end of maintenance phase and every 3 months until disease progression or death until data cutoff on October 4, 2013

| <b>End point values</b>           | Maintenance Phase:<br>Bevacizumab | Maintenance Phase:<br>Bevacizumab +<br>Capecitabine |  |  |
|-----------------------------------|-----------------------------------|-----------------------------------------------------|--|--|
| Subject group type                | Reporting group                   | Reporting group                                     |  |  |
| Number of subjects analysed       | 94                                | 91                                                  |  |  |
| Units: percentage of participants |                                   |                                                     |  |  |
| number (not applicable)           | 88.3                              | 74.7                                                |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Time To Progression (Maintenance Phase Data Cutoff October 4, 2013)

|                 |                                                                     |
|-----------------|---------------------------------------------------------------------|
| End point title | Time To Progression (Maintenance Phase Data Cutoff October 4, 2013) |
|-----------------|---------------------------------------------------------------------|

End point description:

Time to Progression was defined as the time from randomization to the first documented disease progression (using investigator assessments of disease progression by RECIST 1.0). PD was defined as 20% increase in the sum of the longest diameter of target lesions.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Randomization, at the end of every third cycle (every 9 weeks) until the end of maintenance phase and every 3 months until disease progression or death until data cutoff on October 4, 2013

| <b>End point values</b>          | Maintenance Phase:<br>Bevacizumab | Maintenance Phase:<br>Bevacizumab +<br>Capecitabine |  |  |
|----------------------------------|-----------------------------------|-----------------------------------------------------|--|--|
| Subject group type               | Reporting group                   | Reporting group                                     |  |  |
| Number of subjects analysed      | 94                                | 91                                                  |  |  |
| Units: Months                    |                                   |                                                     |  |  |
| median (confidence interval 95%) | 4.3 (3.9 to 6.8)                  | 11.9 (9.8 to 15.4)                                  |  |  |

## Statistical analyses

|                                   |                                                                                |
|-----------------------------------|--------------------------------------------------------------------------------|
| <b>Statistical analysis title</b> | Statistical Analysis 1                                                         |
| Comparison groups                 | Maintenance Phase: Bevacizumab v Maintenance Phase: Bevacizumab + Capecitabine |



|                                         |                         |
|-----------------------------------------|-------------------------|
| Number of subjects included in analysis | 185                     |
| Analysis specification                  | Pre-specified           |
| Analysis type                           | other                   |
| P-value                                 | < 0.0001 <sup>[4]</sup> |
| Method                                  | Logrank                 |
| Parameter estimate                      | Hazard ratio (HR)       |
| Point estimate                          | 0.383                   |
| Confidence interval                     |                         |
| level                                   | 95 %                    |
| sides                                   | 2-sided                 |
| lower limit                             | 0.266                   |
| upper limit                             | 0.551                   |

Notes:

[4] - Stratified by ER status, visceral metastasis (yes/no), response to initial phase, and LDH level.

|                                         |                                                                                |
|-----------------------------------------|--------------------------------------------------------------------------------|
| <b>Statistical analysis title</b>       | Statistical Analysis 2                                                         |
| Comparison groups                       | Maintenance Phase: Bevacizumab v Maintenance Phase: Bevacizumab + Capecitabine |
| Number of subjects included in analysis | 185                                                                            |
| Analysis specification                  | Pre-specified                                                                  |
| Analysis type                           | other                                                                          |
| P-value                                 | < 0.0001 <sup>[5]</sup>                                                        |
| Method                                  | Logrank                                                                        |
| Parameter estimate                      | Hazard ratio (HR)                                                              |
| Point estimate                          | 0.425                                                                          |
| Confidence interval                     |                                                                                |
| level                                   | 95 %                                                                           |
| sides                                   | 2-sided                                                                        |
| lower limit                             | 0.305                                                                          |
| upper limit                             | 0.591                                                                          |

Notes:

[5] - Unstratified analysis

### **Secondary: Quality of Life Assessed As Change From Baseline in Global Health Status Using The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - 30 (EORTC QLQ - C30) (Maintenance Phase Data Cutoff October 4, 2013)**

|                 |                                                                                                                                                                                                                                                    |
|-----------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Quality of Life Assessed As Change From Baseline in Global Health Status Using The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - 30 (EORTC QLQ - C30) (Maintenance Phase Data Cutoff October 4, 2013) |
|-----------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

The EORTC QLQ-C30 incorporates 9 multi-item scales: 5 functional scales (physical, role, cognitive, emotional, and social); 9 symptom scales (fatigue, pain, nausea and vomiting, dyspnoea, insomnia, appetite loss, constipation, diarrhea and financial difficulties); and a global health and quality-of-life scale. Most questions used 4 point scale (1 'Not at all' to 4 'Very much'; 2 questions used 7-point scale (1 'very poor' to 7 'Excellent'). Scores were averaged and transformed to 0-100 scale; higher score=better level of functioning or greater degree of symptoms. The change in global health status was determined to be the difference in values at baseline and each specific visit. The term "baseline" refers to the time of randomization to the maintenance phase. Only timepoints with more than 10 participants in each treatment arm are presented. n=number of participants analyzed at the specific visit.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Randomization and Cycles 3, 6, 9 and 12

| End point values                 | Maintenance Phase:<br>Bevacizumab | Maintenance Phase:<br>Bevacizumab +<br>Capecitabine |  |  |
|----------------------------------|-----------------------------------|-----------------------------------------------------|--|--|
| Subject group type               | Reporting group                   | Reporting group                                     |  |  |
| Number of subjects analysed      | 83                                | 86                                                  |  |  |
| Units: units on a scale          |                                   |                                                     |  |  |
| number (confidence interval 95%) |                                   |                                                     |  |  |
| Randomization (n= 83, 86)        | -3.51 (-9.63 to 2.6)              | -4.46 (-9.4 to 0.48)                                |  |  |
| Cycle 3 (n= 44, 52)              | 0.76 (-6.65 to 8.17)              | -3.21 (-9.99 to 3.58)                               |  |  |
| Cycle 6 (n= 26, 54)              | 4.17 (-6.49 to 14.82)             | -5.4 (-11.67 to 0.87)                               |  |  |
| Cycle 9 (n= 18, 37)              | 8.8 (-4.57 to 22.17)              | -1.8 (-8.92 to 5.32)                                |  |  |
| Cycle 12 (n= 12, 31)             | 0.69 (-17.99 to 19.37)            | 0 (-8.24 to 8.24)                                   |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Participants With Best Overall Confirmed Objective Response of CR or PR Per RECIST 1.0 (Initial Treatment Phase)

|                 |                                                                                                                                |
|-----------------|--------------------------------------------------------------------------------------------------------------------------------|
| End point title | Percentage of Participants With Best Overall Confirmed Objective Response of CR or PR Per RECIST 1.0 (Initial Treatment Phase) |
|-----------------|--------------------------------------------------------------------------------------------------------------------------------|

End point description:

Objective Response was determined by the investigator using RECIST criteria, Version 1.0. An objective response was a complete or partial overall confirmed response as determined by investigators. CR was defined as complete disappearance of all target and non-target lesions and no new lesions. PR was defined as  $\geq 30\%$  decrease in the sum of appropriate diameters of all target measurable lesions, no progress in the non-measurable disease, and no new lesions. Pearson-Clopper one-sample method was used for CI. Only participants who were not randomized at the end of the initial treatment phase were included in this analysis

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Screening and at the end of every third cycle until randomization for an average of 18 weeks

|                                   |                                                         |  |  |  |
|-----------------------------------|---------------------------------------------------------|--|--|--|
| <b>End point values</b>           | Initial Treatment Phase: Bevacizumab Plus (+) Docetaxel |  |  |  |
| Subject group type                | Reporting group                                         |  |  |  |
| Number of subjects analysed       | 102                                                     |  |  |  |
| Units: percentage of participants |                                                         |  |  |  |
| number (confidence interval 95%)  | 8.8 (4.1 to 16.1)                                       |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Participants With Clinical Benefit (CR, PR and SD) Per RECIST 1.0 (Initial Treatment Phase)

|                 |                                                                                                           |
|-----------------|-----------------------------------------------------------------------------------------------------------|
| End point title | Percentage of Participants With Clinical Benefit (CR, PR and SD) Per RECIST 1.0 (Initial Treatment Phase) |
|-----------------|-----------------------------------------------------------------------------------------------------------|

End point description:

CR was defined as complete disappearance of all target and non-target lesions and no new lesions. PR was defined as  $\geq 30\%$  decrease in the sum of appropriate diameters of all target measurable lesions, no progress in the non-measurable disease, and no new lesions. SD was defined as small changes that do not meet above criteria. Only participants who were not randomized at the end of the initial treatment phase were included in this analysis.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Screening and at the end of every third cycle until randomization for an average of 18 weeks

|                                   |                                                         |  |  |  |
|-----------------------------------|---------------------------------------------------------|--|--|--|
| <b>End point values</b>           | Initial Treatment Phase: Bevacizumab Plus (+) Docetaxel |  |  |  |
| Subject group type                | Reporting group                                         |  |  |  |
| Number of subjects analysed       | 102                                                     |  |  |  |
| Units: percentage of participants |                                                         |  |  |  |
| number (confidence interval 95%)  | 56.9 (46.7 to 66.6)                                     |  |  |  |

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Adverse Events (AEs) were recorded from the date of randomization until the end of study at the cutoff date of October 4, 2013.

Adverse event reporting additional description:

AEs were recorded for the Safety population (all participants who received at least one dose of study drug during the maintenance phase). Only Grade 3 and above AEs have been captured per protocol.

|                 |                |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 16.0 |
|--------------------|------|

### Reporting groups

|                       |                                                  |
|-----------------------|--------------------------------------------------|
| Reporting group title | Initial Treatment Phase: Bevacizumab + Docetaxel |
|-----------------------|--------------------------------------------------|

Reporting group description:

During the Initial Phase all participants received bevacizumab 15 mg/kg IV on Day 1 of each 3 week cycle for a minimum of 3 cycles and a maximum of 6 cycles or until disease progression, unacceptable toxicity or participant request for withdrawal, whichever occurred first. Participants also received docetaxel, a recommended dose of 100 mg/m<sup>2</sup> IV administered on Day 1 of each cycle. Doses of 75 to 100 mg/m<sup>2</sup> of docetaxel could be administered at investigator's discretion. At the end of the Initial Treatment Phase, participants with an objective response (PR or CR) or SD following 3-6 cycles of bevacizumab + docetaxel were randomized to receive maintenance therapy with either bevacizumab alone or bevacizumab + capecitabine.

|                       |                                |
|-----------------------|--------------------------------|
| Reporting group title | Maintenance Phase: Bevacizumab |
|-----------------------|--------------------------------|

Reporting group description:

During the Initial Phase all participants received bevacizumab 15 mg/kg IV on Day 1 of each 3 week cycle for a minimum of 3 cycles and a maximum of 6 cycles or until disease progression, unacceptable toxicity or participant request for withdrawal, whichever occurred first along with docetaxel, a recommended dose of 100 mg/m<sup>2</sup> IV administered on Day 1 of each cycle. Doses of 75 to 100 mg/m<sup>2</sup> of docetaxel could be administered at investigator's discretion. At the end of the Initial Phase, participants with an objective response (PR or CR) or SD received 15 mg/kg bevacizumab IV on Day 1 of each 3 week cycle until disease progression, unacceptable toxicity, participant request for withdrawal or end of study, whichever occurred first.

|                       |                                               |
|-----------------------|-----------------------------------------------|
| Reporting group title | Maintenance Phase: Bevacizumab + Capecitabine |
|-----------------------|-----------------------------------------------|

Reporting group description:

During the Initial Phase participants received bevacizumab 15 mg/kg IV on Day 1 of each 3 week cycle for a minimum of 3 cycles and a maximum of 6 cycles or until disease progression, unacceptable toxicity or withdrawal, whichever occurred first, along with docetaxel, a recommended dose of 100 mg/m<sup>2</sup> IV administered on Day 1 of each cycle. Doses of 75 to 100 mg/m<sup>2</sup> of docetaxel could be administered at investigator's discretion. At the end of the Initial Phase, participants with an objective response were randomized to receive bevacizumab 15 mg/kg IV on Day 1 of each 3-week cycle plus capecitabine 1000 mg/m<sup>2</sup> twice daily on Days 1 to 14 of each 3 week cycle until disease progression, unacceptable toxicity, request for withdrawal or end of study, whichever occurred first. If one of the drugs was discontinued before disease progression, treatment was continued with the second drug until disease progression, unacceptable toxicity, withdrawal or end of study, whichever occurred first.

| Serious adverse events                            | Initial Treatment Phase: Bevacizumab + Docetaxel | Maintenance Phase: Bevacizumab | Maintenance Phase: Bevacizumab + Capecitabine |
|---------------------------------------------------|--------------------------------------------------|--------------------------------|-----------------------------------------------|
| Total subjects affected by serious adverse events |                                                  |                                |                                               |
| subjects affected / exposed                       | 78 / 284 (27.46%)                                | 7 / 92 (7.61%)                 | 10 / 91 (10.99%)                              |
| number of deaths (all causes)                     | 54                                               | 51                             | 33                                            |
| number of deaths resulting from adverse events    |                                                  |                                |                                               |

|                                                                     |                 |                |                |
|---------------------------------------------------------------------|-----------------|----------------|----------------|
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                 |                |                |
| Large cell lung cancer                                              |                 |                |                |
| subjects affected / exposed                                         | 1 / 284 (0.35%) | 0 / 92 (0.00%) | 0 / 91 (0.00%) |
| occurrences causally related to treatment / all                     | 0 / 1           | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all                          | 0 / 0           | 0 / 0          | 0 / 0          |
| Vascular disorders                                                  |                 |                |                |
| Hypertension                                                        |                 |                |                |
| subjects affected / exposed                                         | 0 / 284 (0.00%) | 0 / 92 (0.00%) | 1 / 91 (1.10%) |
| occurrences causally related to treatment / all                     | 0 / 0           | 0 / 0          | 1 / 1          |
| deaths causally related to treatment / all                          | 0 / 0           | 0 / 0          | 1 / 1          |
| Embolism                                                            |                 |                |                |
| subjects affected / exposed                                         | 1 / 284 (0.35%) | 1 / 92 (1.09%) | 0 / 91 (0.00%) |
| occurrences causally related to treatment / all                     | 1 / 1           | 1 / 1          | 0 / 0          |
| deaths causally related to treatment / all                          | 0 / 0           | 0 / 0          | 0 / 0          |
| Embolism arterial                                                   |                 |                |                |
| subjects affected / exposed                                         | 1 / 284 (0.35%) | 0 / 92 (0.00%) | 0 / 91 (0.00%) |
| occurrences causally related to treatment / all                     | 0 / 1           | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all                          | 0 / 0           | 0 / 0          | 0 / 0          |
| General disorders and administration site conditions                |                 |                |                |
| Death                                                               |                 |                |                |
| subjects affected / exposed                                         | 1 / 284 (0.35%) | 0 / 92 (0.00%) | 0 / 91 (0.00%) |
| occurrences causally related to treatment / all                     | 0 / 1           | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all                          | 0 / 1           | 0 / 0          | 0 / 0          |
| Mucosal inflammation                                                |                 |                |                |
| subjects affected / exposed                                         | 4 / 284 (1.41%) | 0 / 92 (0.00%) | 0 / 91 (0.00%) |
| occurrences causally related to treatment / all                     | 4 / 4           | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all                          | 0 / 0           | 0 / 0          | 0 / 0          |
| Pyrexia                                                             |                 |                |                |
| subjects affected / exposed                                         | 3 / 284 (1.06%) | 0 / 92 (0.00%) | 0 / 91 (0.00%) |
| occurrences causally related to treatment / all                     | 1 / 3           | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all                          | 0 / 0           | 0 / 0          | 0 / 0          |
| Asthenia                                                            |                 |                |                |

|                                                 |                 |                |                |
|-------------------------------------------------|-----------------|----------------|----------------|
| subjects affected / exposed                     | 1 / 284 (0.35%) | 0 / 92 (0.00%) | 0 / 91 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0          |
| Ulcer                                           |                 |                |                |
| subjects affected / exposed                     | 0 / 284 (0.00%) | 0 / 92 (0.00%) | 1 / 91 (1.10%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0          |
| Respiratory, thoracic and mediastinal disorders |                 |                |                |
| Respiratory distress                            |                 |                |                |
| subjects affected / exposed                     | 1 / 284 (0.35%) | 0 / 92 (0.00%) | 0 / 91 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0          | 0 / 0          |
| Dyspnoea                                        |                 |                |                |
| subjects affected / exposed                     | 2 / 284 (0.70%) | 0 / 92 (0.00%) | 0 / 91 (0.00%) |
| occurrences causally related to treatment / all | 1 / 2           | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0          |
| Epistaxis                                       |                 |                |                |
| subjects affected / exposed                     | 2 / 284 (0.70%) | 0 / 92 (0.00%) | 0 / 91 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2           | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0          |
| Pulmonary embolism                              |                 |                |                |
| subjects affected / exposed                     | 2 / 284 (0.70%) | 0 / 92 (0.00%) | 0 / 91 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2           | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0          |
| Pleural effusion                                |                 |                |                |
| subjects affected / exposed                     | 0 / 284 (0.00%) | 1 / 92 (1.09%) | 0 / 91 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0          |
| Injury, poisoning and procedural complications  |                 |                |                |
| Toxicity to various agents                      |                 |                |                |
| subjects affected / exposed                     | 1 / 284 (0.35%) | 0 / 92 (0.00%) | 0 / 91 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 1 / 1           | 0 / 0          | 0 / 0          |

|                                                 |                 |                |                |
|-------------------------------------------------|-----------------|----------------|----------------|
| Femur fracture                                  |                 |                |                |
| subjects affected / exposed                     | 1 / 284 (0.35%) | 0 / 92 (0.00%) | 0 / 91 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0          |
| Incisional hernia                               |                 |                |                |
| subjects affected / exposed                     | 0 / 284 (0.00%) | 0 / 92 (0.00%) | 1 / 91 (1.10%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0          |
| Wound dehiscence                                |                 |                |                |
| subjects affected / exposed                     | 1 / 284 (0.35%) | 0 / 92 (0.00%) | 0 / 91 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0          |
| Cardiac disorders                               |                 |                |                |
| Myocardial infarction                           |                 |                |                |
| subjects affected / exposed                     | 0 / 284 (0.00%) | 0 / 92 (0.00%) | 2 / 91 (2.20%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 1 / 2          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0          |
| Arrhythmia                                      |                 |                |                |
| subjects affected / exposed                     | 1 / 284 (0.35%) | 0 / 92 (0.00%) | 0 / 91 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0          |
| Atrial fibrillation                             |                 |                |                |
| subjects affected / exposed                     | 1 / 284 (0.35%) | 0 / 92 (0.00%) | 0 / 91 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0          |
| Coronary artery disease                         |                 |                |                |
| subjects affected / exposed                     | 0 / 284 (0.00%) | 0 / 92 (0.00%) | 1 / 91 (1.10%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0          |
| Left ventricular dysfunction                    |                 |                |                |
| subjects affected / exposed                     | 1 / 284 (0.35%) | 0 / 92 (0.00%) | 0 / 91 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0          |
| Nervous system disorders                        |                 |                |                |

|                                                                 |                  |                |                |
|-----------------------------------------------------------------|------------------|----------------|----------------|
| Depressed level of consciousness<br>subjects affected / exposed | 1 / 284 (0.35%)  | 0 / 92 (0.00%) | 0 / 91 (0.00%) |
| occurrences causally related to<br>treatment / all              | 0 / 1            | 0 / 0          | 0 / 0          |
| deaths causally related to<br>treatment / all                   | 0 / 0            | 0 / 0          | 0 / 0          |
| VIIth nerve paralysis<br>subjects affected / exposed            | 0 / 284 (0.00%)  | 1 / 92 (1.09%) | 0 / 91 (0.00%) |
| occurrences causally related to<br>treatment / all              | 0 / 0            | 0 / 1          | 0 / 0          |
| deaths causally related to<br>treatment / all                   | 0 / 0            | 0 / 0          | 0 / 0          |
| Blood and lymphatic system disorders                            |                  |                |                |
| Febrile neutropenia<br>subjects affected / exposed              | 28 / 284 (9.86%) | 0 / 92 (0.00%) | 0 / 91 (0.00%) |
| occurrences causally related to<br>treatment / all              | 29 / 30          | 0 / 0          | 0 / 0          |
| deaths causally related to<br>treatment / all                   | 0 / 0            | 0 / 0          | 0 / 0          |
| Neutropenia<br>subjects affected / exposed                      | 17 / 284 (5.99%) | 0 / 92 (0.00%) | 0 / 91 (0.00%) |
| occurrences causally related to<br>treatment / all              | 18 / 18          | 0 / 0          | 0 / 0          |
| deaths causally related to<br>treatment / all                   | 0 / 0            | 0 / 0          | 0 / 0          |
| Leukopenia<br>subjects affected / exposed                       | 3 / 284 (1.06%)  | 0 / 92 (0.00%) | 0 / 91 (0.00%) |
| occurrences causally related to<br>treatment / all              | 3 / 3            | 0 / 0          | 0 / 0          |
| deaths causally related to<br>treatment / all                   | 0 / 0            | 0 / 0          | 0 / 0          |
| Anaemia<br>subjects affected / exposed                          | 2 / 284 (0.70%)  | 0 / 92 (0.00%) | 0 / 91 (0.00%) |
| occurrences causally related to<br>treatment / all              | 2 / 2            | 0 / 0          | 0 / 0          |
| deaths causally related to<br>treatment / all                   | 0 / 0            | 0 / 0          | 0 / 0          |
| Thrombocytopenia<br>subjects affected / exposed                 | 0 / 284 (0.00%)  | 0 / 92 (0.00%) | 1 / 91 (1.10%) |
| occurrences causally related to<br>treatment / all              | 0 / 0            | 0 / 0          | 0 / 1          |
| deaths causally related to<br>treatment / all                   | 0 / 0            | 0 / 0          | 0 / 0          |
| Ear and labyrinth disorders                                     |                  |                |                |
| Vertigo<br>subjects affected / exposed                          | 1 / 284 (0.35%)  | 0 / 92 (0.00%) | 0 / 91 (0.00%) |
| occurrences causally related to<br>treatment / all              | 0 / 1            | 0 / 0          | 0 / 0          |
| deaths causally related to<br>treatment / all                   | 0 / 0            | 0 / 0          | 0 / 0          |



|                                                 |                 |                |                |
|-------------------------------------------------|-----------------|----------------|----------------|
| Gastrointestinal disorders                      |                 |                |                |
| Intestinal perforation                          |                 |                |                |
| subjects affected / exposed                     | 2 / 284 (0.70%) | 0 / 92 (0.00%) | 0 / 91 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2           | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0          |
| Large intestine perforation                     |                 |                |                |
| subjects affected / exposed                     | 2 / 284 (0.70%) | 0 / 92 (0.00%) | 0 / 91 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2           | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0          |
| Intestinal obstruction                          |                 |                |                |
| subjects affected / exposed                     | 1 / 284 (0.35%) | 1 / 92 (1.09%) | 0 / 91 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0          |
| Colitis                                         |                 |                |                |
| subjects affected / exposed                     | 1 / 284 (0.35%) | 0 / 92 (0.00%) | 0 / 91 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0          |
| Diverticular perforation                        |                 |                |                |
| subjects affected / exposed                     | 1 / 284 (0.35%) | 0 / 92 (0.00%) | 0 / 91 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0          |
| Dysphagia                                       |                 |                |                |
| subjects affected / exposed                     | 0 / 284 (0.00%) | 0 / 92 (0.00%) | 1 / 91 (1.10%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0          |
| Gastric haemorrhage                             |                 |                |                |
| subjects affected / exposed                     | 0 / 284 (0.00%) | 1 / 92 (1.09%) | 0 / 91 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0          |
| Gastritis                                       |                 |                |                |
| subjects affected / exposed                     | 0 / 284 (0.00%) | 1 / 92 (1.09%) | 0 / 91 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0          |
| Gastrointestinal ulcer haemorrhage              |                 |                |                |

|                                                 |                 |                |                |
|-------------------------------------------------|-----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 284 (0.00%) | 0 / 92 (0.00%) | 1 / 91 (1.10%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0          |
| Haematemesis                                    |                 |                |                |
| subjects affected / exposed                     | 1 / 284 (0.35%) | 0 / 92 (0.00%) | 0 / 91 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0          |
| Subileus                                        |                 |                |                |
| subjects affected / exposed                     | 1 / 284 (0.35%) | 0 / 92 (0.00%) | 0 / 91 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0          |
| Upper gastrointestinal haemorrhage              |                 |                |                |
| subjects affected / exposed                     | 1 / 284 (0.35%) | 0 / 92 (0.00%) | 0 / 91 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0          |
| Skin and subcutaneous tissue disorders          |                 |                |                |
| Palmar-plantar erythrodysaesthesia syndrome     |                 |                |                |
| subjects affected / exposed                     | 0 / 284 (0.00%) | 0 / 92 (0.00%) | 1 / 91 (1.10%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0          |
| Renal and urinary disorders                     |                 |                |                |
| Renal failure                                   |                 |                |                |
| subjects affected / exposed                     | 0 / 284 (0.00%) | 1 / 92 (1.09%) | 0 / 91 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1          | 0 / 0          |
| Anuria                                          |                 |                |                |
| subjects affected / exposed                     | 0 / 284 (0.00%) | 1 / 92 (1.09%) | 0 / 91 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0          |
| Musculoskeletal and connective tissue disorders |                 |                |                |
| Back pain                                       |                 |                |                |

|                                                 |                 |                |                |
|-------------------------------------------------|-----------------|----------------|----------------|
| subjects affected / exposed                     | 1 / 284 (0.35%) | 0 / 92 (0.00%) | 0 / 91 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0          |
| Musculoskeletal pain                            |                 |                |                |
| subjects affected / exposed                     | 1 / 284 (0.35%) | 0 / 92 (0.00%) | 0 / 91 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0          |
| Myalgia                                         |                 |                |                |
| subjects affected / exposed                     | 1 / 284 (0.35%) | 0 / 92 (0.00%) | 0 / 91 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0          |
| Infections and infestations                     |                 |                |                |
| Pneumonia                                       |                 |                |                |
| subjects affected / exposed                     | 5 / 284 (1.76%) | 1 / 92 (1.09%) | 0 / 91 (0.00%) |
| occurrences causally related to treatment / all | 2 / 5           | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0          | 0 / 0          |
| Septic shock                                    |                 |                |                |
| subjects affected / exposed                     | 1 / 284 (0.35%) | 0 / 92 (0.00%) | 0 / 91 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 1 / 1           | 0 / 0          | 0 / 0          |
| Gastroenteritis                                 |                 |                |                |
| subjects affected / exposed                     | 2 / 284 (0.70%) | 2 / 92 (2.17%) | 0 / 91 (0.00%) |
| occurrences causally related to treatment / all | 1 / 2           | 0 / 2          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0          |
| Cellulitis                                      |                 |                |                |
| subjects affected / exposed                     | 2 / 284 (0.70%) | 0 / 92 (0.00%) | 0 / 91 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0          |
| Respiratory tract infection                     |                 |                |                |
| subjects affected / exposed                     | 1 / 284 (0.35%) | 0 / 92 (0.00%) | 1 / 91 (1.10%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0          |
| Urinary tract infection                         |                 |                |                |

|                                                 |                 |                |                |
|-------------------------------------------------|-----------------|----------------|----------------|
| subjects affected / exposed                     | 2 / 284 (0.70%) | 0 / 92 (0.00%) | 0 / 91 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2           | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0          |
| Gallbladder empyema                             |                 |                |                |
| subjects affected / exposed                     | 1 / 284 (0.35%) | 0 / 92 (0.00%) | 0 / 91 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0          |
| Infection                                       |                 |                |                |
| subjects affected / exposed                     | 0 / 284 (0.00%) | 0 / 92 (0.00%) | 1 / 91 (1.10%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0          |
| Meningitis                                      |                 |                |                |
| subjects affected / exposed                     | 1 / 284 (0.35%) | 0 / 92 (0.00%) | 0 / 91 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0          |
| Peritonitis                                     |                 |                |                |
| subjects affected / exposed                     | 1 / 284 (0.35%) | 0 / 92 (0.00%) | 0 / 91 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0          |
| Upper respiratory tract infection               |                 |                |                |
| subjects affected / exposed                     | 1 / 284 (0.35%) | 0 / 92 (0.00%) | 0 / 91 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0          |
| Metabolism and nutrition disorders              |                 |                |                |
| Decreased appetite                              |                 |                |                |
| subjects affected / exposed                     | 1 / 284 (0.35%) | 0 / 92 (0.00%) | 0 / 91 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0          |
| Hypercalcaemia                                  |                 |                |                |
| subjects affected / exposed                     | 0 / 284 (0.00%) | 1 / 92 (1.09%) | 0 / 91 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0          |

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

| <b>Non-serious adverse events</b>                     | Initial Treatment Phase: Bevacizumab + Docetaxel | Maintenance Phase: Bevacizumab | Maintenance Phase: Bevacizumab + Capecitabine |
|-------------------------------------------------------|--------------------------------------------------|--------------------------------|-----------------------------------------------|
| Total subjects affected by non-serious adverse events |                                                  |                                |                                               |
| subjects affected / exposed                           | 40 / 284 (14.08%)                                | 4 / 92 (4.35%)                 | 32 / 91 (35.16%)                              |
| Vascular disorders                                    |                                                  |                                |                                               |
| Hypertension                                          |                                                  |                                |                                               |
| subjects affected / exposed                           | 5 / 284 (1.76%)                                  | 3 / 92 (3.26%)                 | 7 / 91 (7.69%)                                |
| occurrences (all)                                     | 5                                                | 4                              | 9                                             |
| Blood and lymphatic system disorders                  |                                                  |                                |                                               |
| Neutropenia                                           |                                                  |                                |                                               |
| subjects affected / exposed                           | 29 / 284 (10.21%)                                | 1 / 92 (1.09%)                 | 2 / 91 (2.20%)                                |
| occurrences (all)                                     | 40                                               | 1                              | 5                                             |
| Skin and subcutaneous tissue disorders                |                                                  |                                |                                               |
| Palmar-plantar erythrodysaesthesia syndrome           |                                                  |                                |                                               |
| subjects affected / exposed                           | 6 / 284 (2.11%)                                  | 0 / 92 (0.00%)                 | 29 / 91 (31.87%)                              |
| occurrences (all)                                     | 7                                                | 0                              | 48                                            |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date              | Amendment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|-------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 20 May 2010       | <ul style="list-style-type: none"><li>• Addition of biomarker collection to explore potential single-nucleotide polymorphisms (SNPs) that may be associated with efficacy and/or safety of bevacizumab therapy in patients with locally recurrent or metastatic breast cancer.</li><li>• Inclusion of new guidance for the management of proteinuria in bevacizumab studies, to make the management of proteinuria the same irrespective of whether it was a first or subsequent occurrence.</li><li>• Inclusion of new guidance to clarify SAE collection throughout the study, from the time informed consent was signed onwards. In addition, the stopping rules for bevacizumab treatment were corrected to include Grade 4 venous thrombosis and a new section regarding reversible posterior leucoencephalopathy syndrome was added for consistency with other bevacizumab studies.</li><li>• Updated the guidance for capecitabine dosing and dose modifications to include numbers of tablets based on the 500 mg tablet (which was the formulation provided for this study).</li></ul>                                                                                                                                                                              |
| 12 August 2012    | <ul style="list-style-type: none"><li>• Updated the patient follow-up for PFS and OS to until 24 months after the last patient had been randomized rather than until at least 24 months after the last patient had been enrolled. Randomization was selected as the reference point (replacing enrolment) as this allowed for a longer follow-up, and therefore more events for the analysis.</li><li>• For China only, included that assessments such as physical examination, vital signs, ECOG PS, laboratory evaluations (specified parameters) and AEs must be performed at the beginning of each treatment cycle (before study drug administration), rather than only if clinically indicated.</li><li>• Updated the guidance for deaths and other SAEs to be reported to Roche within 24 hours of the investigator becoming aware of the event rather than being reported within one working day.</li><li>• Updated the guidance that a pregnancy occurring up to 6 months after completion of bevacizumab must be reported to the investigator rather than the previous interval of up to 90 days.</li><li>• Established an Independent Data Monitoring Committee (IDMC), to independently evaluate the safety of the patients participating in the study.</li></ul> |
| 06 September 2013 | <p>Updated the end of study information to state that the study and investigational sites were to be closed as soon as approval from the regulatory authority and ethics committee occurred. At this time, patients who were still receiving study medication (bevacizumab and/or capecitabine) were to end their study participation. Based on the physician's decision, treatment with bevacizumab and/or capecitabine could be prolonged in accordance with the standard of care and the cost was to be refunded by the Sponsor until disease progression, as initially planned in the protocol.</p> <p>Alternatively, if the Avastin® long-term extension study (AvaLTE / MO25757) was approved in the patients' country, patients were to be offered participation in this study.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported