



## Clinical trial results:

### A Phase III Randomized Study Evaluating the Efficacy and Safety of Continued and Re-induced Bevacizumab in Combination with Chemotherapy for Patients with Locally Recurrent or Metastatic Breast Cancer After First-Line Chemotherapy and Bevacizumab Treatment Summary

|                          |                      |
|--------------------------|----------------------|
| EudraCT number           | 2010-020998-16       |
| Trial protocol           | ES SK HU AT DE GR IT |
| Global end of trial date | 30 March 2015        |

#### Results information

|                                |                  |
|--------------------------------|------------------|
| Result version number          | v1 (current)     |
| This version publication date  | 14 February 2016 |
| First version publication date | 14 February 2016 |

#### Trial information

##### Trial identification

|                       |         |
|-----------------------|---------|
| Sponsor protocol code | MO22998 |
|-----------------------|---------|

##### Additional study identifiers

|                                    |   |
|------------------------------------|---|
| ISRCTN number                      | - |
| ClinicalTrials.gov id (NCT number) | - |
| 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 61 6878333, global.trial_information@roche.com |
| Scientific contact           | Roche Trial Information Hotline, F. Hoffmann-La Roche AG, +41 61 6878333, 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                       | 30 April 2015 |
| Is this the analysis of the primary completion data? | No            |

|                                  |               |
|----------------------------------|---------------|
| Global end of trial reached?     | Yes           |
| Global end of trial date         | 30 March 2015 |
| Was the trial ended prematurely? | No            |

Notes:

## General information about the trial

Main objective of the trial:

This was a Phase III, open-label, randomized, 2-arm study evaluating the efficacy and safety of continued and re-introduced bevacizumab in combination with chemotherapy for participants with locally recurrent (LR) or metastatic breast cancer (mBC) that had progressed during/ following first-line chemotherapy and bevacizumab treatment. Participants whose disease had progressed following previous therapy with bevacizumab plus chemotherapy were randomized on a 1:1 basis to receive standard of care chemotherapy (CT Arm) or standard of care chemotherapy plus bevacizumab (CT+BV Arm).

The primary objective was to determine the clinical benefit of continued or re-introduced bevacizumab treatment in combination with second-line chemotherapy for participants with locally recurrent or mBC whose disease progressed after treatment with first-line chemotherapy combined with bevacizumab, as measured by second-line progression-free survival (PFS).

Protection of trial subjects:

This study was conducted in accordance with the principles of the "Declaration of Helsinki" and "Good Clinical Practice" (GCP) and in compliance with the applicable laws and regulations. The investigators were trained according to applicable standard operating procedures (SOPs) and was documented by the investigator's signature on the protocol agreeing to carry out all of its terms in accordance with the applicable regulations and law and to follow International Conference on Harmonization (ICH) GCP guidelines. Approval from the independent ethics committees (IECs)/institutional review boards (IRBs) was obtained before study start and was documented in a letter to the investigator specifying the date on which the committee met and granted the approval. Approval from the relevant Competent Authority was also obtained prior to starting the study. No modifications were made to the protocol after receipt of the IEC approval. Protocol amendments were prepared by the Sponsor, and were submitted to the IRB/IEC and to regulatory authorities in accordance with local regulatory requirements. Approval was also obtained from the IRB/IEC and regulatory authorities (as locally required) before implementation of any changes.

Background therapy: -

Evidence for comparator: -

|                                                           |                  |
|-----------------------------------------------------------|------------------|
| Actual start date of recruitment                          | 15 February 2011 |
| 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 | Slovakia: 8 |
| Country: Number of subjects enrolled | Spain: 85   |
| Country: Number of subjects enrolled | Austria: 19 |
| Country: Number of subjects enrolled | France: 142 |
| Country: Number of subjects enrolled | Germany: 86 |
| Country: Number of subjects enrolled | Greece: 8   |

|                                      |                 |
|--------------------------------------|-----------------|
| Country: Number of subjects enrolled | Hungary: 31     |
| Country: Number of subjects enrolled | Italy: 72       |
| Country: Number of subjects enrolled | Israel: 22      |
| Country: Number of subjects enrolled | Switzerland: 12 |
| Country: Number of subjects enrolled | Croatia: 6      |
| Country: Number of subjects enrolled | Argentina: 3    |
| Worldwide total number of subjects   | 494             |
| EEA total number of subjects         | 457             |

Notes:

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### 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)                      | 379 |
| From 65 to 84 years                       | 115 |
| 85 years and over                         | 0   |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

A total of 556 participants were screened and of these, 494 participants were randomized.

### Period 1

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

### Arms

|                              |                       |
|------------------------------|-----------------------|
| Are arms mutually exclusive? | Yes                   |
| <b>Arm title</b>             | Chemotherapy (CT) Arm |

Arm description:

Participants received a single-agent chemotherapy at the discretion of the investigator according to the standard of care at the investigator's site until disease progression, unacceptable toxicity, participant request for withdrawal, until the maximum cumulative dose of anthracycline was reached, or end of study (24 months after randomization of the last participant). Upon second-line disease progression participants received a single-agent chemotherapy at the discretion of the investigator according to the standard of care at the investigator's site until disease progression, unacceptable toxicity, participant request for withdrawal, or end of study. Upon subsequent disease progression participants received treatment according the standard of care of the treatment site until end of study.

|                                                           |                                           |
|-----------------------------------------------------------|-------------------------------------------|
| Arm type                                                  | No intervention                           |
| No investigational medicinal product assigned in this arm |                                           |
| <b>Arm title</b>                                          | Chemotherapy Plus Bevacizumab (CT+BV) Arm |

Arm description:

Participants received a single-agent chemotherapy at the discretion of the investigator according to the standard of care at the investigator's site plus bevacizumab, 15 milligrams per kilogram (mg/kg), intravenously (IV), every 3 weeks, or 10 mg/kg, IV, every 2 weeks until disease progression, unacceptable toxicity, participant request for withdrawal, until the maximum cumulative dose of anthracycline was reached, or end of study (24 months after randomization of the last participant). Upon second-line disease progression participants received a single-agent chemotherapy at the discretion of the investigator according to the standard of care at the investigator's site plus bevacizumab, 15 mg/kg, IV, every 3 weeks, or 10 mg/kg, IV, every 2 weeks until disease progression, unacceptable toxicity, participant request for withdrawal, or end of study. Upon subsequent disease progression participants received treatment according the standard of care of the treatment site until end of study.

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

Dosage and administration details:

Bevacizumab was either given as 10 mg/kg given every 2 weeks, or 15 mg/kg given every 3 weeks.

| Number of subjects in period 1 | Chemotherapy (CT)<br>Arm | Chemotherapy Plus<br>Bevacizumab<br>(CT+BV) Arm |
|--------------------------------|--------------------------|-------------------------------------------------|
|                                |                          |                                                 |
| Started                        | 247                      | 247                                             |
| Completed                      | 45                       | 54                                              |
| Not completed                  | 202                      | 193                                             |
| Consent withdrawn by subject   | 32                       | 20                                              |
| Physician decision             | 11                       | 3                                               |
| Death                          | 141                      | 148                                             |
| Not specified                  | -                        | 4                                               |
| Adverse event                  | 5                        | 4                                               |
| Lost to follow-up              | 9                        | 6                                               |
| Participant non-compliance     | 2                        | -                                               |
| Protocol deviation             | 2                        | 8                                               |

## Baseline characteristics

### Reporting groups

|                       |                       |
|-----------------------|-----------------------|
| Reporting group title | Chemotherapy (CT) Arm |
|-----------------------|-----------------------|

Reporting group description:

Participants received a single-agent chemotherapy at the discretion of the investigator according to the standard of care at the investigator's site until disease progression, unacceptable toxicity, participant request for withdrawal, until the maximum cumulative dose of anthracycline was reached, or end of study (24 months after randomization of the last participant). Upon second-line disease progression participants received a single-agent chemotherapy at the discretion of the investigator according to the standard of care at the investigator's site until disease progression, unacceptable toxicity, participant request for withdrawal, or end of study. Upon subsequent disease progression participants received treatment according the standard of care of the treatment site until end of study.

|                       |                                           |
|-----------------------|-------------------------------------------|
| Reporting group title | Chemotherapy Plus Bevacizumab (CT+BV) Arm |
|-----------------------|-------------------------------------------|

Reporting group description:

Participants received a single-agent chemotherapy at the discretion of the investigator according to the standard of care at the investigator's site plus bevacizumab, 15 milligrams per kilogram (mg/kg), intravenously (IV), every 3 weeks, or 10 mg/kg, IV, every 2 weeks until disease progression, unacceptable toxicity, participant request for withdrawal, until the maximum cumulative dose of anthracycline was reached, or end of study (24 months after randomization of the last participant). Upon second-line disease progression participants received a single-agent chemotherapy at the discretion of the investigator according to the standard of care at the investigator's site plus bevacizumab, 15 mg/kg, IV, every 3 weeks, or 10 mg/kg, IV, every 2 weeks until disease progression, unacceptable toxicity, participant request for withdrawal, or end of study. Upon subsequent disease progression participants received treatment according the standard of care of the treatment site until end of study.

| Reporting group values                                                  | Chemotherapy (CT) Arm | Chemotherapy Plus Bevacizumab (CT+BV) Arm | Total |
|-------------------------------------------------------------------------|-----------------------|-------------------------------------------|-------|
| Number of subjects                                                      | 247                   | 247                                       | 494   |
| Age categorical<br>Units: Subjects                                      |                       |                                           |       |
| Age continuous<br>Units: years<br>arithmetic mean<br>standard deviation | 54.7<br>± 10.83       | 55.8<br>± 11.17                           | -     |
| Gender categorical<br>Units: Subjects                                   |                       |                                           |       |
| Female                                                                  | 247                   | 247                                       | 494   |
| Male                                                                    | 0                     | 0                                         | 0     |

## End points

### End points reporting groups

|                       |                       |
|-----------------------|-----------------------|
| Reporting group title | Chemotherapy (CT) Arm |
|-----------------------|-----------------------|

Reporting group description:

Participants received a single-agent chemotherapy at the discretion of the investigator according to the standard of care at the investigator's site until disease progression, unacceptable toxicity, participant request for withdrawal, until the maximum cumulative dose of anthracycline was reached, or end of study (24 months after randomization of the last participant). Upon second-line disease progression participants received a single-agent chemotherapy at the discretion of the investigator according to the standard of care at the investigator's site until disease progression, unacceptable toxicity, participant request for withdrawal, or end of study. Upon subsequent disease progression participants received treatment according the standard of care of the treatment site until end of study.

|                       |                                           |
|-----------------------|-------------------------------------------|
| Reporting group title | Chemotherapy Plus Bevacizumab (CT+BV) Arm |
|-----------------------|-------------------------------------------|

Reporting group description:

Participants received a single-agent chemotherapy at the discretion of the investigator according to the standard of care at the investigator's site plus bevacizumab, 15 milligrams per kilogram (mg/kg), intravenously (IV), every 3 weeks, or 10 mg/kg, IV, every 2 weeks until disease progression, unacceptable toxicity, participant request for withdrawal, until the maximum cumulative dose of anthracycline was reached, or end of study (24 months after randomization of the last participant). Upon second-line disease progression participants received a single-agent chemotherapy at the discretion of the investigator according to the standard of care at the investigator's site plus bevacizumab, 15 mg/kg, IV, every 3 weeks, or 10 mg/kg, IV, every 2 weeks until disease progression, unacceptable toxicity, participant request for withdrawal, or end of study. Upon subsequent disease progression participants received treatment according the standard of care of the treatment site until end of study.

### Primary: Percentage of Participants With Second-Line Progression-Free Survival (PFS) According to Response Evaluation Criteria in Solid Tumors (RECIST) Version (v) 1.1

|                 |                                                                                                                                                                               |
|-----------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Percentage of Participants With Second-Line Progression-Free Survival (PFS) According to Response Evaluation Criteria in Solid Tumors (RECIST) Version (v) 1.1 <sup>[1]</sup> |
|-----------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

Second-line PFS was defined as the time from randomization to progressive disease (PD) or death due to any cause during their second-line of treatment with bevacizumab and/or chemotherapy, whichever occurred first. For target lesions (TLs), PD was defined as at least a 20 percent (%) increase in the sum of the largest diameter (SLD), taking as reference the smallest SLD recorded from baseline or the appearance of one or more new lesions. For non-target lesions (NTLs), PD was defined as the appearance of one or more new lesions and/or unequivocal progression of existing NTLs. Participants without second-line PD or death were censored at the date of last tumor assessment where non-progression was documented.

Analysis population (AP): Intent-to-treat (ITT) population - all randomized participants.

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

End point timeframe:

Baseline [less than or equal to ( $\leq$ ) 28 days after randomization], every 8-9 weeks thereafter according to the standard of care of treatment site until approximately 3 years

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Statistical analysis was planned only for PFS duration and reported in the respective endpoint.

| End point values                  | Chemotherapy (CT) Arm | Chemotherapy Plus Bevacizumab (CT+BV) Arm |  |  |
|-----------------------------------|-----------------------|-------------------------------------------|--|--|
| Subject group type                | Reporting group       | Reporting group                           |  |  |
| Number of subjects analysed       | 247                   | 247                                       |  |  |
| Units: percentage of participants |                       |                                           |  |  |
| number (not applicable)           | 88.7                  | 93.9                                      |  |  |

## Statistical analyses

No statistical analyses for this end point

### Primary: Second-Line PFS

|                 |                 |
|-----------------|-----------------|
| End point title | Second-Line PFS |
|-----------------|-----------------|

End point description:

The median time, in months, from randomization to second-line PFS event. For TLS, PD was defined as at least a 20% increase in the SLD, taking as reference the smallest SLD recorded from baseline or the appearance of one or more new lesions. For NTLs, PD was defined as the appearance of one or more new lesions and/or unequivocal progression of existing NTLs. Participants without second-line PD or death were censored at the date of last tumor assessment where non-progression was documented. AP: ITT population.

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

End point timeframe:

Baseline ( $\leq 28$  days after randomization), every 8-9 weeks thereafter according to the standard of care of the treatment site until approximately 3 years

| End point values                 | Chemotherapy (CT) Arm | Chemotherapy Plus Bevacizumab (CT+BV) Arm |  |  |
|----------------------------------|-----------------------|-------------------------------------------|--|--|
| Subject group type               | Reporting group       | Reporting group                           |  |  |
| Number of subjects analysed      | 247                   | 247                                       |  |  |
| Units: months                    |                       |                                           |  |  |
| median (confidence interval 95%) | 4.2 (3.9 to 5.3)      | 6.3 (5.5 to 7.6)                          |  |  |

## Statistical analyses

|                                         |                                                                   |
|-----------------------------------------|-------------------------------------------------------------------|
| Statistical analysis title              | Statistical Analysis 1                                            |
| Comparison groups                       | Chemotherapy (CT) Arm v Chemotherapy Plus Bevacizumab (CT+BV) Arm |
| Number of subjects included in analysis | 494                                                               |
| Analysis specification                  | Pre-specified                                                     |
| Analysis type                           | superiority <sup>[2]</sup>                                        |
| P-value                                 | = 0.0204                                                          |
| Method                                  | Logrank                                                           |
| Parameter estimate                      | Hazard ratio (HR)                                                 |
| Point estimate                          | 0.79                                                              |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | 0.65    |
| upper limit         | 0.97    |

Notes:

[2] - The 95% confidence interval (CI) was estimated using Cox proportional hazards methodology. The stratification factors used in the analysis were hormone receptor status, first-line PFS, choice of chemotherapy, and lactate dehydrogenase (LDH) level.

|                                         |                                                                   |
|-----------------------------------------|-------------------------------------------------------------------|
| <b>Statistical analysis title</b>       | Statistical Analysis 2                                            |
| Comparison groups                       | Chemotherapy (CT) Arm v Chemotherapy Plus Bevacizumab (CT+BV) Arm |
| Number of subjects included in analysis | 494                                                               |
| Analysis specification                  | Pre-specified                                                     |
| Analysis type                           | superiority <sup>[3]</sup>                                        |
| P-value                                 | = 0.0245                                                          |
| Method                                  | Logrank                                                           |
| Parameter estimate                      | Hazard ratio (HR)                                                 |
| Point estimate                          | 0.81                                                              |
| Confidence interval                     |                                                                   |
| level                                   | 95 %                                                              |
| sides                                   | 2-sided                                                           |
| lower limit                             | 0.67                                                              |
| upper limit                             | 0.97                                                              |

Notes:

[3] - Unstratified analysis.

### **Primary: Percentage of Participants Estimated to be Alive and Free of Second-Line Disease Progression at Month 6**

|                 |                                                                                                                        |
|-----------------|------------------------------------------------------------------------------------------------------------------------|
| End point title | Percentage of Participants Estimated to be Alive and Free of Second-Line Disease Progression at Month 6 <sup>[4]</sup> |
|-----------------|------------------------------------------------------------------------------------------------------------------------|

End point description:

Second-line PFS was defined as the time from randomization to PD or death due to any cause during their second-line of treatment with bevacizumab and/or chemotherapy, whichever occurred first. For TLS, PD was defined as at least a 20% increase in the SLD, taking as reference the smallest SLD recorded from baseline or the appearance of one or more new lesions. For NTLs, PD was defined as the appearance of one or more new lesions and/or unequivocal progression of existing NTLs. Participants without second-line PD or death were censored at the date of last tumor assessment where non-progression was documented.

AP: ITT population.

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

End point timeframe:

Month 6

Notes:

[4] - 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 planned only for PFS duration and reported in the respective endpoint.

| End point values                  | Chemotherapy (CT) Arm | Chemotherapy Plus Bevacizumab (CT+BV) Arm |  |  |
|-----------------------------------|-----------------------|-------------------------------------------|--|--|
| Subject group type                | Reporting group       | Reporting group                           |  |  |
| Number of subjects analysed       | 247                   | 247                                       |  |  |
| Units: percentage of participants |                       |                                           |  |  |
| number (confidence interval 95%)  | 40.7 (34.3 to 47)     | 54.2 (47.7 to 60.3)                       |  |  |

## Statistical analyses

No statistical analyses for this end point

### Primary: Percentage of Participants Estimated to be Alive and Free of Second-Line Disease Progression at Month 12

|                 |                                                                                                                         |
|-----------------|-------------------------------------------------------------------------------------------------------------------------|
| End point title | Percentage of Participants Estimated to be Alive and Free of Second-Line Disease Progression at Month 12 <sup>[5]</sup> |
|-----------------|-------------------------------------------------------------------------------------------------------------------------|

End point description:

Second-line PFS was defined as the time from randomization to PD or death due to any cause during their second-line of treatment with bevacizumab and/or chemotherapy, whichever occurred first. For TLs, PD was defined as at least a 20% increase in the SLD, taking as reference the smallest SLD recorded from BL or the appearance of one or more new lesions. For NTLs, PD was defined as the appearance of one or more new lesions and/or unequivocal progression of existing NTLs. Participants without second-line PD or death were censored at the date of last tumor assessment where non-progression was documented.

AP: ITT population.

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

End point timeframe:

Month 12

Notes:

[5] - 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 planned only for PFS duration and reported in the respective endpoint.

| End point values                  | Chemotherapy (CT) Arm | Chemotherapy Plus Bevacizumab (CT+BV) Arm |  |  |
|-----------------------------------|-----------------------|-------------------------------------------|--|--|
| Subject group type                | Reporting group       | Reporting group                           |  |  |
| Number of subjects analysed       | 247                   | 247                                       |  |  |
| Units: percentage of participants |                       |                                           |  |  |
| number (confidence interval 95%)  | 16.9 (12.3 to 22.2)   | 24.2 (19 to 29.9)                         |  |  |

## Statistical analyses

No statistical analyses for this end point

### Primary: Percentage of Participants Estimated to be Alive and Free of Second-Line Disease Progression at Month 18

|                 |                                                                                                                         |
|-----------------|-------------------------------------------------------------------------------------------------------------------------|
| End point title | Percentage of Participants Estimated to be Alive and Free of Second-Line Disease Progression at Month 18 <sup>[6]</sup> |
|-----------------|-------------------------------------------------------------------------------------------------------------------------|

End point description:

Second-line PFS was defined as the time from randomization to PD or death due to any cause during their second-line of treatment with bevacizumab and/or chemotherapy, whichever occurred first. For TLS, PD was defined as at least a 20% increase in the SLD, taking as reference the smallest SLD recorded from baseline or the appearance of one or more new lesions. For NTLs, PD was defined as the appearance of one or more new lesions and/or unequivocal progression of existing NTLs. Participants without second-line PD or death were censored at the date of last tumor assessment where non-progression was documented.

AP: ITT population.

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

End point timeframe:

Month 18

Notes:

[6] - 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 planned only for PFS duration and reported in the respective endpoint.

| End point values                  | Chemotherapy (CT) Arm | Chemotherapy Plus Bevacizumab (CT+BV) Arm |  |  |
|-----------------------------------|-----------------------|-------------------------------------------|--|--|
| Subject group type                | Reporting group       | Reporting group                           |  |  |
| Number of subjects analysed       | 247                   | 247                                       |  |  |
| Units: percentage of participants |                       |                                           |  |  |
| number (confidence interval 95%)  | 9.9 (6.4 to 14.3)     | 11 (7.4 to 15.5)                          |  |  |

## Statistical analyses

No statistical analyses for this end point

## Primary: Percentage of Participants Estimated to be Alive and Free of Second-Line Disease Progression at Month 24

|                 |                                                                                                                         |
|-----------------|-------------------------------------------------------------------------------------------------------------------------|
| End point title | Percentage of Participants Estimated to be Alive and Free of Second-Line Disease Progression at Month 24 <sup>[7]</sup> |
|-----------------|-------------------------------------------------------------------------------------------------------------------------|

End point description:

Second-line PFS was defined as the time from randomization to PD or death due to any cause during their second-line of treatment with bevacizumab and/or chemotherapy, whichever occurred first. For TLS, PD was defined as at least a 20% increase in the SLD, taking as reference the smallest SLD recorded from baseline or the appearance of one or more new lesions. For NTLs, PD was defined as the appearance of one or more new lesions and/or unequivocal progression of existing NTLs. Participants without second-line PD or death were censored at the date of last tumor assessment where non-progression was documented.

AP: ITT population.

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

End point timeframe:

Month 24

Notes:

[7] - 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 planned only for PFS duration and reported in the respective endpoint.

| End point values                  | Chemotherapy (CT) Arm | Chemotherapy Plus Bevacizumab (CT+BV) Arm |  |  |
|-----------------------------------|-----------------------|-------------------------------------------|--|--|
| Subject group type                | Reporting group       | Reporting group                           |  |  |
| Number of subjects analysed       | 247                   | 247                                       |  |  |
| Units: percentage of participants |                       |                                           |  |  |
| number (confidence interval 95%)  | 6.4 (3.6 to 10.2)     | 6.5 (3.7 to 10.2)                         |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Second-Line PFS by Baseline Risk Factor (Data Cutoff 20 December 2013)

|                 |                                                                        |
|-----------------|------------------------------------------------------------------------|
| End point title | Second-Line PFS by Baseline Risk Factor (Data Cutoff 20 December 2013) |
|-----------------|------------------------------------------------------------------------|

End point description:

The median time in months from randomization to second-line PFS event according to following baseline risk factors: hormone receptor negative, HER2 negative (triple negative), hormone receptor positive/HER-2 negative (HR-pos/HER-neg), first-line PFS < 6 months, first-line PFS ≥ 6 months, taxane chemotherapy (chemo), non-taxane chemo, vinorelbine chemo, LDH ≤ 1.5 upper limit of normal (ULN), LDH > 1.5 ULN, < 65 and <70 years of age, ≥ 65 and ≥ 70 years of age, < 3 and ≥ 3 metastatic organ sites, bevacizumab-free (B-free) interval ≤ 6 weeks and > 6 weeks, disease-free (D-free) interval ≤ 24 months, > 24 months, ≤ 12 months, and > 12 months. Participants without second-line PD or death were censored at the date of last tumor assessment where non-progression was documented. The 95% CI was estimated using Kaplan-Meier methodology.

AP: ITT population. Here, Number of participants analyzed= participants evaluable for this end point and n= participants included for specified risk factor.

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

End point timeframe:

Baseline (≤28 days after randomization), every 8-9 weeks thereafter according to the standard of care of the treatment site until approximately 3 years

| End point values                 | Chemotherapy (CT) Arm | Chemotherapy Plus Bevacizumab (CT+BV) Arm |  |  |
|----------------------------------|-----------------------|-------------------------------------------|--|--|
| Subject group type               | Reporting group       | Reporting group                           |  |  |
| Number of subjects analysed      | 226                   | 219                                       |  |  |
| Units: months                    |                       |                                           |  |  |
| median (confidence interval 95%) |                       |                                           |  |  |
| HR-neg (n=60,56)                 | 2.1 (2 to 3.9)        | 4.9 (3.4 to 6.1)                          |  |  |
| HR-pos/HER-neg (n=187,191)       | 4.7 (4.2 to 6.2)      | 6.7 (6 to 7.8)                            |  |  |
| PFS <6 months (n=69,68)          | 3.9 (2.3 to 4.3)      | 5.1 (4.1 to 6.9)                          |  |  |
| PFS ≥6 months (n=178,179)        | 4.6 (3.9 to 6.1)      | 6.4 (5.8 to 7.6)                          |  |  |
| Taxane chemo (n=32,32)           | 3.2 (1.7 to 5.3)      | 6.9 (4.9 to 9.8)                          |  |  |
| Non-taxane chemo (n=191,188)     | 4.4 (3.9 to 5.8)      | 6 (4.9 to 6.8)                            |  |  |
| Vinorelbine chemo (n=24,27)      | 2.4 (1.8 to 4.3)      | 6.5 (4.2 to 11.1)                         |  |  |
| LDH ≤ 1.5 ULN (n=207,210)        | 4.4 (3.9 to 6)        | 6.3 (5.5 to 7.6)                          |  |  |

|                                        |                   |                   |  |  |
|----------------------------------------|-------------------|-------------------|--|--|
| LDH > 1.5 ULN (n=40,37)                | 2.1 (1.7 to 3.9)  | 5.8 (2.5 to 7.3)  |  |  |
| < 65 years of age (n=196,183)          | 4.2 (3.9 to 4.7)  | 6.1 (4.7 to 6.9)  |  |  |
| ≥ 65 years of age (n=51,64)            | 4.2 (2.2 to 7.8)  | 6.7 (5.5 to 8)    |  |  |
| < 70 years of age (n=226,219)          | 4.2 (3.7 to 4.6)  | 6.2 (5.3 to 7.3)  |  |  |
| ≥ 70 years of age (n=21,28)            | 7.8 (2.2 to 11.9) | 6.7 (4.1 to 11.2) |  |  |
| < 3 metastatic organ sites (n=158,167) | 4.2 (3.9 to 6.1)  | 6.9 (6 to 8.2)    |  |  |
| ≥ 3 metastatic organ sites (n=88,80)   | 4 (2.1 to 4.9)    | 4.7 (4.1 to 6.2)  |  |  |
| B-free ≤ 6 weeks (n=165,149)           | 4.2 (3.6 to 4.6)  | 5.8 (4.4 to 6.6)  |  |  |
| B-free > 6 weeks (n=81,98)             | 4.4 (3.3 to 6.3)  | 7.6 (6 to 9.5)    |  |  |
| D-free ≤ 24 months (n=58,53)           | 2.8 (2 to 3.9)    | 5.8 (4.2 to 6.3)  |  |  |
| D-free > 24 months (n=138,156)         | 4.9 (4 to 6.1)    | 6.5 (5.5 to 8.1)  |  |  |
| D-free ≤ 12 months (n=24,18)           | 2.1 (1.3 to 5.8)  | 5.8 (3.9 to 9.7)  |  |  |
| D-free > 12 months (n=172,191)         | 4.3 (3.9 to 5.7)  | 6.3 (5.3 to 7.6)  |  |  |

## Statistical analyses

|                                         |                                                                   |
|-----------------------------------------|-------------------------------------------------------------------|
| <b>Statistical analysis title</b>       | Subgroup analysis: HR-neg                                         |
| Comparison groups                       | Chemotherapy Plus Bevacizumab (CT+BV) Arm v Chemotherapy (CT) Arm |
| Number of subjects included in analysis | 445                                                               |
| Analysis specification                  | Pre-specified                                                     |
| Analysis type                           | superiority                                                       |
| P-value                                 | = 0.0088                                                          |
| Method                                  | Logrank                                                           |
| Parameter estimate                      | Hazard ratio (HR)                                                 |
| Point estimate                          | 0.59                                                              |
| Confidence interval                     |                                                                   |
| level                                   | 95 %                                                              |
| sides                                   | 2-sided                                                           |
| lower limit                             | 0.4                                                               |
| upper limit                             | 0.88                                                              |

|                                         |                                                                   |
|-----------------------------------------|-------------------------------------------------------------------|
| <b>Statistical analysis title</b>       | Subgroup analysis: HR-pos/ HER-neg                                |
| Comparison groups                       | Chemotherapy (CT) Arm v Chemotherapy Plus Bevacizumab (CT+BV) Arm |
| Number of subjects included in analysis | 445                                                               |
| Analysis specification                  | Pre-specified                                                     |
| Analysis type                           | superiority                                                       |
| P-value                                 | = 0.1196                                                          |
| Method                                  | Logrank                                                           |
| Parameter estimate                      | Hazard ratio (HR)                                                 |
| Point estimate                          | 0.84                                                              |
| Confidence interval                     |                                                                   |
| level                                   | 95 %                                                              |
| sides                                   | 2-sided                                                           |
| lower limit                             | 0.67                                                              |
| upper limit                             | 1.05                                                              |

|                                         |                                                                   |
|-----------------------------------------|-------------------------------------------------------------------|
| <b>Statistical analysis title</b>       | Subgroup analysis PFS < 6 months                                  |
| Comparison groups                       | Chemotherapy Plus Bevacizumab (CT+BV) Arm v Chemotherapy (CT) Arm |
| Number of subjects included in analysis | 445                                                               |
| Analysis specification                  | Pre-specified                                                     |
| Analysis type                           | superiority                                                       |
| P-value                                 | = 0.011                                                           |
| Method                                  | Logrank                                                           |
| Parameter estimate                      | Hazard ratio (HR)                                                 |
| Point estimate                          | 0.62                                                              |
| Confidence interval                     |                                                                   |
| level                                   | 95 %                                                              |
| sides                                   | 2-sided                                                           |
| lower limit                             | 0.43                                                              |
| upper limit                             | 0.9                                                               |

|                                         |                                                                   |
|-----------------------------------------|-------------------------------------------------------------------|
| <b>Statistical analysis title</b>       | Subgroup analysis: PFS ≥ 6 months                                 |
| Comparison groups                       | Chemotherapy (CT) Arm v Chemotherapy Plus Bevacizumab (CT+BV) Arm |
| Number of subjects included in analysis | 445                                                               |
| Analysis specification                  | Pre-specified                                                     |
| Analysis type                           | superiority                                                       |
| P-value                                 | = 0.0816                                                          |
| Method                                  | Logrank                                                           |
| Parameter estimate                      | Hazard ratio (HR)                                                 |
| Point estimate                          | 0.82                                                              |
| Confidence interval                     |                                                                   |
| level                                   | 95 %                                                              |
| sides                                   | 2-sided                                                           |
| lower limit                             | 0.65                                                              |
| upper limit                             | 1.03                                                              |

|                                         |                                                                   |
|-----------------------------------------|-------------------------------------------------------------------|
| <b>Statistical analysis title</b>       | Subgroup analysis: taxane chemo                                   |
| Comparison groups                       | Chemotherapy (CT) Arm v Chemotherapy Plus Bevacizumab (CT+BV) Arm |
| Number of subjects included in analysis | 445                                                               |
| Analysis specification                  | Pre-specified                                                     |
| Analysis type                           | superiority                                                       |
| P-value                                 | = 0.0395                                                          |
| Method                                  | Logrank                                                           |
| Parameter estimate                      | Hazard ratio (HR)                                                 |
| Point estimate                          | 0.55                                                              |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | 0.31    |
| upper limit         | 0.98    |

|                                         |                                                                   |
|-----------------------------------------|-------------------------------------------------------------------|
| <b>Statistical analysis title</b>       | Subgroup analysis: nontaxane chemo                                |
| Comparison groups                       | Chemotherapy (CT) Arm v Chemotherapy Plus Bevacizumab (CT+BV) Arm |
| Number of subjects included in analysis | 445                                                               |
| Analysis specification                  | Pre-specified                                                     |
| Analysis type                           | superiority                                                       |
| P-value                                 | = 0.1385                                                          |
| Method                                  | Logrank                                                           |
| Parameter estimate                      | Hazard ratio (HR)                                                 |
| Point estimate                          | 0.84                                                              |
| Confidence interval                     |                                                                   |
| level                                   | 95 %                                                              |
| sides                                   | 2-sided                                                           |
| lower limit                             | 0.68                                                              |
| upper limit                             | 1.06                                                              |

|                                         |                                                                   |
|-----------------------------------------|-------------------------------------------------------------------|
| <b>Statistical analysis title</b>       | Subgroup analysis: vinorelbine chemo                              |
| Comparison groups                       | Chemotherapy (CT) Arm v Chemotherapy Plus Bevacizumab (CT+BV) Arm |
| Number of subjects included in analysis | 445                                                               |
| Analysis specification                  | Pre-specified                                                     |
| Analysis type                           | superiority                                                       |
| P-value                                 | = 0.0029                                                          |
| Method                                  | Logrank                                                           |
| Parameter estimate                      | Hazard ratio (HR)                                                 |
| Point estimate                          | 0.41                                                              |
| Confidence interval                     |                                                                   |
| level                                   | 95 %                                                              |
| sides                                   | 2-sided                                                           |
| lower limit                             | 0.22                                                              |
| upper limit                             | 0.75                                                              |

|                                   |                                                                   |
|-----------------------------------|-------------------------------------------------------------------|
| <b>Statistical analysis title</b> | Subgroup analysis: LDH $\leq$ 1.5 ULN                             |
| Comparison groups                 | Chemotherapy (CT) Arm v Chemotherapy Plus Bevacizumab (CT+BV) Arm |

|                                         |                   |
|-----------------------------------------|-------------------|
| Number of subjects included in analysis | 445               |
| Analysis specification                  | Pre-specified     |
| Analysis type                           | superiority       |
| P-value                                 | = 0.0171          |
| Method                                  | Logrank           |
| Parameter estimate                      | Hazard ratio (HR) |
| Point estimate                          | 0.77              |
| Confidence interval                     |                   |
| level                                   | 95 %              |
| sides                                   | 2-sided           |
| lower limit                             | 0.62              |
| upper limit                             | 0.96              |

|                                         |                                                                   |
|-----------------------------------------|-------------------------------------------------------------------|
| <b>Statistical analysis title</b>       | Subgroup analysis: LDH > 1.5 ULN                                  |
| Comparison groups                       | Chemotherapy (CT) Arm v Chemotherapy Plus Bevacizumab (CT+BV) Arm |
| Number of subjects included in analysis | 445                                                               |
| Analysis specification                  | Pre-specified                                                     |
| Analysis type                           | superiority                                                       |
| P-value                                 | = 0.1797                                                          |
| Method                                  | Logrank                                                           |
| Parameter estimate                      | Hazard ratio (HR)                                                 |
| Point estimate                          | 0.73                                                              |
| Confidence interval                     |                                                                   |
| level                                   | 95 %                                                              |
| sides                                   | 2-sided                                                           |
| lower limit                             | 0.46                                                              |
| upper limit                             | 1.16                                                              |

|                                         |                                                                   |
|-----------------------------------------|-------------------------------------------------------------------|
| <b>Statistical analysis title</b>       | Subgroup analysis: < 65 years of age                              |
| Comparison groups                       | Chemotherapy (CT) Arm v Chemotherapy Plus Bevacizumab (CT+BV) Arm |
| Number of subjects included in analysis | 445                                                               |
| Analysis specification                  | Pre-specified                                                     |
| Analysis type                           | superiority                                                       |
| P-value                                 | = 0.0229                                                          |
| Method                                  | Logrank                                                           |
| Parameter estimate                      | Hazard ratio (HR)                                                 |
| Point estimate                          | 0.77                                                              |
| Confidence interval                     |                                                                   |
| level                                   | 95 %                                                              |
| sides                                   | 2-sided                                                           |
| lower limit                             | 0.62                                                              |
| upper limit                             | 0.97                                                              |

|                                         |                                                                   |
|-----------------------------------------|-------------------------------------------------------------------|
| <b>Statistical analysis title</b>       | Subgroup analysis: $\geq 65$ years of age                         |
| Comparison groups                       | Chemotherapy (CT) Arm v Chemotherapy Plus Bevacizumab (CT+BV) Arm |
| Number of subjects included in analysis | 445                                                               |
| Analysis specification                  | Pre-specified                                                     |
| Analysis type                           | superiority                                                       |
| P-value                                 | = 0.2139                                                          |
| Method                                  | Logrank                                                           |
| Parameter estimate                      | Hazard ratio (HR)                                                 |
| Point estimate                          | 0.77                                                              |
| Confidence interval                     |                                                                   |
| level                                   | 95 %                                                              |
| sides                                   | 2-sided                                                           |
| lower limit                             | 0.51                                                              |
| upper limit                             | 1.16                                                              |

|                                         |                                                                   |
|-----------------------------------------|-------------------------------------------------------------------|
| <b>Statistical analysis title</b>       | Subgroup analysis: $< 70$ years of age                            |
| Comparison groups                       | Chemotherapy (CT) Arm v Chemotherapy Plus Bevacizumab (CT+BV) Arm |
| Number of subjects included in analysis | 445                                                               |
| Analysis specification                  | Pre-specified                                                     |
| Analysis type                           | superiority                                                       |
| P-value                                 | = 0.0021                                                          |
| Method                                  | Logrank                                                           |
| Parameter estimate                      | Hazard ratio (HR)                                                 |
| Point estimate                          | 0.73                                                              |
| Confidence interval                     |                                                                   |
| level                                   | 95 %                                                              |
| sides                                   | 2-sided                                                           |
| lower limit                             | 0.59                                                              |
| upper limit                             | 0.89                                                              |

|                                         |                                                                   |
|-----------------------------------------|-------------------------------------------------------------------|
| <b>Statistical analysis title</b>       | Subgroup analysis: $\geq 70$ years of age                         |
| Comparison groups                       | Chemotherapy (CT) Arm v Chemotherapy Plus Bevacizumab (CT+BV) Arm |
| Number of subjects included in analysis | 445                                                               |
| Analysis specification                  | Pre-specified                                                     |
| Analysis type                           | superiority                                                       |
| P-value                                 | = 0.5216                                                          |
| Method                                  | Logrank                                                           |
| Parameter estimate                      | Hazard ratio (HR)                                                 |
| Point estimate                          | 1.24                                                              |
| Confidence interval                     |                                                                   |
| level                                   | 95 %                                                              |
| sides                                   | 2-sided                                                           |
| lower limit                             | 0.64                                                              |
| upper limit                             | 2.39                                                              |

|                                         |                                                                   |
|-----------------------------------------|-------------------------------------------------------------------|
| <b>Statistical analysis title</b>       | Subgroup analysis: < 3 metastatic organ sites                     |
| Comparison groups                       | Chemotherapy (CT) Arm v Chemotherapy Plus Bevacizumab (CT+BV) Arm |
| Number of subjects included in analysis | 445                                                               |
| Analysis specification                  | Pre-specified                                                     |
| Analysis type                           | superiority                                                       |
| P-value                                 | = 0.0148                                                          |
| Method                                  | Logrank                                                           |
| Parameter estimate                      | Hazard ratio (HR)                                                 |
| Point estimate                          | 0.74                                                              |
| Confidence interval                     |                                                                   |
| level                                   | 95 %                                                              |
| sides                                   | 2-sided                                                           |
| lower limit                             | 0.58                                                              |
| upper limit                             | 0.94                                                              |

|                                         |                                                                   |
|-----------------------------------------|-------------------------------------------------------------------|
| <b>Statistical analysis title</b>       | Subgroup analysis: ≥ 3 metastatic organ sites                     |
| Comparison groups                       | Chemotherapy (CT) Arm v Chemotherapy Plus Bevacizumab (CT+BV) Arm |
| Number of subjects included in analysis | 445                                                               |
| Analysis specification                  | Pre-specified                                                     |
| Analysis type                           | superiority                                                       |
| P-value                                 | = 0.3102                                                          |
| Method                                  | Logrank                                                           |
| Parameter estimate                      | Hazard ratio (HR)                                                 |
| Point estimate                          | 0.84                                                              |
| Confidence interval                     |                                                                   |
| level                                   | 95 %                                                              |
| sides                                   | 2-sided                                                           |
| lower limit                             | 0.61                                                              |
| upper limit                             | 1.17                                                              |

|                                         |                                                                   |
|-----------------------------------------|-------------------------------------------------------------------|
| <b>Statistical analysis title</b>       | Subgroup analysis: B-free ≤ 6 weeks                               |
| Comparison groups                       | Chemotherapy (CT) Arm v Chemotherapy Plus Bevacizumab (CT+BV) Arm |
| Number of subjects included in analysis | 445                                                               |
| Analysis specification                  | Pre-specified                                                     |
| Analysis type                           | superiority                                                       |
| P-value                                 | = 0.0967                                                          |
| Method                                  | Logrank                                                           |
| Parameter estimate                      | Hazard ratio (HR)                                                 |
| Point estimate                          | 0.82                                                              |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | 0.64    |
| upper limit         | 1.04    |

|                                         |                                                                   |
|-----------------------------------------|-------------------------------------------------------------------|
| <b>Statistical analysis title</b>       | Subgroup analysis: B-free > 6 weeks                               |
| Comparison groups                       | Chemotherapy (CT) Arm v Chemotherapy Plus Bevacizumab (CT+BV) Arm |
| Number of subjects included in analysis | 445                                                               |
| Analysis specification                  | Pre-specified                                                     |
| Analysis type                           | superiority                                                       |
| P-value                                 | = 0.0489                                                          |
| Method                                  | Logrank                                                           |
| Parameter estimate                      | Hazard ratio (HR)                                                 |
| Point estimate                          | 0.72                                                              |
| Confidence interval                     |                                                                   |
| level                                   | 95 %                                                              |
| sides                                   | 2-sided                                                           |
| lower limit                             | 0.51                                                              |
| upper limit                             | 1                                                                 |

|                                         |                                                                   |
|-----------------------------------------|-------------------------------------------------------------------|
| <b>Statistical analysis title</b>       | Subgroup analysis: D-free ≤ 24 months                             |
| Comparison groups                       | Chemotherapy (CT) Arm v Chemotherapy Plus Bevacizumab (CT+BV) Arm |
| Number of subjects included in analysis | 445                                                               |
| Analysis specification                  | Pre-specified                                                     |
| Analysis type                           | superiority                                                       |
| P-value                                 | = 0.0176                                                          |
| Method                                  | Logrank                                                           |
| Parameter estimate                      | Hazard ratio (HR)                                                 |
| Point estimate                          | 0.62                                                              |
| Confidence interval                     |                                                                   |
| level                                   | 95 %                                                              |
| sides                                   | 2-sided                                                           |
| lower limit                             | 0.41                                                              |
| upper limit                             | 0.92                                                              |

|                                   |                                                                   |
|-----------------------------------|-------------------------------------------------------------------|
| <b>Statistical analysis title</b> | Subgroup analysis: D-free > 24 months                             |
| Comparison groups                 | Chemotherapy (CT) Arm v Chemotherapy Plus Bevacizumab (CT+BV) Arm |

|                                         |                   |
|-----------------------------------------|-------------------|
| Number of subjects included in analysis | 445               |
| Analysis specification                  | Pre-specified     |
| Analysis type                           | superiority       |
| P-value                                 | = 0.2318          |
| Method                                  | Logrank           |
| Parameter estimate                      | Hazard ratio (HR) |
| Point estimate                          | 0.85              |
| Confidence interval                     |                   |
| level                                   | 95 %              |
| sides                                   | 2-sided           |
| lower limit                             | 0.66              |
| upper limit                             | 1.11              |

|                                         |                                                                   |
|-----------------------------------------|-------------------------------------------------------------------|
| <b>Statistical analysis title</b>       | Subgroup analysis: D-free $\leq$ 12 months                        |
| Comparison groups                       | Chemotherapy (CT) Arm v Chemotherapy Plus Bevacizumab (CT+BV) Arm |
| Number of subjects included in analysis | 445                                                               |
| Analysis specification                  | Pre-specified                                                     |
| Analysis type                           | superiority                                                       |
| P-value                                 | = 0.0568                                                          |
| Method                                  | Logrank                                                           |
| Parameter estimate                      | Hazard ratio (HR)                                                 |
| Point estimate                          | 0.52                                                              |
| Confidence interval                     |                                                                   |
| level                                   | 95 %                                                              |
| sides                                   | 2-sided                                                           |
| lower limit                             | 0.26                                                              |
| upper limit                             | 1.03                                                              |

|                                         |                                                                   |
|-----------------------------------------|-------------------------------------------------------------------|
| <b>Statistical analysis title</b>       | Subgroup analysis: D-free > 12 months                             |
| Comparison groups                       | Chemotherapy (CT) Arm v Chemotherapy Plus Bevacizumab (CT+BV) Arm |
| Number of subjects included in analysis | 445                                                               |
| Analysis specification                  | Pre-specified                                                     |
| Analysis type                           | superiority                                                       |
| P-value                                 | = 0.1143                                                          |
| Method                                  | Logrank                                                           |
| Parameter estimate                      | Hazard ratio (HR)                                                 |
| Point estimate                          | 0.83                                                              |
| Confidence interval                     |                                                                   |
| level                                   | 95 %                                                              |
| sides                                   | 2-sided                                                           |
| lower limit                             | 0.66                                                              |
| upper limit                             | 1.05                                                              |

## Secondary: Percentage of Participants With a Second-Line Best Overall Response (BOR) of Complete Response (CR) or Partial Response (PR) According to RECIST v1.1 (Data Cutoff 20 December 2013)

|                 |                                                                                                                                                                                      |
|-----------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Percentage of Participants With a Second-Line Best Overall Response (BOR) of Complete Response (CR) or Partial Response (PR) According to RECIST v1.1 (Data Cutoff 20 December 2013) |
|-----------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

### End point description:

BOR was defined as a confirmed CR or PR during second-line treatment. For TLs, CR was defined as the disappearance of all TLs, and PR was defined as at least a 30% decrease in the SLD of the TLs, taking as a reference the baseline SLD. For NTLs, CR was defined as the disappearance of all NTLs and normalization of tumor marker levels. The 95% CI was determined using the Pearson-Clopper method. AP: ITT population; only randomized participants with measurable disease at baseline were included in the analysis.

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

### End point timeframe:

Baseline ( $\leq 28$  days after randomization), every 8-9 weeks thereafter according to the standard of care of the treatment site until approximately 3 years

| End point values                  | Chemotherapy (CT) Arm | Chemotherapy Plus Bevacizumab (CT+BV) Arm |  |  |
|-----------------------------------|-----------------------|-------------------------------------------|--|--|
| Subject group type                | Reporting group       | Reporting group                           |  |  |
| Number of subjects analysed       | 185                   | 182                                       |  |  |
| Units: percentage of participants |                       |                                           |  |  |
| number (confidence interval 95%)  | 16.8 (11.7 to 22.9)   | 20.9 (15.2 to 27.5)                       |  |  |

## Statistical analyses

|                                         |                                                                   |
|-----------------------------------------|-------------------------------------------------------------------|
| Statistical analysis title              | Statistical Analysis 1                                            |
| Comparison groups                       | Chemotherapy (CT) Arm v Chemotherapy Plus Bevacizumab (CT+BV) Arm |
| Number of subjects included in analysis | 367                                                               |
| Analysis specification                  | Pre-specified                                                     |
| Analysis type                           | superiority <sup>[8]</sup>                                        |
| P-value                                 | = 0.3457 <sup>[9]</sup>                                           |
| Method                                  | Chi-squared                                                       |
| Parameter estimate                      | Mean difference (final values)                                    |
| Point estimate                          | 4.1                                                               |
| Confidence interval                     |                                                                   |
| level                                   | 95 %                                                              |
| sides                                   | 2-sided                                                           |
| lower limit                             | -4.2                                                              |
| upper limit                             | 12.4                                                              |

### Notes:

[8] - The 95% CI was estimated using Hauck-Anderson methodology.

[9] - P-value was calculated using two-sided chi-square test using Schouten correction.

## Secondary: Percentage of Participants With a Second-Line CR, PR, Stable Disease

**(SD), and PD According to RECIST v1.1 (Data Cutoff 20 December 2013)**

|                 |                                                                                                                                           |
|-----------------|-------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Percentage of Participants With a Second-Line CR, PR, Stable Disease (SD), and PD According to RECIST v1.1 (Data Cutoff 20 December 2013) |
|-----------------|-------------------------------------------------------------------------------------------------------------------------------------------|

## End point description:

For TLs, CR was defined as the disappearance of all TLs; PR was defined as at least a 30% decrease in the SLD of the TLs, taking as a reference the baseline SLD; SD was defined as neither sufficient decrease in SLD to qualify for PR nor sufficient increase in SLD to qualify for PD; and PD was defined as at least a 20% increase in the SLD of TLs, taking as reference the smallest SLD recorded since the treatment started. For NTLs, CR was defined as the disappearance of all NTLs and normalization of tumor marker levels; SD was defined as the persistence of 1 or more NTLs and/or maintenance of tumor marker levels above normal limits; and PD was defined as the appearance of 1 or more new lesions and/or unequivocal progression of existing NTLs. The 95% CI was determined using the Pearson-Clopper method.

AP: ITT population; only randomized participants with measurable disease at baseline were included in the analysis.

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

## End point timeframe:

Baseline ( $\leq 28$  days after randomization), every 8-9 weeks thereafter according to the standard of care of the treatment site until approximately 3 years

| End point values                  | Chemotherapy (CT) Arm | Chemotherapy Plus Bevacizumab (CT+BV) Arm |  |  |
|-----------------------------------|-----------------------|-------------------------------------------|--|--|
| Subject group type                | Reporting group       | Reporting group                           |  |  |
| Number of subjects analysed       | 185                   | 182                                       |  |  |
| Units: percentage of participants |                       |                                           |  |  |
| number (confidence interval 95%)  |                       |                                           |  |  |
| CR                                | 1.1 (0.1 to 3.9)      | 0.5 (0 to 3)                              |  |  |
| PR                                | 15.7 (10.8 to 21.7)   | 20.3 (14.7 to 26.9)                       |  |  |
| SD                                | 33.5 (26.8 to 40.8)   | 48.9 (41.4 to 56.4)                       |  |  |
| PD                                | 41.1 (33.9 to 48.5)   | 24.2 (18.1 to 31.1)                       |  |  |
| Unable to assess                  | 8.6 (5 to 13.7)       | 6 (3.1 to 10.6)                           |  |  |

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Duration of Second-Line Objective Response (Data Cutoff 20 December 2013)**

|                 |                                                                           |
|-----------------|---------------------------------------------------------------------------|
| End point title | Duration of Second-Line Objective Response (Data Cutoff 20 December 2013) |
|-----------------|---------------------------------------------------------------------------|

## End point description:

The median time in months from the date of the first second-line documentation of CR or PR according to RECIST v1.1 to the date of the first second-line documentation of PD or death due to any cause. For TLs, CR was disappearance of all TLs; PR was at least a 30% decrease in the SLD of the TLs, taking as reference the baseline SLD; and PD was at least a 20% increase in the SLD of TLs, taking as reference the smallest SLD recorded since the treatment started. For NTLs, CR was disappearance of all NTLs and normalization of tumor marker levels, and PD was defined as the appearance of 1 or more new lesions and/or unequivocal progression of existing NTLs. Participants with CR or PR who had experienced

neither disease progression nor died were censored at the date of the last available tumor assessment when the participant was known to be progression free.

AP: ITT population; only randomized participants with a CR or PR were included in the analysis.

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

End point timeframe:

Baseline ( $\leq 28$  days after randomization), every 8-9 weeks thereafter according to the standard of care of the treatment site until approximately 3 years

| End point values                 | Chemotherapy (CT) Arm | Chemotherapy Plus Bevacizumab (CT+BV) Arm |  |  |
|----------------------------------|-----------------------|-------------------------------------------|--|--|
| Subject group type               | Reporting group       | Reporting group                           |  |  |
| Number of subjects analysed      | 31                    | 38                                        |  |  |
| Units: months                    |                       |                                           |  |  |
| median (confidence interval 95%) | 10.6 (4.4 to 16.7)    | 8.3 (6.1 to 10.3)                         |  |  |

## Statistical analyses

|                                   |                        |
|-----------------------------------|------------------------|
| <b>Statistical analysis title</b> | Statistical Analysis 1 |
|-----------------------------------|------------------------|

Statistical analysis description:

The 95% CI was estimated using Cox proportional hazards methodology. The stratification factors used in stratified analysis were hormone receptor status, first-line PFS, choice of chemotherapy, and LDH level.

|                                         |                                                                   |
|-----------------------------------------|-------------------------------------------------------------------|
| Comparison groups                       | Chemotherapy (CT) Arm v Chemotherapy Plus Bevacizumab (CT+BV) Arm |
| Number of subjects included in analysis | 69                                                                |
| Analysis specification                  | Pre-specified                                                     |
| Analysis type                           | superiority                                                       |
| P-value                                 | = 0.9825                                                          |
| Method                                  | Logrank                                                           |
| Parameter estimate                      | Hazard ratio (HR)                                                 |
| Point estimate                          | 1.01                                                              |
| Confidence interval                     |                                                                   |
| level                                   | 95 %                                                              |
| sides                                   | 2-sided                                                           |
| lower limit                             | 0.51                                                              |
| upper limit                             | 1.99                                                              |

|                                   |                        |
|-----------------------------------|------------------------|
| <b>Statistical analysis title</b> | Statistical Analysis 2 |
|-----------------------------------|------------------------|

Statistical analysis description:

Unstratified analysis.

|                   |                                                                   |
|-------------------|-------------------------------------------------------------------|
| Comparison groups | Chemotherapy (CT) Arm v Chemotherapy Plus Bevacizumab (CT+BV) Arm |
|-------------------|-------------------------------------------------------------------|

|                                         |                   |
|-----------------------------------------|-------------------|
| Number of subjects included in analysis | 69                |
| Analysis specification                  | Pre-specified     |
| Analysis type                           | superiority       |
| P-value                                 | = 0.3601          |
| Method                                  | Logrank           |
| Parameter estimate                      | Hazard ratio (HR) |
| Point estimate                          | 1.31              |
| Confidence interval                     |                   |
| level                                   | 95 %              |
| sides                                   | 2-sided           |
| lower limit                             | 0.73              |
| upper limit                             | 2.34              |

---

**Secondary: Percentage of Participants With a Second-Line Documented CR or PR According to RECIST v1.1 Estimated to be Alive and Free of Disease Progression at Months 3, 6, and 9 (Data Cutoff 20 December 2013)**

---

|                 |                                                                                                                                                                                                       |
|-----------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Percentage of Participants With a Second-Line Documented CR or PR According to RECIST v1.1 Estimated to be Alive and Free of Disease Progression at Months 3, 6, and 9 (Data Cutoff 20 December 2013) |
|-----------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

Duration of objective response was median time in months from date of first second-line documentation of CR or PR to date of first second-line documentation of PD or death due to any cause. For TLs, CR was disappearance of all TLs; PR was at least a 30% decrease in SLD of TLs, taking as a reference the baseline SLD; and PD was as at least a 20% increase in SLD of TLs, taking as reference smallest SLD recorded since treatment started. For NTLs, CR was disappearance of all NTLs and normalization of tumor marker levels, and PD was appearance of one or more new lesions and/or unequivocal progression of existing NTLs. Participants with CR or PR who had experienced neither disease progression nor died were censored at date of last available tumor assessment when the participant was known to be progression free.

AP: ITT population - only randomized participants with CR or PR included in analysis. "99.9 and 999.9": data unavailable as all participants were alive and free of PD at Month 3.

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

End point timeframe:

Months 3, 6, and 9

---

| <b>End point values</b>           | Chemotherapy (CT) Arm | Chemotherapy Plus Bevacizumab (CT+BV) Arm |  |  |
|-----------------------------------|-----------------------|-------------------------------------------|--|--|
| Subject group type                | Reporting group       | Reporting group                           |  |  |
| Number of subjects analysed       | 31                    | 38                                        |  |  |
| Units: percentage of participants |                       |                                           |  |  |
| number (confidence interval 95%)  |                       |                                           |  |  |
| Month 3                           | 96.7 (78.6 to 99.5)   | 100 (99.9 to 999.9)                       |  |  |
| Month 6                           | 69 (48.9 to 82.5)     | 72.8 (55.3 to 84.4)                       |  |  |
| Month 9                           | 60.9 (40.4 to 76.3)   | 40.8 (24.6 to 56.3)                       |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Participants With Third-Line PFS According to RECIST v1.1

|                 |                                                                         |
|-----------------|-------------------------------------------------------------------------|
| End point title | Percentage of Participants With Third-Line PFS According to RECIST v1.1 |
|-----------------|-------------------------------------------------------------------------|

End point description:

Third-line PFS was defined as the time from the date of first dose of third-line bevacizumab and/or chemotherapy to the date of third-line PD or death due to any cause. For TLs, PD was defined at least a 20% increase in the SLD, taking as reference the smallest SLD recorded from baseline or the appearance of one or more new lesions. For NTLs, PD was defined as the appearance of 1 or more new lesions and/or unequivocal progression of existing NTLs. Participants without second-line PD or death were censored at the date of last tumor assessment where non-progression was documented. Participants without third-line PD or death were censored at the date of last tumor assessment where non-progression was documented.

AP: Third line ITT population: all randomized participants who received third-line treatment.

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

End point timeframe:

First dose of third-line treatment until PD or death due to any cause (assessed every 8-9 weeks, over a period of approximately 14 months)

| End point values                  | Chemotherapy (CT) Arm | Chemotherapy Plus Bevacizumab (CT+BV) Arm |  |  |
|-----------------------------------|-----------------------|-------------------------------------------|--|--|
| Subject group type                | Reporting group       | Reporting group                           |  |  |
| Number of subjects analysed       | 105                   | 129                                       |  |  |
| Units: percentage of participants |                       |                                           |  |  |
| number (not applicable)           | 94.3                  | 96.1                                      |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Third-Line PFS

|                 |                |
|-----------------|----------------|
| End point title | Third-Line PFS |
|-----------------|----------------|

End point description:

The median time, in months, from the first dose of third-line bevacizumab and/or chemotherapy to third-line PD or death, due to any cause. For TLs, PD was defined as at least a 20% increase in SLD, taking as reference the smallest SLD recorded from baseline or the appearance of 1 or more new lesions. For NTLs, PD was defined as the appearance of 1 or more new lesions and/or unequivocal progression of NTLs. Participants without third-line PD or death were censored at the date of last tumor assessment where non-progression was documented.

AP: Third line ITT population.

|                                                                                                                                            |           |
|--------------------------------------------------------------------------------------------------------------------------------------------|-----------|
| End point type                                                                                                                             | Secondary |
| End point timeframe:                                                                                                                       |           |
| First dose of third-line treatment until PD or death due to any cause (assessed every 8-9 weeks, over a period of approximately 14 months) |           |

| End point values                 | Chemotherapy (CT) Arm | Chemotherapy Plus Bevacizumab (CT+BV) Arm |  |  |
|----------------------------------|-----------------------|-------------------------------------------|--|--|
| Subject group type               | Reporting group       | Reporting group                           |  |  |
| Number of subjects analysed      | 105                   | 129                                       |  |  |
| Units: months                    |                       |                                           |  |  |
| median (confidence interval 95%) | 2.9 (2.2 to 3.9)      | 3.8 (2.4 to 5.1)                          |  |  |

## Statistical analyses

| Statistical analysis title                                                                                                                                                                                       | Statistical Analysis 1                                            |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------|
| Statistical analysis description:                                                                                                                                                                                |                                                                   |
| The 95% CI was estimated using Cox proportional hazards methodology. The stratification factors used in stratified analysis were hormone receptor status, first-line PFS, choice of chemotherapy, and LDH level. |                                                                   |
| Comparison groups                                                                                                                                                                                                | Chemotherapy (CT) Arm v Chemotherapy Plus Bevacizumab (CT+BV) Arm |
| Number of subjects included in analysis                                                                                                                                                                          | 234                                                               |
| Analysis specification                                                                                                                                                                                           | Pre-specified                                                     |
| Analysis type                                                                                                                                                                                                    | superiority                                                       |
| P-value                                                                                                                                                                                                          | = 0.108                                                           |
| Method                                                                                                                                                                                                           | Logrank                                                           |
| Parameter estimate                                                                                                                                                                                               | Hazard ratio (HR)                                                 |
| Point estimate                                                                                                                                                                                                   | 0.79                                                              |
| Confidence interval                                                                                                                                                                                              |                                                                   |
| level                                                                                                                                                                                                            | 95 %                                                              |
| sides                                                                                                                                                                                                            | 2-sided                                                           |
| lower limit                                                                                                                                                                                                      | 0.59                                                              |
| upper limit                                                                                                                                                                                                      | 1.06                                                              |

| Statistical analysis title                            | Statistical Analysis 2                                            |
|-------------------------------------------------------|-------------------------------------------------------------------|
| Statistical analysis description:                     |                                                                   |
| The 95% CI was estimated using unstratified analysis. |                                                                   |
| Comparison groups                                     | Chemotherapy Plus Bevacizumab (CT+BV) Arm v Chemotherapy (CT) Arm |

|                                         |                   |
|-----------------------------------------|-------------------|
| Number of subjects included in analysis | 234               |
| Analysis specification                  | Pre-specified     |
| Analysis type                           | superiority       |
| P-value                                 | = 0.0625          |
| Method                                  | Logrank           |
| Parameter estimate                      | Hazard ratio (HR) |
| Point estimate                          | 0.78              |
| Confidence interval                     |                   |
| level                                   | 95 %              |
| sides                                   | 2-sided           |
| lower limit                             | 0.59              |
| upper limit                             | 1.02              |

### Secondary: Percentage of Participants With Second- and Third-Line PFS According to RECIST v1.1

|                 |                                                                                     |
|-----------------|-------------------------------------------------------------------------------------|
| End point title | Percentage of Participants With Second- and Third-Line PFS According to RECIST v1.1 |
|-----------------|-------------------------------------------------------------------------------------|

End point description:

Second- and third-line PFS was defined as the time from the date randomization to the date of third-line PD or death due to any cause. For TLs, PD was defined at least a 20% increase in the SLD, taking as reference the smallest SLD recorded from baseline or the appearance of one or more new lesions. For NTLs, PD was defined as the appearance of 1 or more new lesions and/or unequivocal progression of existing NTLs. Participants without third-line PD or death were censored at the date of last tumor assessment where non-progression was documented.

AP: ITT population.

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

End point timeframe:

Baseline ( $\leq 28$  days after randomization), every 8-9 weeks thereafter according to the standard of care of the treatment site until approximately 4 years

| End point values                  | Chemotherapy (CT) Arm | Chemotherapy Plus Bevacizumab (CT+BV) Arm |  |  |
|-----------------------------------|-----------------------|-------------------------------------------|--|--|
| Subject group type                | Reporting group       | Reporting group                           |  |  |
| Number of subjects analysed       | 247                   | 247                                       |  |  |
| Units: percentage of participants |                       |                                           |  |  |
| number (not applicable)           | 71.7                  | 83.4                                      |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Second- and Third-Line PFS

|                 |                            |
|-----------------|----------------------------|
| End point title | Second- and Third-Line PFS |
|-----------------|----------------------------|

End point description:

The median time, in months, from randomization to third-line PFS event. For TLs, PD was defined as at

least a 20% increase in SLD, taking as reference the smallest SLD recorded from the baseline or the appearance of one or more lesions. For NTLs, PD was defined as the appearance of one or more lesions and/or unequivocal progression of existing NTLs. Participants without third-line PD or death were censored at the date of last tumor assessment where non-progression was documented.

AP: ITT population.

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

End point timeframe:

Baseline ( $\leq 28$  days after randomization), every 8-9 weeks thereafter according to the standard of care of the treatment site until approximately 4 years

| End point values                 | Chemotherapy (CT) Arm | Chemotherapy Plus Bevacizumab (CT+BV) Arm |  |  |
|----------------------------------|-----------------------|-------------------------------------------|--|--|
| Subject group type               | Reporting group       | Reporting group                           |  |  |
| Number of subjects analysed      | 247                   | 247                                       |  |  |
| Units: months                    |                       |                                           |  |  |
| median (confidence interval 95%) | 10.7 (9.2 to 12.5)    | 12.8 (10.7 to 14.5)                       |  |  |

## Statistical analyses

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

Statistical analysis description:

The 95% CI was estimated using Cox proportional hazards methodology. The stratification factors used in stratified analysis were hormone receptor status, first-line PFS, choice of chemotherapy, and LDH level.

|                                         |                                                                   |
|-----------------------------------------|-------------------------------------------------------------------|
| Comparison groups                       | Chemotherapy (CT) Arm v Chemotherapy Plus Bevacizumab (CT+BV) Arm |
| Number of subjects included in analysis | 494                                                               |
| Analysis specification                  | Pre-specified                                                     |
| Analysis type                           | superiority                                                       |
| P-value                                 | = 0.1349                                                          |
| Method                                  | Logrank                                                           |
| Parameter estimate                      | Hazard ratio (HR)                                                 |
| Point estimate                          | 0.85                                                              |
| Confidence interval                     |                                                                   |
| level                                   | 95 %                                                              |
| sides                                   | 2-sided                                                           |
| lower limit                             | 0.68                                                              |
| upper limit                             | 1.05                                                              |

|                            |                        |
|----------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 2 |
|----------------------------|------------------------|

Statistical analysis description:

The 95% CI was estimated using unstratified analysis.

|                   |                                                                   |
|-------------------|-------------------------------------------------------------------|
| Comparison groups | Chemotherapy (CT) Arm v Chemotherapy Plus Bevacizumab (CT+BV) Arm |
|-------------------|-------------------------------------------------------------------|

|                                         |                   |
|-----------------------------------------|-------------------|
| Number of subjects included in analysis | 494               |
| Analysis specification                  | Pre-specified     |
| Analysis type                           | superiority       |
| P-value                                 | = 0.0863          |
| Method                                  | Logrank           |
| Parameter estimate                      | Hazard ratio (HR) |
| Point estimate                          | 0.84              |
| Confidence interval                     |                   |
| level                                   | 95 %              |
| sides                                   | 2-sided           |
| lower limit                             | 0.68              |
| upper limit                             | 1.03              |

### Secondary: Percentage of Participants With Second- and Third-Line Tumor Progression

|                 |                                                                          |
|-----------------|--------------------------------------------------------------------------|
| End point title | Percentage of Participants With Second- and Third-Line Tumor Progression |
|-----------------|--------------------------------------------------------------------------|

End point description:

Second- and third-line tumor progression was defined as the time from the date of randomization to the date of third-line PD according to RECIST v1.1 or death due to progression of disease. For TLs, PD was defined at least a 20% increase in the SLD, taking as reference the smallest SLD recorded from baseline or the appearance of one or more new lesions. For NTLs, PD was defined as the appearance of one or more new lesions and/or unequivocal progression of existing NTLs. Participants without third-line PD or death due to progression of disease were censored at the date of last tumor assessment where non-progression was documented.

AP: ITT population.

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

End point timeframe:

Baseline (≤28 days after randomization), every 8-9 weeks thereafter according to the standard of care of the treatment site until approximately 4 years

| End point values                  | Chemotherapy (CT) Arm | Chemotherapy Plus Bevacizumab (CT+BV) Arm |  |  |
|-----------------------------------|-----------------------|-------------------------------------------|--|--|
| Subject group type                | Reporting group       | Reporting group                           |  |  |
| Number of subjects analysed       | 247                   | 247                                       |  |  |
| Units: percentage of participants |                       |                                           |  |  |
| number (not applicable)           | 67.2                  | 75.3                                      |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Time to Second- and Third-Line Tumor Progression

|                 |                                                  |
|-----------------|--------------------------------------------------|
| End point title | Time to Second- and Third-Line Tumor Progression |
|-----------------|--------------------------------------------------|

**End point description:**

Time to second- and third-line tumor progression was defined as the interval from the date of randomization until the earlier date of the third-line disease progression or death due to progression of disease. For TLs, PD was defined as at least a 20% increase in SLD, taking as reference the smallest SLD recorded from baseline or the appearance of one or more lesions. For NTLs, PD was defined as the appearance of one or more new lesions and/or unequivocal progression of existing NTLs. Participants without third-line PD or death were censored at the date of last tumor assessment where non-progression was documented.

AP: ITT population.

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

**End point timeframe:**

Baseline ( $\leq 28$  days after randomization), every 8-9 weeks thereafter according to the standard of care of the treatment site until approximately 4 years

| End point values                 | Chemotherapy (CT) Arm | Chemotherapy Plus Bevacizumab (CT+BV) Arm |  |  |
|----------------------------------|-----------------------|-------------------------------------------|--|--|
| Subject group type               | Reporting group       | Reporting group                           |  |  |
| Number of subjects analysed      | 247                   | 247                                       |  |  |
| Units: months                    |                       |                                           |  |  |
| median (confidence interval 95%) | 11.2 (9.4 to 12.7)    | 13.3 (12 to 15.5)                         |  |  |

**Statistical analyses**

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

**Statistical analysis description:**

The 95% CI was estimated using Cox proportional hazards methodology. The stratification factors used in stratified analysis were hormone receptor status, first-line PFS, choice of chemotherapy, and LDH level.

|                                         |                                                                   |
|-----------------------------------------|-------------------------------------------------------------------|
| Comparison groups                       | Chemotherapy (CT) Arm v Chemotherapy Plus Bevacizumab (CT+BV) Arm |
| Number of subjects included in analysis | 494                                                               |
| Analysis specification                  | Pre-specified                                                     |
| Analysis type                           | superiority                                                       |
| P-value                                 | = 0.0744                                                          |
| Method                                  | Logrank                                                           |
| Parameter estimate                      | Hazard ratio (HR)                                                 |
| Point estimate                          | 0.81                                                              |
| Confidence interval                     |                                                                   |
| level                                   | 95 %                                                              |
| sides                                   | 2-sided                                                           |
| lower limit                             | 0.65                                                              |
| upper limit                             | 1.02                                                              |

|                            |                        |
|----------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 2 |
|----------------------------|------------------------|

Statistical analysis description:

The 95% CI was estimated using unstratified analysis.

|                                         |                                                                   |
|-----------------------------------------|-------------------------------------------------------------------|
| Comparison groups                       | Chemotherapy (CT) Arm v Chemotherapy Plus Bevacizumab (CT+BV) Arm |
| Number of subjects included in analysis | 494                                                               |
| Analysis specification                  | Pre-specified                                                     |
| Analysis type                           | superiority                                                       |
| P-value                                 | = 0.0503                                                          |
| Method                                  | Logrank                                                           |
| Parameter estimate                      | Hazard ratio (HR)                                                 |
| Point estimate                          | 0.81                                                              |
| Confidence interval                     |                                                                   |
| level                                   | 95 %                                                              |
| sides                                   | 2-sided                                                           |
| lower limit                             | 0.66                                                              |
| upper limit                             | 1                                                                 |

### Secondary: Percentage of Participants Who Died

|                                                                                                                       |                                     |
|-----------------------------------------------------------------------------------------------------------------------|-------------------------------------|
| End point title                                                                                                       | Percentage of Participants Who Died |
| End point description:<br>Percentage of participants who died due to any reason were reported.<br>AP: ITT population. |                                     |
| End point type                                                                                                        | Secondary                           |
| End point timeframe:<br>Baseline until death (up to approximately 4 years)                                            |                                     |

| End point values                  | Chemotherapy (CT) Arm | Chemotherapy Plus Bevacizumab (CT+BV) Arm |  |  |
|-----------------------------------|-----------------------|-------------------------------------------|--|--|
| Subject group type                | Reporting group       | Reporting group                           |  |  |
| Number of subjects analysed       | 247                   | 247                                       |  |  |
| Units: percentage of participants |                       |                                           |  |  |
| number (not applicable)           | 63.2                  | 66                                        |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Overall Survival (OS)

|                                                                                                                                                                                                                                                                       |                       |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|
| End point title                                                                                                                                                                                                                                                       | Overall Survival (OS) |
| End point description:<br>OS was defined as the median time, in months, from the date of randomization to the date of death, due to any cause. Participants who had not died were censored at the date the patient was last known to be alive.<br>AP: ITT population. |                       |

|                                                    |           |
|----------------------------------------------------|-----------|
| End point type                                     | Secondary |
| End point timeframe:                               |           |
| Baseline until death (up to approximately 4 years) |           |

| End point values                 | Chemotherapy (CT) Arm | Chemotherapy Plus Bevacizumab (CT+BV) Arm |  |  |
|----------------------------------|-----------------------|-------------------------------------------|--|--|
| Subject group type               | Reporting group       | Reporting group                           |  |  |
| Number of subjects analysed      | 247                   | 247                                       |  |  |
| Units: months                    |                       |                                           |  |  |
| median (confidence interval 95%) | 18.7 (15.4 to 21.2)   | 19.7 (17.6 to 21)                         |  |  |

## Statistical analyses

| Statistical analysis title                                                                                                                                                                                       | Statistical Analysis 1                                            |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------|
| Statistical analysis description:                                                                                                                                                                                |                                                                   |
| The 95% CI was estimated using Cox proportional hazards methodology. The stratification factors used in stratified analysis were hormone receptor status, first-line PFS, choice of chemotherapy, and LDH level. |                                                                   |
| Comparison groups                                                                                                                                                                                                | Chemotherapy (CT) Arm v Chemotherapy Plus Bevacizumab (CT+BV) Arm |
| Number of subjects included in analysis                                                                                                                                                                          | 494                                                               |
| Analysis specification                                                                                                                                                                                           | Pre-specified                                                     |
| Analysis type                                                                                                                                                                                                    | superiority                                                       |
| P-value                                                                                                                                                                                                          | = 0.7253                                                          |
| Method                                                                                                                                                                                                           | Logrank                                                           |
| Parameter estimate                                                                                                                                                                                               | Hazard ratio (HR)                                                 |
| Point estimate                                                                                                                                                                                                   | 0.96                                                              |
| Confidence interval                                                                                                                                                                                              |                                                                   |
| level                                                                                                                                                                                                            | 95 %                                                              |
| sides                                                                                                                                                                                                            | 2-sided                                                           |
| lower limit                                                                                                                                                                                                      | 0.76                                                              |
| upper limit                                                                                                                                                                                                      | 1.21                                                              |

| Statistical analysis title                           | Statistical Analysis 2                                            |
|------------------------------------------------------|-------------------------------------------------------------------|
| Statistical analysis description:                    |                                                                   |
| The 95% CI was estimated using unstratified analysis |                                                                   |
| Comparison groups                                    | Chemotherapy (CT) Arm v Chemotherapy Plus Bevacizumab (CT+BV) Arm |

|                                         |                   |
|-----------------------------------------|-------------------|
| Number of subjects included in analysis | 494               |
| Analysis specification                  | Pre-specified     |
| Analysis type                           | superiority       |
| P-value                                 | = 0.5332          |
| Method                                  | Logrank           |
| Parameter estimate                      | Hazard ratio (HR) |
| Point estimate                          | 0.93              |
| Confidence interval                     |                   |
| level                                   | 95 %              |
| sides                                   | 2-sided           |
| lower limit                             | 0.75              |
| upper limit                             | 1.16              |

### Secondary: Percentage of Participants Estimated to be Surviving at Months 6, 12, 18, and 24

|                 |                                                                                  |
|-----------------|----------------------------------------------------------------------------------|
| End point title | Percentage of Participants Estimated to be Surviving at Months 6, 12, 18, and 24 |
|-----------------|----------------------------------------------------------------------------------|

End point description:

OS was defined as the median time, in months, from the date of randomization to the date of death, due to any cause. Participants who had not died were censored at the date the participant was last known to be alive.

AP: ITT population.

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

End point timeframe:

Months 6, 12, 18, and 24

| End point values                  | Chemotherapy (CT) Arm | Chemotherapy Plus Bevacizumab (CT+BV) Arm |  |  |
|-----------------------------------|-----------------------|-------------------------------------------|--|--|
| Subject group type                | Reporting group       | Reporting group                           |  |  |
| Number of subjects analysed       | 247                   | 247                                       |  |  |
| Units: percentage of participants |                       |                                           |  |  |
| number (confidence interval 95%)  |                       |                                           |  |  |
| Month 6                           | 85.2 (79.9 to 89.2)   | 90.4 (85.9 to 93.5)                       |  |  |
| Month 12                          | 68.6 (62 to 74.3)     | 72.4 (66.2 to 77.7)                       |  |  |
| Month 18                          | 52.8 (46 to 59.3)     | 54.9 (48.2 to 61)                         |  |  |
| Month 24                          | 38.4 (31.8 to 44.9)   | 37.6 (31.3 to 43.9)                       |  |  |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Participants Experiencing Problems by European Quality of Life Instrument (EQ-5D) Category (Data Cutoff 20 December 2013)

|                 |                                                                                                                                         |
|-----------------|-----------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Percentage of Participants Experiencing Problems by European Quality of Life Instrument (EQ-5D) Category (Data Cutoff 20 December 2013) |
|-----------------|-----------------------------------------------------------------------------------------------------------------------------------------|

End point description:

EQ-5D is composed of 5 single-item measures and participants (pts) responded to questions assessing health status by responding with either 'no problems', 'some problems', or 'extreme problems' in the following categories: mobility (M) ('no problems'='I have no problems in walking about' to 'extreme problems'='I am confined to bed'), self-care (SC) ('no problems'='I have no problems with SC' to 'extreme problems'='I am unable to wash or dress myself'), usual activities (UA) ('no problems'='I have no problems performing my UA' to 'extreme problems'='I am unable to perform my UA'), pain/discomfort (P/D) ('no problems'='I have no P/D' to 'extreme problems'='I have extreme P/D'), and anxiety/depression (A/D) ('no problems'='I am not anxious or depressed' to 'extreme problems'='I am extremely anxious or depressed').

AP: ITT population. Here, Number of pts analyzed = pts evaluable for this end point and n= number of pts completing questionnaires at specified time point.

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

End point timeframe:

Baseline (BL), during second-line treatment at Weeks 8 and 16 (4-week cycles) or Weeks 9 and 18 (3-week cycles) and at second-line PD (up to approximately 3 years)

| End point values                          | Chemotherapy (CT) Arm | Chemotherapy Plus Bevacizumab (CT+BV) Arm |  |  |
|-------------------------------------------|-----------------------|-------------------------------------------|--|--|
| Subject group type                        | Reporting group       | Reporting group                           |  |  |
| Number of subjects analysed               | 214                   | 224                                       |  |  |
| Units: percentage of participants         |                       |                                           |  |  |
| number (not applicable)                   |                       |                                           |  |  |
| BL: M, no problems (n=214,224)            | 60.3                  | 64.3                                      |  |  |
| BL: M, some problems (n=214,224)          | 36.4                  | 34.8                                      |  |  |
| BL: M, extreme problems (n=214,224)       | 0.5                   | 0.4                                       |  |  |
| BL: SC, no problems (n=214,224)           | 82.7                  | 85.7                                      |  |  |
| BL: SC, some problems (n=214,224)         | 12.6                  | 11.2                                      |  |  |
| BL: SC, extreme problems (n=214,224)      | 0.5                   | 1.8                                       |  |  |
| BL: UA, no problems (n=214,224)           | 53.7                  | 46.4                                      |  |  |
| BL: UA, some problems (n=214,224)         | 40.2                  | 48.7                                      |  |  |
| BL: UA, extreme problems (n=214,224)      | 2.8                   | 4                                         |  |  |
| BL: P/D, no problems (n=214,224)          | 24.3                  | 27.7                                      |  |  |
| BL: P/D, some problems (n=214,224)        | 68.7                  | 66.1                                      |  |  |
| BL: P/D, extreme problems (n=214,224)     | 4.2                   | 5.4                                       |  |  |
| BL: A/D, no problems (n=214,224)          | 33.6                  | 34.8                                      |  |  |
| BL: A/D, some problems (n=214,224)        | 56.5                  | 58.5                                      |  |  |
| BL: A/D, extreme problems (n=214,224)     | 5.6                   | 5.8                                       |  |  |
| Week 8/9: M, no problems (n=133,141)      | 61.7                  | 51.8                                      |  |  |
| Week 8/9: M, some problems (n=133,141)    | 34.6                  | 43.3                                      |  |  |
| Week 8/9: M, extreme problems (n=133,141) | 1.5                   | 2.1                                       |  |  |
| Week 8/9: SC, no problems (n=133,141)     | 82                    | 75.9                                      |  |  |

|                                                  |      |      |  |  |
|--------------------------------------------------|------|------|--|--|
| Week 8/9: SC, some problems<br>(n=133,141)       | 13.5 | 17   |  |  |
| Week 8/9: SC, extreme problems<br>(n=133,141)    | 1.5  | 3.5  |  |  |
| Week 8/9: UA, no problems<br>(n=133,141)         | 53.4 | 40.4 |  |  |
| Week 8/9: UA, some problems<br>(n=133,141)       | 40.6 | 51.8 |  |  |
| Week 8/9: UA, extreme problems<br>(n=133,141)    | 3    | 5    |  |  |
| Week 8/9: P/D, no problems<br>(n=133,141)        | 29.3 | 23.4 |  |  |
| Week 8/9: P/D, some problems<br>(n=133,141)      | 61.7 | 68.1 |  |  |
| Week 8/9: P/D, extreme problems<br>(n=133,141)   | 5.3  | 6.4  |  |  |
| Week 8/9: A/D, no problems<br>(n=133,141)        | 49.6 | 46.8 |  |  |
| Week 8/9: A/D, some problems<br>(n=133,141)      | 40.6 | 48.2 |  |  |
| Week 8/9: A/D, extreme problems<br>(n=133,141)   | 6.8  | 2.8  |  |  |
| Week 16/18: M, no problems<br>(n=84,123)         | 66.7 | 49.6 |  |  |
| Week 16/18: M, some problems<br>(n=84,123)       | 29.8 | 47.2 |  |  |
| Week 16/18: M, extreme problems<br>(n=84,123)    | 0    | 2.4  |  |  |
| Week 16/18: SC, no problems<br>(n=84,123)        | 81   | 78.9 |  |  |
| Week 16/18: SC, some problems<br>(n=84,123)      | 14.3 | 17.1 |  |  |
| Week 16/18: SC, extreme problems<br>(n=84,123)   | 0    | 3.3  |  |  |
| Week 16/18: UA, no problems<br>(n=84,123)        | 50   | 36.6 |  |  |
| Week 16/18: UA, some problems<br>(n=84,123)      | 42.9 | 56.1 |  |  |
| Week 16/18: UA, extreme problems<br>(n=84,123)   | 3.6  | 4.1  |  |  |
| Week 16/18: P/D, no problems<br>(n=84,123)       | 34.5 | 19.5 |  |  |
| Week 16/18: P/D, some problems<br>(n=84,123)     | 59.5 | 76.4 |  |  |
| Week 16/18: P/D, extreme problems<br>(n=84,123)  | 1.2  | 3.3  |  |  |
| Week 16/18: A/D, no problems<br>(n=84,123)       | 51.2 | 49.6 |  |  |
| Week 16/18: A/D, some problems<br>(n=84,123)     | 44   | 43.1 |  |  |
| Week 16/18: A/D, extreme problems<br>(n=84,123)  | 0    | 5.7  |  |  |
| Second-line PD: M, no problems<br>(n=82,76)      | 59.8 | 47.4 |  |  |
| Second-line PD: M, some problems<br>(n=82,76)    | 34.1 | 48.7 |  |  |
| Second-line PD: M, extreme problems<br>(n=82,76) | 2.4  | 3.9  |  |  |
| Second-line PD: SC, no problems<br>(n=82,76)     | 76.8 | 75   |  |  |
| Second-line PD: SC, some problems<br>(n=82,76)   | 15.9 | 18.4 |  |  |

|                                                 |      |      |  |  |
|-------------------------------------------------|------|------|--|--|
| Second-line PD: SC, extreme problems (n=82,76)  | 1.2  | 6.6  |  |  |
| Second-line PD: UA, no problems (n=82,76)       | 39   | 30.3 |  |  |
| Second-line PD: UA, some problems (n=82,76)     | 50   | 59.2 |  |  |
| Second-line PD: UA, extreme problems (n=82,76)  | 6.1  | 10.5 |  |  |
| Second-line PD: P/D, no problems (n=82,76)      | 19.5 | 18.4 |  |  |
| Second-line PD: P/D, some problems (n=82,76)    | 67.1 | 69.7 |  |  |
| Second-line PD: P/D, extreme problems (n=82,76) | 8.5  | 11.8 |  |  |
| Second-line PD: A/D, no problems (n=82,76)      | 36.6 | 26.3 |  |  |
| Second-line PD: A/D, some problems (n=82,76)    | 50   | 61.8 |  |  |
| Second-line PD: A/D, extreme problems (n=82,76) | 7.3  | 11.8 |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Quality of Life Assessed As an Index Score Using the EQ-5D (Data Cutoff 20 December 2013)

|                 |                                                                                           |
|-----------------|-------------------------------------------------------------------------------------------|
| End point title | Quality of Life Assessed As an Index Score Using the EQ-5D (Data Cutoff 20 December 2013) |
|-----------------|-------------------------------------------------------------------------------------------|

End point description:

EQ-5D is composed of 5 single-item measures where participants responded to questions assessing health status by responding with either "no problems", "some problems", or "extreme problems" in the following categories: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Based on large population surveys, an algorithm was used to combine the responses to each of these 5 measures into 1 single EQ-5D index score ranging from -0.59 (extreme problems) to +1 (no problems). AP: ITT population. Here, Number of participants analyzed = participants evaluable for this end point and n= number of participants completing questionnaires at the specified time point.

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

End point timeframe:

Baseline, during second-line treatment at Weeks 8 and 16 (4-week cycles) or Weeks 9 and 18 (3-week cycles) and at second-line PD (up to approximately 3 years)

| End point values                          | Chemotherapy (CT) Arm | Chemotherapy Plus Bevacizumab (CT+BV) Arm |  |  |
|-------------------------------------------|-----------------------|-------------------------------------------|--|--|
| Subject group type                        | Reporting group       | Reporting group                           |  |  |
| Number of subjects analysed               | 202                   | 219                                       |  |  |
| Units: scores on a scale                  |                       |                                           |  |  |
| arithmetic mean (confidence interval 95%) |                       |                                           |  |  |

|                          |                           |                           |  |  |
|--------------------------|---------------------------|---------------------------|--|--|
| Baseline (n= 202, 219)   | 0.6806 (0.6489 to 0.7122) | 0.6725 (0.6389 to 0.7061) |  |  |
| Week 8/9 (n=127,135)     | 0.6953 (0.647 to 0.7437)  | 0.6515 (0.6057 to 0.6973) |  |  |
| Week 16/18 (n=80,118)    | 0.7496 (0.7114 to 0.7879) | 0.6534 (0.6058 to 0.701)  |  |  |
| Second-line PD (n=77,76) | 0.629 (0.5642 to 0.6938)  | 0.5553 (0.4736 to 0.637)  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline in EQ-5D Index Scores (Data Cutoff 20 December 2013)

|                 |                                                                           |
|-----------------|---------------------------------------------------------------------------|
| End point title | Change From Baseline in EQ-5D Index Scores (Data Cutoff 20 December 2013) |
|-----------------|---------------------------------------------------------------------------|

End point description:

EQ-5D is composed of 5 single-item measures where participants responded to questions assessing health status by responding with either "no problems", "some problems", or "extreme problems" in the following categories: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Based on large population surveys, an algorithm was used to combine the responses to each of these 5 measures into 1 single EQ-5D index score ranging from -0.59 (extreme problems) to +1 (no problems) where a negative value indicated a worsening of perceived quality of life and a positive value indicated an improvement of perceived quality of life.

AP: ITT population. Here, Number of participants analyzed = participants evaluable for this end point and n=number of participants completing the questionnaires at the specified timepoint.

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

End point timeframe:

Baseline, during second-line treatment at Weeks 8 and 16 (4-week cycles) or Weeks 9 and 18 (3-week cycles) and at second-line PD (up to approximately 3 years)

| End point values                          | Chemotherapy (CT) Arm        | Chemotherapy Plus Bevacizumab (CT+BV) Arm |  |  |
|-------------------------------------------|------------------------------|-------------------------------------------|--|--|
| Subject group type                        | Reporting group              | Reporting group                           |  |  |
| Number of subjects analysed               | 107                          | 122                                       |  |  |
| Units: scores on a scale                  |                              |                                           |  |  |
| arithmetic mean (confidence interval 95%) |                              |                                           |  |  |
| Week 8/9 (n=107,122)                      | -0.0103 (-0.0482 to 0.0276)  | -0.037 (-0.0868 to 0.0127)                |  |  |
| Week 16/18 (n=68,110)                     | 0.0387 (-0.0025 to 0.08)     | -0.0508 (-0.1038 to 0.0021)               |  |  |
| Second-line PD (n=69,71)                  | -0.0884 (-0.1398 to -0.0371) | -0.087 (-0.1649 to -0.0107)               |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Quality of Life Assessed Using the EQ-5D Visual Analogue Scale (VAS) Scores (Data Cutoff 20 December 2013)

|                 |                                                                                                            |
|-----------------|------------------------------------------------------------------------------------------------------------|
| End point title | Quality of Life Assessed Using the EQ-5D Visual Analogue Scale (VAS) Scores (Data Cutoff 20 December 2013) |
|-----------------|------------------------------------------------------------------------------------------------------------|

End point description:

The participant was asked to rate their overall health on a 0-100 millimeter (mm) vertical scale, where the lowest endpoint=0 (labeled as worst imaginable health state) and the highest endpoint =100 (labeled as the best imaginable health state). The participant marked the line corresponding to their assessment and the distance from the bottom was measured in mm. A higher value indicated a better health state.

AP: ITT population. Here, Number of participants analyzed = participants evaluable for this end point and n=number of participants completing the questionnaires at specified timepoint.

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

End point timeframe:

Baseline, during second-line treatment at Weeks 8 and 16 (4-week cycles) or Weeks 9 and 18 (3-week cycles) and at second-line PD (up to approximately 3 years)

| End point values                          | Chemotherapy (CT) Arm | Chemotherapy Plus Bevacizumab (CT+BV) Arm |  |  |
|-------------------------------------------|-----------------------|-------------------------------------------|--|--|
| Subject group type                        | Reporting group       | Reporting group                           |  |  |
| Number of subjects analysed               | 200                   | 212                                       |  |  |
| Units: millimeters (mm)                   |                       |                                           |  |  |
| arithmetic mean (confidence interval 95%) |                       |                                           |  |  |
| BL (n=200,212)                            | 66.5 (64.1 to 69)     | 63.4 (60.8 to 65.9)                       |  |  |
| Week 8/9 (n=123,135)                      | 69.3 (66.4 to 72.1)   | 66.5 (63.7 to 69.2)                       |  |  |
| Week 16/18 (n=75,119)                     | 67.3 (63.3 to 71.3)   | 66.4 (63.2 to 69.5)                       |  |  |
| Second-line PD (n=78,75)                  | 63.7 (59.5 to 68)     | 61.7 (57 to 66.5)                         |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change From Baseline in VAS Scores (Data Cutoff 20 December 2013)

|                 |                                                    |
|-----------------|----------------------------------------------------|
| End point title | Change From Baseline in VAS Scores (Data Cutoff 20 |
|-----------------|----------------------------------------------------|

**End point description:**

The participant was asked to rate their overall health on a 0-100 mm vertical scale, where the lowest endpoint =0 (labeled as worst imaginable health state) and the highest endpoint =100 (labeled as the best imaginable health state). The participant marked the line corresponding to their assessment and the distance from the bottom was measured in mm. A negative value indicated a worsening of perceived quality of life and a positive value indicated an improvement of perceived quality of life.

AP: ITT population. Here, Number of participants analyzed = participants evaluable for this end point and n=number of participants completing the questionnaires at the corresponding timepoint.

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

**End point timeframe:**

Baseline, during second-line treatment at Weeks 8 and 16 (4-week cycles) or Weeks 9 and 18 (3-week cycles) and at second-line PD (up to approximately 3 years)

| <b>End point values</b>                   | Chemotherapy (CT) Arm | Chemotherapy Plus Bevacizumab (CT+BV) Arm |  |  |
|-------------------------------------------|-----------------------|-------------------------------------------|--|--|
| Subject group type                        | Reporting group       | Reporting group                           |  |  |
| Number of subjects analysed               | 106                   | 118                                       |  |  |
| Units: millimeters (mm)                   |                       |                                           |  |  |
| arithmetic mean (confidence interval 95%) |                       |                                           |  |  |
| Week 8/9 (n=106,118)                      | -2 (-4.8 to 0.9)      | 2 (-1.4 to 5.3)                           |  |  |
| Week 16/18 (n=66,107)                     | -0.2 (-4.7 to 4.3)    | 2 (-1.6 to 5.5)                           |  |  |
| Second-line PD (n=70,69)                  | -5.1 (-9.1 to -1)     | -1.3 (-5.5 to 3)                          |  |  |

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Functional Assessment of Cancer Therapy-Breast (FACT-B) Scores (Data Cutoff 20 December 2013)**

|                 |                                                                                               |
|-----------------|-----------------------------------------------------------------------------------------------|
| End point title | Functional Assessment of Cancer Therapy-Breast (FACT-B) Scores (Data Cutoff 20 December 2013) |
|-----------------|-----------------------------------------------------------------------------------------------|

**End point description:**

FACT-B is composed of 5 multi-item sections and pts responded to questions assessing symptoms (scale: 0-4; 0='not at all' and 4='very much'): physical well-being (PWB; 7 items, total score 0-28), social/family well-being (SWB; 7 items, total score 0-28), emotional well-being (EWB; 6 items, total score 0-24), functional well-being (FWB; 7 items, total score 0-28); and breast cancer score based on the additional concerns section of FACT-B (10 items, total score 0-40). FACT-B Trial Outcomes Index (TOI)= sum of PWB, FWB, and breast cancer score subscale scores (total score 0-96). FACT-B total score=sum of PWB, SWB, EWB, FWB, and breast cancer score subscales scores (total score 0-148). A higher value indicated a better quality of life.

ITT population. No of pts analyzed = pts evaluable for this OM and n=no of pts completing the questionnaires at specified timepoint.

The data 9.99, 99.9, 999.9, 999, 9999, 99999 signifies data not available.

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

**End point timeframe:**

BL (≤28 days after randomization), every 8-9 weeks thereafter until second-line PD (up to approximately 3 years)

| <b>End point values</b>                      | Chemotherapy<br>(CT) Arm          | Chemotherapy<br>Plus<br>Bevacizumab<br>(CT+BV) Arm |  |  |
|----------------------------------------------|-----------------------------------|----------------------------------------------------|--|--|
| Subject group type                           | Reporting group                   | Reporting group                                    |  |  |
| Number of subjects analysed                  | 215                               | 224                                                |  |  |
| Units: scores on a scale                     |                                   |                                                    |  |  |
| median (confidence interval 95%)             |                                   |                                                    |  |  |
| BL: PWB (n=215,222)                          | 20.621 (19.9<br>to 21.342)        | 20.253 (19.5<br>to 21.006)                         |  |  |
| BL: SWB (n=214,223)                          | 20.722 (20.028<br>to 21.416)      | 20.674 (19.923<br>to 21.425)                       |  |  |
| BL: EWB (n=215,224)                          | 14.847 (14.176<br>to 15.519)      | 15.062 (14.419<br>to 15.704)                       |  |  |
| BL: FWB (n=215,224)                          | 16.091 (15.289<br>to 16.894)      | 15.726 (14.951<br>to 16.502)                       |  |  |
| BL: Breast Cancer Score (n=210,224)          | 24.986 (24.103<br>to 25.869)      | 24.388 (23.578<br>to 25.198)                       |  |  |
| BL: FACT-B TOI (n=204,219)                   | 61.677 (59.658<br>to 63.696)      | 60.277 (58.365<br>to 62.189)                       |  |  |
| BL: Total FACT-G Score (n=207,218)           | 72.169 (69.919<br>to 74.419)      | 71.864 (69.786<br>to 73.942)                       |  |  |
| BL: Total FACT-B Score (n=201,218)           | 96.908 (94.063<br>to 99.753)      | 96.115 (93.485<br>to 98.746)                       |  |  |
| Week 8/9: PWB (n=129,138)                    | 20.413 (19.413<br>to 21.413)      | 19.156 (18.158<br>to 20.153)                       |  |  |
| Week 8/9: SWB (n=127,135)                    | 20.833 (19.888<br>to 21.779)      | 21.116 (20.245<br>to 21.987)                       |  |  |
| Week 8/9: EWB (n=129,139)                    | 15.943 (15.07<br>to 16.815)       | 16.671 (15.9<br>to 17.441)                         |  |  |
| Week 8/9: FWB (n=129,139)                    | 16.662 (15.609<br>to 17.715)      | 16.169 (15.18<br>to 17.158)                        |  |  |
| Week 8/9: Breast Cancer Score<br>(n=128,139) | 26.276 (25.188<br>to 27.364)      | 25.884 (24.928<br>to 26.839)                       |  |  |
| Week 8/9: FACT-B TOI (n=126,136)             | 63.547 (60.975<br>to 66.118)      | 61.279 (58.811<br>to 63.747)                       |  |  |
| Week 8/9: Total FACT-G Score<br>(n=122,134)  | 74.255 (71.212<br>to 77.299)      | 73.393 (70.603<br>to 76.184)                       |  |  |
| Week 8/9: Total FACT-B Score<br>(n=123,134)  | 100.375<br>(96.582 to<br>104.169) | 99.213 (95.667<br>to 102.76)                       |  |  |

|                                      |                             |                            |  |  |
|--------------------------------------|-----------------------------|----------------------------|--|--|
| Week 16/18: PWB (n=83,107)           | 21.733 (20.721 to 22.744)   | 19.629 (18.571 to 20.688)  |  |  |
| Week 16/18: SWB (n=80,105)           | 20.93 (19.855 to 22.006)    | 20.843 (19.829 to 21.857)  |  |  |
| Week 16/18: EWB (n=80,107)           | 17.33 (16.26 to 18.4)       | 16.806 (15.961 to 17.65)   |  |  |
| Week 16/18: FWB (n=81,106)           | 17.055 (15.818 to 18.291)   | 15.92 (14.787 to 17.053)   |  |  |
| Week 16/18: Breast Cancer (n=81,106) | 26.923 (25.493 to 28.354)   | 25.755 (24.63 to 26.88)    |  |  |
| Week 16/18: FACT-B TOI (n=78,105)    | 65.628 (62.539 to 68.717)   | 61.107 (58.309 to 63.905)  |  |  |
| Week 16/18: Total FACT-G (n=78,102)  | 76.794 (73.269 to 80.318)   | 73.269 (70.116 to 76.421)  |  |  |
| Week 16/18: Total FACT-B (n=76,103)  | 103.503 (98.819 to 108.187) | 98.906 (94.865 to 102.948) |  |  |
| Week 24/27: PWB (n=48,80)            | 21.94 (20.599 to 23.282)    | 18.965 (17.515 to 20.416)  |  |  |
| Week 24/27: SWB (n=47,78)            | 20.84 (19.468 to 22.211)    | 21.399 (20.192 to 22.606)  |  |  |
| Week 24/27: EWB (n=45,78)            | 17.098 (15.719 to 18.477)   | 16.438 (15.411 to 17.436)  |  |  |
| Week 24/27: FWB (n=45,79)            | 18.244 (16.754 to 19.734)   | 16.051 (14.861 to 17.241)  |  |  |
| Week 24/27: Breast Cancer (n=46,79)  | 26.067 (24.146 to 27.988)   | 24.632 (23.231 to 26.033)  |  |  |
| Week 24/27: FACT-B TOI (n=44,77)     | 65.882 (61.991 to 69.653)   | 60.014 (56.548 to 63.48)   |  |  |
| Week 24/27: Total FACT-G (n=44,77)   | 78.305 (74.166 to 82.443)   | 73.083 (69.365 to 76.801)  |  |  |
| Week 24/27: Total FACT-B (n=43,77)   | 104.011 (98.433 to 109.588) | 97.795 (92.995 to 102.595) |  |  |
| Week 32/36: PWB (n=26,44)            | 22.949 (21.427 to 24.471)   | 19.686 (18.121 to 21.25)   |  |  |
| Week 32/36: SWB (n=25,43)            | 22.14 (20.433 to 23.847)    | 21.222 (19.645 to 22.798)  |  |  |
| Week 32/36: EWB (n=26,44)            | 18.385 (16.69 to 20.079)    | 16.755 (15.481 to 18.028)  |  |  |
| Week 32/36: FWB (n=26,44)            | 19.615 (17.875 to 21.356)   | 17.195 (15.585 to 18.805)  |  |  |
| Week 32/36: Breast Cancer (n=26,43)  | 29.568 (27.722 to 31.415)   | 26.163 (24.457 to 27.869)  |  |  |

|                                     |                              |                             |  |  |
|-------------------------------------|------------------------------|-----------------------------|--|--|
| Week 32/36: FACT-B TOI (n=26,42)    | 72.132 (68.549 to 75.716)    | 63.017 (59.199 to 66.836)   |  |  |
| Week 32/36: Total FACT-G (n=25,42)  | 83.087 (78.178 to 87.995)    | 74.879 (70.566 to 79.191)   |  |  |
| Week 32/36: Total FACT-B (n=25,42)  | 112.904 (107.315 to 118.494) | 100.904 (95.302 to 106.506) |  |  |
| Week 40/45: PWB (n=20,27)           | 22.215 (20.583 to 23.847)    | 20.63 (18.82 to 22.44)      |  |  |
| Week 40/45: SWB (n=21,26)           | 19.658 (17.955 to 21.361)    | 20.915 (19.146 to 22.685)   |  |  |
| Week 40/45: EWB (n=20,27)           | 17.56 (15.708 to 19.412)     | 16.067 (13.875 to 18.259)   |  |  |
| Week 40/45: FWB (n=20,27)           | 18.45 (16.12 to 20.78)       | 16.519 (13.901 to 19.136)   |  |  |
| Week 40/45: Breast Cancer (n=21,27) | 29.386 (27.156 to 31.616)    | 23.819 (21.013 to 26.625)   |  |  |
| Week 40/45: FACT-B TOI (n=19,27)    | 68.75 (63.981 to 73.518)     | 60.967 (55.065 to 66.87)    |  |  |
| Week 40/45: Total FACT-G (n=19,26)  | 76.955 (71.48 to 82.43)      | 75.235 (68.901 to 81.568)   |  |  |
| Week 40/45: Total FACT-B (n=19,26)  | 105.54 (98.512 to 112.568)   | 99.072 (90.613 to 107.531)  |  |  |
| Week 48/54: PWB (n=13,24)           | 23.308 (21.283 to 25.333)    | 20.033 (18.124 to 21.943)   |  |  |
| Week 48/54: SWB (n=13,23)           | 20.74 (18.953 to 22.527)     | 20.45 (18.31 to 22.59)      |  |  |
| Week 48/54: EWB (n=13,23)           | 19.308 (17.522 to 21.093)    | 17.27 (15.494 to 19.045)    |  |  |
| Week 48/54: FWB (n=13,23)           | 18.538 (16.586 to 20.491)    | 16.268 (13.949 to 18.587)   |  |  |
| Week 48/54: Breast Cancer (n=13,23) | 28.912 (26.879 to 30.945)    | 26.237 (22.842 to 29.632)   |  |  |
| Week 48/54: Fact-B TOI (n=13,23)    | 70.758 (66.403 to 75.114)    | 62.679 (55.941 to 69.418)   |  |  |
| Week 48/54: Total FACT-G (n=13,23)  | 81.894 (76.424 to 87.363)    | 74.162 (67.865 to 80.458)   |  |  |
| Week 48/54: Total FACT-B (n=13,23)  | 110.806 (104.704 to 116.908) | 100.399 (91.294 to 109.503) |  |  |
| Week 56/63: PWB (n=8,14)            | 21.792 (18.958 to 24.626)    | 20.298 (17.412 to 23.184)   |  |  |
| Week 56/63: SWB (n=8,14)            | 19.583 (15.598 to 23.569)    | 20.817 (17.629 to 24.004)   |  |  |
| Week 56/63: EWB (n=7,14)            | 17.143 (13.389 to 20.897)    | 15.714 (12.606 to 18.823)   |  |  |

|                                    |                             |                             |  |  |
|------------------------------------|-----------------------------|-----------------------------|--|--|
| Week 56/63: FWB (n=7,14)           | 17.143 (13.876 to 20.41)    | 16.476 (12.633 to 20.319)   |  |  |
| Week 56/63: Breast Cancer (n=8,14) | 28.24 (23.931 to 32.548)    | 25.459 (21.407 to 29.512)   |  |  |
| Week 56/63: FACT-B TOI (n=7,14)    | 66.179 (55.888 to 76.469)   | 62.233 (53.524 to 70.942)   |  |  |
| Week 56/63: Total FACT-G (n=6,14)  | 73.667 (58.381 to 88.952)   | 73.305 (62.863 to 83.746)   |  |  |
| Week 56/63: Total FACT-B (n=6,14)  | 101.042 (81.841 to 120.242) | 98.764 (85.368 to 112.16)   |  |  |
| Week 64/72: PWB (n=7,9)            | 21.857 (17.376 to 26.338)   | 21.889 (19.569 to 24.209)   |  |  |
| Week 64/72: SWB (n=7,9)            | 18.976 (16.352 to 21.6)     | 22.685 (19.417 to 25.953)   |  |  |
| Week 64/72: EWB (n=7,9)            | 18.143 (13.758 to 22.527)   | 17.889 (14.274 to 21.503)   |  |  |
| Week 64/72: FWB (n=7,9)            | 18.429 (14.658 to 22.199)   | 16.037 (12.89 to 19.184)    |  |  |
| Week 64/72: Breast Cancer (n=7,9)  | 27.464 (22.941 to 31.988)   | 26.889 (22.584 to 31.194)   |  |  |
| Week 64/72: FACT-B TOI (n=7,9)     | 67.75 (56.306 to 79.194)    | 64.815 (56.516 to 73.114)   |  |  |
| Week 64/72: Total FACT-G (n=7,9)   | 77.405 (63.847 to 90.963)   | 78.5 (68.852 to 88.148)     |  |  |
| Week 64/72: Total FACT-B (n=7,9)   | 104.869 (87.586 to 122.152) | 105.389 (92.415 to 118.363) |  |  |
| Week 72/81: PWB (n=6,7)            | 23.083 (18.906 to 27.26)    | 21 (16.407 to 25.593)       |  |  |
| Week 72/81: SWB (n=5,7)            | 19.667 (16.238 to 23.095)   | 20.043 (14.019 to 26.067)   |  |  |
| Week 72/81: EWB (n=6,7)            | 17.5 (13.476 to 21.524)     | 18.114 (14.13 to 22.098)    |  |  |
| Week 72/81: FWB (n=6,7)            | 17.333 (14.316 to 20.351)   | 16.429 (11.339 to 21.518)   |  |  |
| Week 72/81: Breast Cancer (n=6,6)  | 28.597 (24.421 to 32.774)   | 25.333 (20.25 to 30.417)    |  |  |
| Week 72/81: FACT-B TOI (n=6,6)     | 69.014 (59.566 to 78.462)   | 60.833 (47.031 to 74.635)   |  |  |
| Week 72/81: Total FACT-G (n=5,7)   | 76.467 (62.045 to 90.889)   | 75.586 (57.141 to 94.03)    |  |  |
| Week 72/81: Total FACT-B (n=5,6)   | 106.117 (88.146 to 124.087) | 97.211 (73.196 to 121.226)  |  |  |
| Week 80/90: PWB (n=2,3)            | 19.25 (-32.634 to 71.134)   | 18 (2.487 to 33.513)        |  |  |

|                                     |                              |                            |  |  |
|-------------------------------------|------------------------------|----------------------------|--|--|
| Week 80/90: SWB (n=2,3)             | 18.375 (7.257 to 29.493)     | 19.944 (3.434 to 36.455)   |  |  |
| Week 80/90: EWB (n=2,3)             | 14 (-49.531 to 77.531)       | 15.733 (-3.285 to 34.752)  |  |  |
| Week 80/90: FWB (n=2,3)             | 15 (-35.825 to 65.825)       | 12.333 (-1.348 to 26.015)  |  |  |
| Week 80/90: Breast Cancer (n=2,3)   | 21.667 (0.49 to 42.844)      | 25 (14.172 to 35.828)      |  |  |
| Week 80/90: FACT-B TOI (n=2,3)      | 55.917 (-67.969 to 179.802)  | 55.333 (20.085 to 90.581)  |  |  |
| Week 80/90: Total FACT-G (n=2,3)    | 66.625 (-110.732 to 243.982) | 66.011 (2.191 to 129.831)  |  |  |
| Week 80/90: Total FACT-B (n=2,3)    | 88.292 (-110.243 to 286.826) | 91.011 (20.313 to 161.709) |  |  |
| Week 88/99: PWB (n=0,1)             | 9999 (999 to 99999)          | 22 (9.99 to 99.9)          |  |  |
| Week 88/99: SWB (n=0,1)             | 9999 (999 to 99999)          | 23.333 (9.99 to 99.9)      |  |  |
| Week 88/99: EWB (n=0,1)             | 9999 (999 to 99999)          | 20 (9.99 to 99.9)          |  |  |
| Week 88/99: FWB (n=0,1)             | 9999 (999 to 99999)          | 21 (9.99 to 99.9)          |  |  |
| Week 88/99: Breast Cancer (n=0,1)   | 9999 (999 to 99999)          | 35 (9.99 to 99.9)          |  |  |
| Week 88/99: FACT-B TOI (n=0,1)      | 9999 (999 to 99999)          | 78 (9.99 to 99.9)          |  |  |
| Week 88/99: Total FACT-G (n=0,1)    | 9999 (999 to 99999)          | 86.333 (9.99 to 99.9)      |  |  |
| Week 88/99: Total FACT-B (n=0,1)    | 9999 (999 to 99999)          | 121.333 (99.9 to 999.9)    |  |  |
| Week 96/108: PWB (n=2,1)            | 26 (9.99 to 99.9)            | 22 (9.99 to 99.9)          |  |  |
| Week 96/108: SWB (n=2,1)            | 24.383 (-3.782 to 52.549)    | 21 (9.99 to 99.9)          |  |  |
| Week 96/108: EWB (n=2,2)            | 22 (9.294 to 34.706)         | 18 (-7.412 to 43.412)      |  |  |
| Week 96/108: FWB (n=2,2)            | 21.083 (7.318 to 34.848)     | 10.5 (-46.678 to 67.678)   |  |  |
| Week 96/108: Breast Cancer (n=2,2)  | 30.389 (-2.788 to 63.566)    | 24.5 (-7.266 to 56.266)    |  |  |
| Week 96/108: FACT-B TOI (n=2,1)     | 77.472 (58.06 to 96.884)     | 59 (9.99 to 99.9)          |  |  |
| Week 96/108: Total FACT-G (n=2,1)   | 93.467 (38.83 to 148.103)    | 74 (9.99 to 999.9)         |  |  |
| Week 96/108: Total FACT-B (n=2,1)   | 123.856 (102.396 to 145.315) | 96 (9.99 to 999.9)         |  |  |
| Week 104/117: PWB (n=1,3)           | 27 (9.99 to 99.9)            | 21.333 (17.539 to 25.128)  |  |  |
| Week 104/117: SWB (n=1,2)           | 26.6 (9.99 to 99.9)          | 20.5 (14.147 to 26.853)    |  |  |
| Week 104/117: EWB (n=1,3)           | 22 (9.99 to 99.9)            | 18 (6.616 to 29.384)       |  |  |
| Week 104/117: FWB (n=1,3)           | 22 (9.99 to 99.9)            | 11 (-1.908 to 23.908)      |  |  |
| Week 104/117: Breast Cancer (n=1,3) | 27.143 (9.99 to 99.9)        | 28 (19.395 to 36.605)      |  |  |

|                                         |                           |                            |  |  |
|-----------------------------------------|---------------------------|----------------------------|--|--|
| Week 104/117: FACT-B TOI (n=1,3)        | 76.143 (9.99 to 99.9)     | 60.333 (45.778 to 74.889)  |  |  |
| Week 104/117: Total FACT-G (n=1,2)      | 97.6 (9.99 to 99.9)       | 70.5 (-50.209 to 191.209)  |  |  |
| Week 104/117: Total FACT-B (n=1,2)      | 124.743 (99.9 to 999.9)   | 100.5 (-20.209 to 221.209) |  |  |
| Week 112/126: PWB (n=0,1)               | 9999 (999 to 99999)       | 14 (9.99 to 99.9)          |  |  |
| Week 112/126: SWB (n=0,1)               | 9999 (999 to 99999)       | 15.4 (9.99 to 99.9)        |  |  |
| Week 112/126: EWB (n=0,1)               | 9999 (999 to 99999)       | 15 (9.99 to 99.9)          |  |  |
| Week 112/126: FWB (n=0,1)               | 9999 (999 to 99999)       | 11 (9.99 to 99.9)          |  |  |
| Week 112/126: Breast Cancer (n=0,1)     | 9999 (999 to 99999)       | 20 (9.99 to 99.9)          |  |  |
| Week 112/126: FACT-B TOI (n=0,1)        | 9999 (999 to 99999)       | 45 (9.99 to 99.9)          |  |  |
| Week 112/126: Total FACT-G (n=0,1)      | 9999 (999 to 99999)       | 55.4 (9.99 to 99.9)        |  |  |
| Week 112/126: Total FACT-B (n=0,1)      | 9999 (999 to 99999)       | 75.4 (9.99 to 99.9)        |  |  |
| Second-Line PD: PWB (n=89,81)           | 19.086 (17.873 to 20.299) | 17.412 (15.977 to 18.846)  |  |  |
| Second-Line PD: SWB (n=88,79)           | 20.623 (19.456 to 21.79)  | 21.487 (20.335 to 22.639)  |  |  |
| Second-Line PD: EWB (n=88,80)           | 15.111 (14.102 to 16.121) | 14.175 (12.872 to 15.478)  |  |  |
| Second-Line PD: FWB (n=88,80)           | 15.447 (14.122 to 16.772) | 15.235 (13.877 to 16.593)  |  |  |
| Second-Line PD: Breast Cancer (n=85,81) | 24.978 (23.602 to 26.354) | 24.445 (22.989 to 25.901)  |  |  |
| Second-Line PD: FACT-B TOI (n=84,80)    | 59.23 (56.033 to 62.428)  | 57.002 (53.234 to 60.77)   |  |  |
| Second-Line PD: Total FACT-G (n=86,78)  | 69.829 (66.264 to 73.393) | 68.485 (64.384 to 72.586)  |  |  |
| Second-Line PD: Total FACT-B (n=82,78)  | 94.93 (90.24 to 99.619)   | 92.983 (87.645 to 98.32)   |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline in FACT-B Scores (Data Cutoff 20 December 2013)

|                 |                                                                      |
|-----------------|----------------------------------------------------------------------|
| End point title | Change From Baseline in FACT-B Scores (Data Cutoff 20 December 2013) |
|-----------------|----------------------------------------------------------------------|

End point description:

FACT-B is composed of 5 multi-item sections where pts responded to questions assessing symptoms (scale: 0-4; 0='not at all' and 4='very much'), as follows: PWB (7 items, total score 0-28), SWB (7

items, total score 0-28), EWB (6 items, total score 0-24), FWB (7 items, total score 0-28), and breast cancer score based on the additional concerns section of FACT-B (10 items, total score 0-40). FACT-B TOI score=sum of PWB, FWB, and breast cancer score subscale scores (total score 0-96). FACT-G total score=sum of PWB, SWB, EWB, and FWB subscales scores (total score 0-108). FACT-B total score=sum of PWB, SWB, EWB, FWB, and breast cancer score subscale scores (total score 0-148). Higher value indicated better perceived quality of life.

ITT population. No of pts analyzed = pts evaluable for end point and n=no of pts completing the questionnaires at specified timepoint.

The data -9.99, -99.9, 9.99, 99.9, 999, 9999, 99999 signifies data not available.

|                                                                                                                        |           |
|------------------------------------------------------------------------------------------------------------------------|-----------|
| End point type                                                                                                         | Secondary |
| End point timeframe:                                                                                                   |           |
| Baseline (≤28 days after randomization), every 8-9 weeks thereafter until second-line PD (up to approximately 3 years) |           |

| End point values                          | Chemotherapy (CT) Arm     | Chemotherapy Plus Bevacizumab (CT+BV) Arm |  |  |
|-------------------------------------------|---------------------------|-------------------------------------------|--|--|
| Subject group type                        | Reporting group           | Reporting group                           |  |  |
| Number of subjects analysed               | 118                       | 128                                       |  |  |
| Units: scores on a scale                  |                           |                                           |  |  |
| arithmetic mean (confidence interval 95%) |                           |                                           |  |  |
| Week 8/9: PWB (n=118,125)                 | -1.281 (-2.219 to -0.344) | -1.289 (-2.239 to -0.338)                 |  |  |
| Week 8/9: SWB (n=116,125)                 | 0.356 (-0.283 to 0.994)   | 0.707 (-0.226 to 1.64)                    |  |  |
| Week 8/9: EWB (n=116,128)                 | 0.408 (-0.274 to 1.089)   | 1.024 (0.314 to 1.734)                    |  |  |
| Week 8/9: FWB (n=117,128)                 | -0.226 (-1.043 to 0.591)  | -0.24 (-1.027 to 0.548)                   |  |  |
| Week 8/9: Breast Cancer Score (n=113,128) | 0.228 (-0.659 to 1.116)   | 0.95 (0.121 to 1.78)                      |  |  |
| Week 8/9: FACT-B TOI (n=110,122)          | -1.361 (-3.295 to 0.573)  | -0.357 (-2.407 to 1.693)                  |  |  |
| Week 8/9: Total FACT-G Score (n=110,122)  | -0.76 (-2.92 to 1.399)    | 0.369 (-1.945 to 2.684)                   |  |  |
| Week 8/9: Total FACT-B Score (n=108,120)  | -0.728 (-3.332 to 1.876)  | 1.342 (-1.544 to 4.229)                   |  |  |
| Week 16/18: PWB (n=77,97)                 | 0.294 (-0.733 to 1.322)   | -1.823 (-2.871 to -0.775)                 |  |  |
| Week 16/18: SWB (n=74,97)                 | -0.443 (-1.411 to 0.525)  | 0.359 (-0.678 to 1.397)                   |  |  |
| Week 16/18: EWB (n=73,98)                 | 1.197 (0.415 to 1.979)    | 0.921 (0.186 to 1.657)                    |  |  |
| Week 16/18: FWB (n=75,98)                 | -0.548 (-1.666 to 0.57)   | -0.517 (-1.422 to 0.389)                  |  |  |
| Week 16/18: Breast Cancer (n=72,97)       | 0.578 (-0.658 to 1.815)   | 0.546 (-0.423 to 1.514)                   |  |  |
| Week 16/18: FACT-TOI (n=68,95)            | -0.483 (-3.149 to 2.183)  | -1.732 (-4.049 to 0.586)                  |  |  |
| Week 16/18: Total FACT-G (n=71,93)        | -0.019 (-2.97 to 2.931)   | -0.836 (-3.494 to 1.821)                  |  |  |
| Week 16/18: Total Fact-B (n=66,93)        | -0.007 (-3.744 to 3.73)   | -0.127 (-3.421 to 3.167)                  |  |  |
| Week 24/27: PWB (n=44,73)                 | 0.181 (-1.236 to 1.598)   | -1.996 (-3.306 to -0.685)                 |  |  |

|                                     |                          |                          |  |  |
|-------------------------------------|--------------------------|--------------------------|--|--|
| Week 24/27: SWB (n=44,72)           | -0.193 (-1.49 to 1.104)  | 1.375 (-0.001 to 2.75)   |  |  |
| Week 24/27: EWB (n=42,72)           | 0.867 (-0.101 to 1.834)  | 1.217 (0.366 to 2.067)   |  |  |
| Week 24/27: FWB (n=42,72)           | 0.119 (-1.405 to 1.643)  | 0.056 (-1.053 to 1.166)  |  |  |
| Week 24/27: Breast Cancer (n=40,72) | -0.038 (-1.723 to 1.647) | 0.078 (-1.106 to 1.262)  |  |  |
| Week 24/27: FACT-B TOI (n=38,70)    | 0.221 (-3.411 to 3.853)  | -1.573 (-4.383 to 1.238) |  |  |
| Week 24/27: Total FACT-G (n=40,70)  | 0.764 (-3.066 to 4.595)  | 0.817 (-2.497 to 4.131)  |  |  |
| Week 24/27: Total FACT-B (n=37,70)  | 0.793 (-4.106 to 5.693)  | 1.157 (-2.828 to 5.142)  |  |  |
| Week 32/36: PWB (n=25,39)           | 0.88 (-0.913 to 2.673)   | -1.235 (-2.799 to 0.329) |  |  |
| Week 32/36: SWB (n=24,40)           | -0.388 (-1.754 to 0.979) | 1.036 (-1.209 to 3.281)  |  |  |
| Week 32/36: EWB (n=25,40)           | 1.064 (-0.298 to 2.426)  | 1.555 (0.204 to 2.906)   |  |  |
| Week 32/36: FWB (n=25,40)           | 1.38 (-0.103 to 2.863)   | 1.635 (-0.201 to 3.471)  |  |  |
| Week 32/36: Breast Cancer (n=23,40) | 0.928 (-1.916 to 3.771)  | 1.278 (-0.435 to 2.99)   |  |  |
| Week 32/36: FACT-B TOI (n=23,38)    | 3.123 (-1.39 to 7.637)   | 1.471 (-2.522 to 5.464)  |  |  |
| Week 32/36: Total FACT-G (n=24,39)  | 2.617 (-1.313 to 6.547)  | 3.197 (-1.346 to 7.74)   |  |  |
| Week 32/36: Total FACT-B (n=22,38)  | 3.529 (-2.074 to 9.132)  | 3.896 (-1.579 to 9.37)   |  |  |
| Week 40/45: PWB (n=18,25)           | 0.137 (-2.051 to 2.325)  | -0.68 (-2.93 to 1.57)    |  |  |
| Week 40/45: SWB (n=19,24)           | -0.589 (-2.436 to 1.259) | 0.951 (-1.59 to 3.492)   |  |  |
| Week 40/45: EWB (n=18,25)           | 0.2 (-1.598 to 1.998)    | 1.048 (-0.658 to 2.754)  |  |  |
| Week 40/45: FWB (n=18,25)           | 1.417 (-0.562 to 3.395)  | 0.857 (-0.893 to 2.608)  |  |  |
| Week 40/45: Breast Cancer (n=18,25) | 1.395 (-1.268 to 4.058)  | 0.444 (-2.358 to 3.247)  |  |  |
| Week 40/45: FACT-B TOI (n=16,25)    | 2.432 (-2.496 to 7.36)   | 0.622 (-4.688 to 5.932)  |  |  |
| Week 40/45: Total FACT-G (n=17,24)  | 1.444 (-3.342 to 6.231)  | 2.432 (-3.035 to 7.899)  |  |  |
| Week 40/45: Total FACT-B (n=16,24)  | 1.916 (-3.95 to 7.782)   | 2.673 (-4.258 to 9.603)  |  |  |
| Week 48/54: PWB (n=13,20)           | 1.295 (-2.037 to 4.627)  | -1.833 (-3.721 to 0.055) |  |  |
| Week 48/54: SWB (n=13,20)           | 1.529 (-0.316 to 3.375)  | 2.008 (-1.083 to 5.099)  |  |  |
| Week 48/54: EWB (n=13,20)           | 1.492 (0.492 to 2.492)   | 1.71 (-0.183 to 3.603)   |  |  |
| Week 48/54: FWB (n=13,20)           | 2.269 (0.174 to 4.365)   | 1.592 (-0.872 to 4.055)  |  |  |
| Week 48/54: Breast Cancer (n=12,20) | 0.599 (-1.714 to 2.912)  | 1.897 (-0.463 to 4.258)  |  |  |
| Week 48/54: FACT-B TOI (n=12,20)    | 4.044 (-2.832 to 10.919) | 1.656 (-3.691 to 7.002)  |  |  |
| Week 48/54: Total FACT-G (n=13,20)  | 6.586 (1.392 to 11.78)   | 3.477 (-2.596 to 9.55)   |  |  |
| Week 48/54: Total FACT-B (n=12,20)  | 7.067 (0.241 to 13.894)  | 5.374 (-2.391 to 13.139) |  |  |

|                                    |                            |                           |  |  |
|------------------------------------|----------------------------|---------------------------|--|--|
| Week 56/63: PWB (n=8,13)           | -2.063 (-6.094 to 1.969)   | -0.526 (-3.996 to 2.944)  |  |  |
| Week 56/63: SWB (n=8,13)           | -1.5 (-5.699 to 2.699)     | 3.033 (-1.729 to 7.796)   |  |  |
| Week 56/63: EWB (n=7,13)           | 0.857 (-2.781 to 4.495)    | 0.954 (-2.19 to 4.097)    |  |  |
| Week 56/63: FWB (n=7,13)           | 0 (-4.835 to 4.835)        | 5.654 (0.511 to 10.797)   |  |  |
| Week 56/63: Breast Cancer (n=8,13) | -0.83 (-6.133 to 4.474)    | 1.675 (-1.291 to 4.641)   |  |  |
| Week 56/63: FACT-B TOI (n=7,13)    | -3.591 (-17.803 to 10.621) | 6.803 (1.093 to 14.699)   |  |  |
| Week 56/63: Total FACT-G (n=6,13)  | -4.083 (-22.93 to 14.764)  | 9.115 (-3.82 to 22.05)    |  |  |
| Week 56/63: Total FACT-B (n=6,13)  | -5.301 (-29.74 to 19.138)  | 10.791 (-3.114 to 24.695) |  |  |
| Week 64/72: PWB (n=7,9)            | 0 (-6.733 to 6.733)        | 0.926 (-1.491 to 3.342)   |  |  |
| Week 64/72: SWB (n=7,9)            | -2.014 (-5.182 to 1.154)   | 3.57 (-1.034 to 8.174)    |  |  |
| Week 64/72: EWB (n=7,9)            | -0.057 (-3.537 to 3.423)   | 3.667 (-0.63 to 7.964)    |  |  |
| Week 64/72: FWB (n=7,9)            | 0.214 (-4.531 to 4.959)    | 3.222 (-2.143 to 8.588)   |  |  |
| Week 64/72: Breast Cancer (n=7,9)  | -2.298 (-7.507 to 2.912)   | 3.086 (-1.361 to 7.534)   |  |  |
| Week 64/72: FACT-B TOI (n=7,9)     | -2.083 (-17.13 to 12.963)  | 7.235 (-3.624 to 18.093)  |  |  |
| Week 64/72: Total FACT-G (n=7,9)   | -1.857 (-17.855 to 14.14)  | 11.385 (-3.116 to 25.886) |  |  |
| Week 64/72: Total FACT-B (n=7,9)   | -4.155 (-24.302 to 15.993) | 14.472 (-4.192 to 33.135) |  |  |
| Week 72/81: PWB (n=5,7)            | 2.133 (-6.045 to 10.311)   | -0.429 (-3.965 to 3.108)  |  |  |
| Week 72/81: SWB (n=4,7)            | -1.208 (-5.126 to 2.71)    | 6.829 (-3.189 to 16.846)  |  |  |
| Week 72/81: EWB (n=5,7)            | -0.6 (-5.042 to 3.842)     | 4.686 (-0.608 to 9.979)   |  |  |
| Week 72/81: FWB (n=5,7)            | 0 (-5.341 to 5.341)        | 7.381 (-1.169 to 15.931)  |  |  |
| Week 72/81: Breast Cancer (n=5,6)  | -0.461 (-6.531 to 5.609)   | 3.667 (-3.41 to 10.743)   |  |  |
| Week 72/81: FACT-B TOI (n=5,6)     | 1.672 (-12.563 to 15.907)  | 8.278 (-7.45 to 24.005)   |  |  |
| Week 72/81: Total FACT-G (n=4,7)   | -0.167 (-22.161 to 21.828) | 18.467 (-1.867 to 38.801) |  |  |
| Week 72/81: Total FACT-B (n=4,6)   | 1.174 (-23.085 to 25.432)  | 16.906 (-9.207 to 43.018) |  |  |
| Week 80/90: PWB (n=2,3)            | -3.75 (-30.221 to 22.721)  | 3 (-11.605 to 5.605)      |  |  |
| Week 80/90: SWB (n=2,3)            | -0.875 (-34.229 to 32.479) | 7.344 (-9.614 to 24.303)  |  |  |
| Week 80/90: EWB (n=2,3)            | -4 (-42.119 to 34.119)     | 4.733 (-18.466 to 27.932) |  |  |
| Week 80/90: FWB (n=2,3)            | -1 (-64.531 to 62.531)     | 2.556 (-9.165 to 14.276)  |  |  |

|                                     |                               |                             |  |  |
|-------------------------------------|-------------------------------|-----------------------------|--|--|
| Week 80/90: Breast Cancer (n=2,3)   | -5.833 (-29.128 to 17.461)    | 3.667 (-11.512 to 18.845)   |  |  |
| Week 80/90: FACT-B TOI (n=2,3)      | -10.583 (-77.291 to 56.124)   | 3.222 (-30.212 to 36.657)   |  |  |
| Week 80/90: Total FACT-G (n=2,3)    | -9.625 (-171.1 to 151.85)     | 11.633 (-41.554 to 64.821)  |  |  |
| Week 80/90: Total FACT-B (n=2,3)    | -15.458 (-153.638 to 122.722) | 15.3 (-48.177 to 78.777)    |  |  |
| Week 88/99: PWB (n=0,1)             | 9999 (999 to 99999)           | -6 (-9.99 to 9.99)          |  |  |
| Week 88/99: SWB (n=0,1)             | 9999 (999 to 99999)           | 23.333 (9.99 to 99.9)       |  |  |
| Week 88/99: EWB (n=0,1)             | 9999 (999 to 99999)           | 0 (-9.99 to 9.99)           |  |  |
| Week 88/99: FWB (n=0,1)             | 9999 (999 to 99999)           | 21 (9.99 to 99.9)           |  |  |
| Week 88/99: Breast Cancer (n=0,1)   | 9999 (999 to 99999)           | 3 (-9.99 to 9.99)           |  |  |
| Week 88/99: FACT TOI (n=0,1)        | 9999 (999 to 99999)           | 18 (9.99 to 99.9)           |  |  |
| Week 88/99: Total FACT-G (n=0,1)    | 9999 (999 to 99999)           | 38.333 (9.99 to 99.9)       |  |  |
| Week 88/99: Total FACT-B (n=0,1)    | 9999 (999 to 99999)           | 41.333 (9.99 to 99.9)       |  |  |
| Week 96/108: PWB (n=2,1)            | 7.333 (-51.962 to 66.629)     | -3 (-9.99 to 9.99)          |  |  |
| Week 96/108: SWB (n=2,1)            | 2.183 (-23.441 to 27.808)     | 1.4 (-9.99 to 9.99)         |  |  |
| Week 96/108: EWB (n=2,1)            | 0 (-12.706 to 12.706)         | 6 (-9.99 to 9.99)           |  |  |
| Week 96/108: FWB (n=2,1)            | 6.583 (-13.535 to 26.701)     | -1.333 (-9.99 to 9.99)      |  |  |
| Week 96/108: Breast Cancer (n=2,1)  | 3.167 (-41.305 to 47.638)     | -3 (-9.99 to 9.99)          |  |  |
| Week 96/108: FACT-B TOI (n=2,1)     | 17.083 (11.789 to 22.378)     | -7.333 (-9.99 to 9.99)      |  |  |
| Week 96/108: Total FACT-G (n=2,1)   | 16.1 (15.253 to 16.947)       | 3.067 (-9.99 to 9.99)       |  |  |
| Week 96/108: Total FACT-B (n=2,1)   | 19.267 (-24.358 to 62.891)    | 0.067 (-9.99 to 9.99)       |  |  |
| Week 104/117: PWB (n=1,2)           | 3.667 (-9.99 to 9.99)         | -2 (-40.119 to 36.119)      |  |  |
| Week 104/117: SWB (n=1,1)           | 4.2 (-9.99 to 9.99)           | 8.8 (-9.99 to 9.99)         |  |  |
| Week 104/117: EWB (n=1,2)           | 0 (-9.99 to 9.99)             | 10 (-28.119 to 48.119)      |  |  |
| Week 104/117: FWB (n=1,2)           | 8 (-9.99 to 9.99)             | 2.333 (-56.962 to 61.629)   |  |  |
| Week 104/117: Breast Cancer (n=1,2) | 6.032 (-9.99 to 9.99)         | 4 (-59.531 to 67.531)       |  |  |
| Week 104/117: FACT-B TOI (n=1,2)    | 17.698 (9.99 to 99.9)         | 4.333 (-156.612 to 165.279) |  |  |
| Week 104/117: Total FACT-G (n=1,1)  | 15.867 (9.99 to 99.9)         | 29.8 (9.99 to 99.9)         |  |  |
| Week 104/117: Total FACT-B (n=1,1)  | 21.898 (9.99 to 99.9)         | 38.8 (9.99 to 99.9)         |  |  |

|                                         |                          |                           |  |  |
|-----------------------------------------|--------------------------|---------------------------|--|--|
| Week 112/126: PWB (n=0,1)               | 9999 (999 to 99999)      | -11 (-99.9 to 9.99)       |  |  |
| Week 112/126: SWB (n=0,1)               | 9999 (999 to 99999)      | -4.2 (-9.99 to 9.99)      |  |  |
| Week 112/126: EWB (n=0,1)               | 9999 (999 to 99999)      | 5 (-9.99 to 9.99)         |  |  |
| Week 112/126: FWB (n=0,1)               | 9999 (999 to 99999)      | -5.333 (-9.99 to 9.99)    |  |  |
| Week 112/126: Breast Cancer (n=0,1)     | 9999 (999 to 99999)      | -5 (-9.99 to 9.99)        |  |  |
| Week 112/126: FACT-B TOI (n=0,1)        | 9999 (999 to 99999)      | -21.333 (-99.9 to 9.99)   |  |  |
| Week 112/126: Total FACT-G (n=0,1)      | 9999 (999 to 99999)      | -15.533 (-99.9 to 9.99)   |  |  |
| Week 112/126: Total FACT-B (n=0,1)      | 9999 (999 to 99999)      | -20.533 (-99.9 to 9.99)   |  |  |
| Second-Line PD: PWB (n=81,77)           | -0.871 (-1.916 to 0.174) | -2.507 (-3.783 to -1.231) |  |  |
| Second-Line PD: SWB (n=80,75)           | -0.106 (-0.902 to 0.69)  | -0.766 (-1.788 to 0.256)  |  |  |
| Second-Line PD: EWB (n=80,76)           | -0.44 (-1.553 to 0.673)  | -0.508 (-1.562 to 0.546)  |  |  |
| Second-Line PD: FWB (n=80,76)           | -1.415 (-2.59 to -0.239) | -0.773 (-1.809 to 0.263)  |  |  |
| Second-Line PD: Breast Cancer (n=77,77) | 0.12 (-1.182 to 1.421)   | 0.241 (-0.878 to 1.36)    |  |  |
| Second-Line PD: FACT-B TOI (n=74,76)    | -2.311 (-5.07 to 0.447)  | -3.003 (-5.734 to -0.273) |  |  |
| Second-Line PD: Total FACT-G (n=76,74)  | -2.771 (-5.902 to 0.361) | -4.702 (-7.941 to -1.462) |  |  |
| Second-Line PD: Total FACT-B (n=72,74)  | -2.719 (-6.633 to 1.195) | -4.44 (-8.515 to -0.366)  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Baseline up to approximately 4 years

Adverse event reporting additional description:

All randomized participants who received at least 1 dose of bevacizumab and/or chemotherapy were included in the analysis.

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 17.1 |
|--------------------|------|

### Reporting groups

|                       |        |
|-----------------------|--------|
| Reporting group title | CT Arm |
|-----------------------|--------|

Reporting group description:

Participants received a single-agent chemotherapy at the discretion of the investigator according to the standard of care at the investigator's site until disease progression, unacceptable toxicity, participant request for withdrawal, until the maximum cumulative dose of anthracycline was reached, or end of study (24 months after randomization of the last participant). Upon second-line disease progression participants received a single-agent chemotherapy at the discretion of the investigator according to the standard of care at the investigator's site until disease progression, unacceptable toxicity, participant request for withdrawal, or end of study. Upon subsequent disease progression participants received treatment according the standard of care of the treatment site until end of study.

|                       |           |
|-----------------------|-----------|
| Reporting group title | CT+BV Arm |
|-----------------------|-----------|

Reporting group description:

Participants received a single-agent chemotherapy at the discretion of the investigator according to the standard of care at the investigator's site plus bevacizumab, 15 mg/kg, IV, every 3 weeks, or 10 mg/kg, IV, every 2 weeks until disease progression, unacceptable toxicity, participant request for withdrawal, until the maximum cumulative dose of anthracycline was reached, or end of study (24 months after randomization of the last participant). Upon second-line disease progression participants received a single-agent chemotherapy at the discretion of the investigator according to the standard of care at the investigator's site plus bevacizumab, 15 mg/kg, IV, every 3 weeks, or 10 mg/kg, IV, every 2 weeks until disease progression, unacceptable toxicity, participant request for withdrawal, or end of study. Upon subsequent disease progression participants received treatment according the standard of care of the treatment site until end of study.

| Serious adverse events                                              | CT Arm            | CT+BV Arm         |  |
|---------------------------------------------------------------------|-------------------|-------------------|--|
| Total subjects affected by serious adverse events                   |                   |                   |  |
| subjects affected / exposed                                         | 55 / 238 (23.11%) | 89 / 245 (36.33%) |  |
| number of deaths (all causes)                                       | 6                 | 8                 |  |
| number of deaths resulting from adverse events                      |                   |                   |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                   |                   |  |
| Endometrial adenocarcinoma                                          |                   |                   |  |
| alternative assessment type: Systematic                             |                   |                   |  |
| subjects affected / exposed                                         | 0 / 238 (0.00%)   | 1 / 245 (0.41%)   |  |
| occurrences causally related to treatment / all                     | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all                          | 0 / 0             | 0 / 0             |  |

|                                                                                                                                                                                                                                              |                                   |                                   |  |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------|-----------------------------------|--|
| Metastases to liver<br>alternative assessment type:<br>Systematic<br>subjects affected / exposed<br>occurrences causally related to<br>treatment / all<br>deaths causally related to<br>treatment / all                                      | 0 / 238 (0.00%)<br>0 / 0<br>0 / 0 | 1 / 245 (0.41%)<br>0 / 1<br>0 / 0 |  |
| Vascular disorders<br>Embolism venous<br>alternative assessment type:<br>Systematic<br>subjects affected / exposed<br>occurrences causally related to<br>treatment / all<br>deaths causally related to<br>treatment / all                    | 1 / 238 (0.42%)<br>1 / 1<br>0 / 0 | 3 / 245 (1.22%)<br>3 / 3<br>0 / 0 |  |
| Haemorrhage<br>alternative assessment type:<br>Systematic<br>subjects affected / exposed<br>occurrences causally related to<br>treatment / all<br>deaths causally related to<br>treatment / all                                              | 1 / 238 (0.42%)<br>1 / 1<br>0 / 0 | 1 / 245 (0.41%)<br>1 / 1<br>0 / 0 |  |
| Embolism arterial<br>subjects affected / exposed<br>occurrences causally related to<br>treatment / all<br>deaths causally related to<br>treatment / all                                                                                      | 0 / 238 (0.00%)<br>0 / 0<br>0 / 0 | 1 / 245 (0.41%)<br>1 / 1<br>0 / 0 |  |
| Infarction<br>subjects affected / exposed<br>occurrences causally related to<br>treatment / all<br>deaths causally related to<br>treatment / all                                                                                             | 0 / 238 (0.00%)<br>0 / 0<br>0 / 0 | 1 / 245 (0.41%)<br>0 / 1<br>0 / 0 |  |
| Surgical and medical procedures<br>Salpingo-oophorectomy<br>alternative assessment type:<br>Systematic<br>subjects affected / exposed<br>occurrences causally related to<br>treatment / all<br>deaths causally related to<br>treatment / all | 0 / 238 (0.00%)<br>0 / 0<br>0 / 0 | 1 / 245 (0.41%)<br>0 / 1<br>0 / 0 |  |
| Tooth extraction<br>alternative assessment type:<br>Systematic                                                                                                                                                                               |                                   |                                   |  |

|                                                      |                 |                 |  |
|------------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                          | 1 / 238 (0.42%) | 0 / 245 (0.00%) |  |
| occurrences causally related to treatment / all      | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Large intestine anastomosis                          |                 |                 |  |
| subjects affected / exposed                          | 1 / 238 (0.42%) | 0 / 245 (0.00%) |  |
| occurrences causally related to treatment / all      | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| General disorders and administration site conditions |                 |                 |  |
| Pyrexia                                              |                 |                 |  |
| alternative assessment type: Systematic              |                 |                 |  |
| subjects affected / exposed                          | 2 / 238 (0.84%) | 4 / 245 (1.63%) |  |
| occurrences causally related to treatment / all      | 2 / 2           | 0 / 4           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Fatigue                                              |                 |                 |  |
| alternative assessment type: Systematic              |                 |                 |  |
| subjects affected / exposed                          | 2 / 238 (0.84%) | 2 / 245 (0.82%) |  |
| occurrences causally related to treatment / all      | 3 / 3           | 0 / 3           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Mucosal inflammation                                 |                 |                 |  |
| alternative assessment type: Systematic              |                 |                 |  |
| subjects affected / exposed                          | 1 / 238 (0.42%) | 3 / 245 (1.22%) |  |
| occurrences causally related to treatment / all      | 1 / 1           | 0 / 4           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| General physical health deterioration                |                 |                 |  |
| alternative assessment type: Systematic              |                 |                 |  |
| subjects affected / exposed                          | 1 / 238 (0.42%) | 2 / 245 (0.82%) |  |
| occurrences causally related to treatment / all      | 1 / 1           | 0 / 2           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Chest discomfort                                     |                 |                 |  |
| alternative assessment type: Systematic              |                 |                 |  |
| subjects affected / exposed                          | 1 / 238 (0.42%) | 0 / 245 (0.00%) |  |
| occurrences causally related to treatment / all      | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |

|                                                    |                 |                 |  |
|----------------------------------------------------|-----------------|-----------------|--|
| Chest pain                                         |                 |                 |  |
| alternative assessment type:<br>Systematic         |                 |                 |  |
| subjects affected / exposed                        | 1 / 238 (0.42%) | 0 / 245 (0.00%) |  |
| occurrences causally related to<br>treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to<br>treatment / all      | 0 / 0           | 0 / 0           |  |
| Device dislocation                                 |                 |                 |  |
| alternative assessment type:<br>Systematic         |                 |                 |  |
| subjects affected / exposed                        | 1 / 238 (0.42%) | 0 / 245 (0.00%) |  |
| occurrences causally related to<br>treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to<br>treatment / all      | 0 / 0           | 0 / 0           |  |
| Device failure                                     |                 |                 |  |
| alternative assessment type:<br>Systematic         |                 |                 |  |
| subjects affected / exposed                        | 0 / 238 (0.00%) | 1 / 245 (0.41%) |  |
| occurrences causally related to<br>treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to<br>treatment / all      | 0 / 0           | 0 / 0           |  |
| Device occlusion                                   |                 |                 |  |
| alternative assessment type:<br>Systematic         |                 |                 |  |
| subjects affected / exposed                        | 1 / 238 (0.42%) | 0 / 245 (0.00%) |  |
| occurrences causally related to<br>treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to<br>treatment / all      | 0 / 0           | 0 / 0           |  |
| Impaired healing                                   |                 |                 |  |
| alternative assessment type:<br>Systematic         |                 |                 |  |
| subjects affected / exposed                        | 0 / 238 (0.00%) | 1 / 245 (0.41%) |  |
| occurrences causally related to<br>treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to<br>treatment / all      | 0 / 0           | 0 / 0           |  |
| Multi-organ failure                                |                 |                 |  |
| alternative assessment type:<br>Systematic         |                 |                 |  |
| subjects affected / exposed                        | 0 / 238 (0.00%) | 1 / 245 (0.41%) |  |
| occurrences causally related to<br>treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to<br>treatment / all      | 0 / 0           | 0 / 1           |  |
| Pain                                               |                 |                 |  |
| alternative assessment type:<br>Systematic         |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 238 (0.42%) | 0 / 245 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Sudden death                                    |                 |                 |  |
| alternative assessment type: Systematic         |                 |                 |  |
| subjects affected / exposed                     | 0 / 238 (0.00%) | 1 / 245 (0.41%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 1 / 1           |  |
| Patient-device incompatibility                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 238 (0.00%) | 1 / 245 (0.41%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Reproductive system and breast disorders        |                 |                 |  |
| Menstrual disorder                              |                 |                 |  |
| alternative assessment type: Systematic         |                 |                 |  |
| subjects affected / exposed                     | 1 / 238 (0.42%) | 0 / 245 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Metrorrhagia                                    |                 |                 |  |
| alternative assessment type: Systematic         |                 |                 |  |
| subjects affected / exposed                     | 1 / 238 (0.42%) | 0 / 245 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Respiratory, thoracic and mediastinal disorders |                 |                 |  |
| Pulmonary embolism                              |                 |                 |  |
| alternative assessment type: Systematic         |                 |                 |  |
| subjects affected / exposed                     | 2 / 238 (0.84%) | 6 / 245 (2.45%) |  |
| occurrences causally related to treatment / all | 2 / 2           | 5 / 6           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Dyspnoea                                        |                 |                 |  |
| alternative assessment type: Systematic         |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 238 (0.42%) | 3 / 245 (1.22%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 1 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pleural effusion                                |                 |                 |  |
| alternative assessment type: Systematic         |                 |                 |  |
| subjects affected / exposed                     | 1 / 238 (0.42%) | 2 / 245 (0.82%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 1 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pneumonia aspiration                            |                 |                 |  |
| alternative assessment type: Systematic         |                 |                 |  |
| subjects affected / exposed                     | 1 / 238 (0.42%) | 0 / 245 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pneumothorax                                    |                 |                 |  |
| alternative assessment type: Systematic         |                 |                 |  |
| subjects affected / exposed                     | 0 / 238 (0.00%) | 1 / 245 (0.41%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Psychiatric disorders                           |                 |                 |  |
| Depression                                      |                 |                 |  |
| alternative assessment type: Systematic         |                 |                 |  |
| subjects affected / exposed                     | 1 / 238 (0.42%) | 1 / 245 (0.41%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Confusional state                               |                 |                 |  |
| alternative assessment type: Systematic         |                 |                 |  |
| subjects affected / exposed                     | 1 / 238 (0.42%) | 0 / 245 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Investigations                                  |                 |                 |  |
| Gamma-glutamyltransferase increased             |                 |                 |  |
| alternative assessment type: Systematic         |                 |                 |  |

|                                                                                                                       |                 |                 |  |
|-----------------------------------------------------------------------------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                                                                                           | 1 / 238 (0.42%) | 1 / 245 (0.41%) |  |
| occurrences causally related to treatment / all                                                                       | 1 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all                                                                            | 0 / 0           | 0 / 0           |  |
| Alanine aminotransferase increased<br>alternative assessment type:<br>Systematic                                      |                 |                 |  |
| subjects affected / exposed                                                                                           | 0 / 238 (0.00%) | 1 / 245 (0.41%) |  |
| occurrences causally related to treatment / all                                                                       | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all                                                                            | 0 / 0           | 0 / 0           |  |
| Aspartate aminotransferase increased<br>alternative assessment type:<br>Systematic                                    |                 |                 |  |
| subjects affected / exposed                                                                                           | 0 / 238 (0.00%) | 1 / 245 (0.41%) |  |
| occurrences causally related to treatment / all                                                                       | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all                                                                            | 0 / 0           | 0 / 0           |  |
| Biopsy liver<br>alternative assessment type:<br>Systematic                                                            |                 |                 |  |
| subjects affected / exposed                                                                                           | 1 / 238 (0.42%) | 0 / 245 (0.00%) |  |
| occurrences causally related to treatment / all                                                                       | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all                                                                            | 0 / 0           | 0 / 0           |  |
| Blood bilirubin increased<br>alternative assessment type:<br>Systematic                                               |                 |                 |  |
| subjects affected / exposed                                                                                           | 0 / 238 (0.00%) | 1 / 245 (0.41%) |  |
| occurrences causally related to treatment / all                                                                       | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all                                                                            | 0 / 0           | 0 / 0           |  |
| Blood potassium increased<br>alternative assessment type:<br>Systematic                                               |                 |                 |  |
| subjects affected / exposed                                                                                           | 1 / 238 (0.42%) | 0 / 245 (0.00%) |  |
| occurrences causally related to treatment / all                                                                       | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all                                                                            | 0 / 0           | 0 / 0           |  |
| Injury, poisoning and procedural complications<br>Femoral neck fracture<br>alternative assessment type:<br>Systematic |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 238 (0.42%) | 1 / 245 (0.41%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Foot fracture                                   |                 |                 |  |
| alternative assessment type: Systematic         |                 |                 |  |
| subjects affected / exposed                     | 1 / 238 (0.42%) | 0 / 245 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Head injury                                     |                 |                 |  |
| alternative assessment type: Systematic         |                 |                 |  |
| subjects affected / exposed                     | 0 / 238 (0.00%) | 1 / 245 (0.41%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Subdural haematoma                              |                 |                 |  |
| alternative assessment type: Systematic         |                 |                 |  |
| subjects affected / exposed                     | 0 / 238 (0.00%) | 1 / 245 (0.41%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardiac disorders                               |                 |                 |  |
| Cardiac failure                                 |                 |                 |  |
| alternative assessment type: Systematic         |                 |                 |  |
| subjects affected / exposed                     | 1 / 238 (0.42%) | 2 / 245 (0.82%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 1 / 2           |  |
| deaths causally related to treatment / all      | 1 / 1           | 0 / 1           |  |
| Acute coronary syndrome                         |                 |                 |  |
| alternative assessment type: Systematic         |                 |                 |  |
| subjects affected / exposed                     | 0 / 238 (0.00%) | 1 / 245 (0.41%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Angina pectoris                                 |                 |                 |  |
| alternative assessment type: Systematic         |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 238 (0.42%) | 1 / 245 (0.41%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Atrial fibrillation                             |                 |                 |  |
| alternative assessment type: Systematic         |                 |                 |  |
| subjects affected / exposed                     | 0 / 238 (0.00%) | 1 / 245 (0.41%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Atrial tachycardia                              |                 |                 |  |
| alternative assessment type: Systematic         |                 |                 |  |
| subjects affected / exposed                     | 1 / 238 (0.42%) | 0 / 245 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 1 / 1           | 0 / 0           |  |
| Cardiac failure congestive                      |                 |                 |  |
| alternative assessment type: Systematic         |                 |                 |  |
| subjects affected / exposed                     | 0 / 238 (0.00%) | 2 / 245 (0.82%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Cardiotoxicity                                  |                 |                 |  |
| alternative assessment type: Systematic         |                 |                 |  |
| subjects affected / exposed                     | 0 / 238 (0.00%) | 1 / 245 (0.41%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Congestive cardiomyopathy                       |                 |                 |  |
| alternative assessment type: Systematic         |                 |                 |  |
| subjects affected / exposed                     | 0 / 238 (0.00%) | 1 / 245 (0.41%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Left ventricular dysfunction                    |                 |                 |  |
| alternative assessment type: Systematic         |                 |                 |  |
| subjects affected / exposed                     | 0 / 238 (0.00%) | 1 / 245 (0.41%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

|                                                                                            |                 |                 |  |
|--------------------------------------------------------------------------------------------|-----------------|-----------------|--|
| Left ventricular failure<br>alternative assessment type:<br>Systematic                     |                 |                 |  |
| subjects affected / exposed                                                                | 0 / 238 (0.00%) | 1 / 245 (0.41%) |  |
| occurrences causally related to<br>treatment / all                                         | 0 / 0           | 1 / 1           |  |
| deaths causally related to<br>treatment / all                                              | 0 / 0           | 0 / 0           |  |
| Mitral valve incompetence<br>alternative assessment type:<br>Systematic                    |                 |                 |  |
| subjects affected / exposed                                                                | 1 / 238 (0.42%) | 0 / 245 (0.00%) |  |
| occurrences causally related to<br>treatment / all                                         | 1 / 1           | 0 / 0           |  |
| deaths causally related to<br>treatment / all                                              | 1 / 1           | 0 / 0           |  |
| Sinus tachycardia<br>alternative assessment type:<br>Systematic                            |                 |                 |  |
| subjects affected / exposed                                                                | 1 / 238 (0.42%) | 0 / 245 (0.00%) |  |
| occurrences causally related to<br>treatment / all                                         | 1 / 1           | 0 / 0           |  |
| deaths causally related to<br>treatment / all                                              | 0 / 0           | 0 / 0           |  |
| Tachycardia<br>alternative assessment type:<br>Systematic                                  |                 |                 |  |
| subjects affected / exposed                                                                | 0 / 238 (0.00%) | 1 / 245 (0.41%) |  |
| occurrences causally related to<br>treatment / all                                         | 0 / 0           | 0 / 1           |  |
| deaths causally related to<br>treatment / all                                              | 0 / 0           | 0 / 0           |  |
| Ischaemic cardiomyopathy<br>subjects affected / exposed                                    | 1 / 238 (0.42%) | 0 / 245 (0.00%) |  |
| occurrences causally related to<br>treatment / all                                         | 1 / 1           | 0 / 0           |  |
| deaths causally related to<br>treatment / all                                              | 1 / 1           | 0 / 0           |  |
| Supraventricular tachycardia<br>subjects affected / exposed                                | 0 / 238 (0.00%) | 1 / 245 (0.41%) |  |
| occurrences causally related to<br>treatment / all                                         | 0 / 0           | 0 / 1           |  |
| deaths causally related to<br>treatment / all                                              | 0 / 0           | 0 / 0           |  |
| Nervous system disorders<br>Ischaemic stroke<br>alternative assessment type:<br>Systematic |                 |                 |  |

|                                                                        |                 |                 |  |
|------------------------------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                                            | 2 / 238 (0.84%) | 0 / 245 (0.00%) |  |
| occurrences causally related to treatment / all                        | 2 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all                             | 0 / 0           | 0 / 0           |  |
| Cerebrovascular accident<br>alternative assessment type:<br>Systematic |                 |                 |  |
| subjects affected / exposed                                            | 1 / 238 (0.42%) | 0 / 245 (0.00%) |  |
| occurrences causally related to treatment / all                        | 2 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all                             | 0 / 0           | 0 / 0           |  |
| Cerebrovascular disorder<br>alternative assessment type:<br>Systematic |                 |                 |  |
| subjects affected / exposed                                            | 1 / 238 (0.42%) | 0 / 245 (0.00%) |  |
| occurrences causally related to treatment / all                        | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all                             | 1 / 1           | 0 / 0           |  |
| Convulsion<br>alternative assessment type:<br>Systematic               |                 |                 |  |
| subjects affected / exposed                                            | 0 / 238 (0.00%) | 2 / 245 (0.82%) |  |
| occurrences causally related to treatment / all                        | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all                             | 0 / 0           | 0 / 0           |  |
| Facial paresis<br>alternative assessment type:<br>Systematic           |                 |                 |  |
| subjects affected / exposed                                            | 0 / 238 (0.00%) | 1 / 245 (0.41%) |  |
| occurrences causally related to treatment / all                        | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all                             | 0 / 0           | 0 / 0           |  |
| Headache<br>alternative assessment type:<br>Systematic                 |                 |                 |  |
| subjects affected / exposed                                            | 1 / 238 (0.42%) | 0 / 245 (0.00%) |  |
| occurrences causally related to treatment / all                        | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all                             | 0 / 0           | 0 / 0           |  |
| Motor dysfunction<br>alternative assessment type:<br>Systematic        |                 |                 |  |
| subjects affected / exposed                                            | 1 / 238 (0.42%) | 0 / 245 (0.00%) |  |
| occurrences causally related to treatment / all                        | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all                             | 0 / 0           | 0 / 0           |  |

|                                                    |                 |                  |  |
|----------------------------------------------------|-----------------|------------------|--|
| Partial seizures                                   |                 |                  |  |
| alternative assessment type:<br>Systematic         |                 |                  |  |
| subjects affected / exposed                        | 1 / 238 (0.42%) | 0 / 245 (0.00%)  |  |
| occurrences causally related to<br>treatment / all | 1 / 1           | 0 / 0            |  |
| deaths causally related to<br>treatment / all      | 0 / 0           | 0 / 0            |  |
| Polyneuropathy                                     |                 |                  |  |
| alternative assessment type:<br>Systematic         |                 |                  |  |
| subjects affected / exposed                        | 1 / 238 (0.42%) | 0 / 245 (0.00%)  |  |
| occurrences causally related to<br>treatment / all | 1 / 1           | 0 / 0            |  |
| deaths causally related to<br>treatment / all      | 0 / 0           | 0 / 0            |  |
| Spinal cord compression                            |                 |                  |  |
| alternative assessment type:<br>Systematic         |                 |                  |  |
| subjects affected / exposed                        | 1 / 238 (0.42%) | 0 / 245 (0.00%)  |  |
| occurrences causally related to<br>treatment / all | 1 / 1           | 0 / 0            |  |
| deaths causally related to<br>treatment / all      | 0 / 0           | 0 / 0            |  |
| Ruptured cerebral aneurysm                         |                 |                  |  |
| subjects affected / exposed                        | 0 / 238 (0.00%) | 1 / 245 (0.41%)  |  |
| occurrences causally related to<br>treatment / all | 0 / 0           | 1 / 1            |  |
| deaths causally related to<br>treatment / all      | 0 / 0           | 1 / 1            |  |
| Blood and lymphatic system disorders               |                 |                  |  |
| Febrile neutropenia                                |                 |                  |  |
| alternative assessment type:<br>Systematic         |                 |                  |  |
| subjects affected / exposed                        | 5 / 238 (2.10%) | 12 / 245 (4.90%) |  |
| occurrences causally related to<br>treatment / all | 5 / 5           | 0 / 13           |  |
| deaths causally related to<br>treatment / all      | 0 / 0           | 0 / 0            |  |
| Neutropenia                                        |                 |                  |  |
| alternative assessment type:<br>Systematic         |                 |                  |  |
| subjects affected / exposed                        | 6 / 238 (2.52%) | 10 / 245 (4.08%) |  |
| occurrences causally related to<br>treatment / all | 7 / 7           | 0 / 15           |  |
| deaths causally related to<br>treatment / all      | 0 / 0           | 0 / 0            |  |
| Thrombocytopenia                                   |                 |                  |  |
| alternative assessment type:<br>Systematic         |                 |                  |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 238 (0.00%) | 5 / 245 (2.04%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 5           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Leukopenia                                      |                 |                 |  |
| alternative assessment type: Systematic         |                 |                 |  |
| subjects affected / exposed                     | 1 / 238 (0.42%) | 2 / 245 (0.82%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Anaemia                                         |                 |                 |  |
| alternative assessment type: Systematic         |                 |                 |  |
| subjects affected / exposed                     | 1 / 238 (0.42%) | 1 / 245 (0.41%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pancytopenia                                    |                 |                 |  |
| alternative assessment type: Systematic         |                 |                 |  |
| subjects affected / exposed                     | 0 / 238 (0.00%) | 1 / 245 (0.41%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastrointestinal disorders                      |                 |                 |  |
| Diarrhoea                                       |                 |                 |  |
| alternative assessment type: Systematic         |                 |                 |  |
| subjects affected / exposed                     | 2 / 238 (0.84%) | 4 / 245 (1.63%) |  |
| occurrences causally related to treatment / all | 2 / 2           | 0 / 4           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Nausea                                          |                 |                 |  |
| alternative assessment type: Systematic         |                 |                 |  |
| subjects affected / exposed                     | 1 / 238 (0.42%) | 1 / 245 (0.41%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Vomiting                                        |                 |                 |  |
| alternative assessment type: Systematic         |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 238 (0.42%) | 2 / 245 (0.82%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 1 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Abdominal pain                                  |                 |                 |  |
| alternative assessment type: Systematic         |                 |                 |  |
| subjects affected / exposed                     | 1 / 238 (0.42%) | 1 / 245 (0.41%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Anal fissure                                    |                 |                 |  |
| alternative assessment type: Systematic         |                 |                 |  |
| subjects affected / exposed                     | 0 / 238 (0.00%) | 1 / 245 (0.41%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Diverticular perforation                        |                 |                 |  |
| alternative assessment type: Systematic         |                 |                 |  |
| subjects affected / exposed                     | 0 / 238 (0.00%) | 1 / 245 (0.41%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastrointestinal disorder                       |                 |                 |  |
| alternative assessment type: Systematic         |                 |                 |  |
| subjects affected / exposed                     | 0 / 238 (0.00%) | 1 / 245 (0.41%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Faecaloma                                       |                 |                 |  |
| alternative assessment type: Systematic         |                 |                 |  |
| subjects affected / exposed                     | 0 / 238 (0.00%) | 1 / 245 (0.41%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Ileus paralytic                                 |                 |                 |  |
| alternative assessment type: Systematic         |                 |                 |  |
| subjects affected / exposed                     | 1 / 238 (0.42%) | 0 / 245 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

|                                                    |                 |                 |  |
|----------------------------------------------------|-----------------|-----------------|--|
| Melaena                                            |                 |                 |  |
| alternative assessment type:<br>Systematic         |                 |                 |  |
| subjects affected / exposed                        | 0 / 238 (0.00%) | 1 / 245 (0.41%) |  |
| occurrences causally related to<br>treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to<br>treatment / all      | 0 / 0           | 0 / 0           |  |
| Pancreatitis                                       |                 |                 |  |
| alternative assessment type:<br>Systematic         |                 |                 |  |
| subjects affected / exposed                        | 1 / 238 (0.42%) | 0 / 245 (0.00%) |  |
| occurrences causally related to<br>treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to<br>treatment / all      | 1 / 1           | 0 / 0           |  |
| Subileus                                           |                 |                 |  |
| alternative assessment type:<br>Systematic         |                 |                 |  |
| subjects affected / exposed                        | 0 / 238 (0.00%) | 1 / 245 (0.41%) |  |
| occurrences causally related to<br>treatment / all | 0 / 0           | 0 / 4           |  |
| deaths causally related to<br>treatment / all      | 0 / 0           | 0 / 0           |  |
| Hepatobiliary disorders                            |                 |                 |  |
| Cholelithiasis                                     |                 |                 |  |
| alternative assessment type:<br>Systematic         |                 |                 |  |
| subjects affected / exposed                        | 0 / 238 (0.00%) | 2 / 245 (0.82%) |  |
| occurrences causally related to<br>treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to<br>treatment / all      | 0 / 0           | 0 / 0           |  |
| Cholangitis                                        |                 |                 |  |
| alternative assessment type:<br>Systematic         |                 |                 |  |
| subjects affected / exposed                        | 1 / 238 (0.42%) | 0 / 245 (0.00%) |  |
| occurrences causally related to<br>treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to<br>treatment / all      | 0 / 0           | 0 / 0           |  |
| Cholecystitis                                      |                 |                 |  |
| alternative assessment type:<br>Systematic         |                 |                 |  |
| subjects affected / exposed                        | 0 / 238 (0.00%) | 1 / 245 (0.41%) |  |
| occurrences causally related to<br>treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to<br>treatment / all      | 0 / 0           | 0 / 0           |  |
| Hepatitis toxic                                    |                 |                 |  |
| alternative assessment type:<br>Systematic         |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 238 (0.00%) | 1 / 245 (0.41%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Skin and subcutaneous tissue disorders          |                 |                 |  |
| Skin ulcer                                      |                 |                 |  |
| alternative assessment type: Systematic         |                 |                 |  |
| subjects affected / exposed                     | 0 / 238 (0.00%) | 1 / 245 (0.41%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Renal and urinary disorders                     |                 |                 |  |
| Obstructive uropathy                            |                 |                 |  |
| alternative assessment type: Systematic         |                 |                 |  |
| subjects affected / exposed                     | 1 / 238 (0.42%) | 0 / 245 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Postrenal failure                               |                 |                 |  |
| alternative assessment type: Systematic         |                 |                 |  |
| subjects affected / exposed                     | 0 / 238 (0.00%) | 1 / 245 (0.41%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Musculoskeletal and connective tissue disorders |                 |                 |  |
| Bone pain                                       |                 |                 |  |
| alternative assessment type: Systematic         |                 |                 |  |
| subjects affected / exposed                     | 1 / 238 (0.42%) | 2 / 245 (0.82%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Osteonecrosis of jaw                            |                 |                 |  |
| alternative assessment type: Systematic         |                 |                 |  |
| subjects affected / exposed                     | 0 / 238 (0.00%) | 2 / 245 (0.82%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Musculoskeletal pain                            |                 |                 |  |
| alternative assessment type: Systematic         |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 238 (0.00%) | 1 / 245 (0.41%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pathological fracture                           |                 |                 |  |
| alternative assessment type: Systematic         |                 |                 |  |
| subjects affected / exposed                     | 1 / 238 (0.42%) | 0 / 245 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Osteolysis                                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 238 (0.00%) | 1 / 245 (0.41%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Infections and infestations                     |                 |                 |  |
| Infection                                       |                 |                 |  |
| alternative assessment type: Systematic         |                 |                 |  |
| subjects affected / exposed                     | 2 / 238 (0.84%) | 3 / 245 (1.22%) |  |
| occurrences causally related to treatment / all | 2 / 2           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Bronchitis                                      |                 |                 |  |
| alternative assessment type: Systematic         |                 |                 |  |
| subjects affected / exposed                     | 0 / 238 (0.00%) | 3 / 245 (1.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 4           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pneumonia                                       |                 |                 |  |
| alternative assessment type: Systematic         |                 |                 |  |
| subjects affected / exposed                     | 0 / 238 (0.00%) | 2 / 245 (0.82%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Anal abscess                                    |                 |                 |  |
| alternative assessment type: Systematic         |                 |                 |  |
| subjects affected / exposed                     | 0 / 238 (0.00%) | 1 / 245 (0.41%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

|                                                                        |                 |                 |  |  |
|------------------------------------------------------------------------|-----------------|-----------------|--|--|
| Device related infection<br>alternative assessment type:<br>Systematic |                 |                 |  |  |
| subjects affected / exposed                                            | 1 / 238 (0.42%) | 0 / 245 (0.00%) |  |  |
| occurrences causally related to<br>treatment / all                     | 1 / 1           | 0 / 0           |  |  |
| deaths causally related to<br>treatment / all                          | 0 / 0           | 0 / 0           |  |  |
| Device related sepsis<br>alternative assessment type:<br>Systematic    |                 |                 |  |  |
| subjects affected / exposed                                            | 1 / 238 (0.42%) | 0 / 245 (0.00%) |  |  |
| occurrences causally related to<br>treatment / all                     | 1 / 1           | 0 / 0           |  |  |
| deaths causally related to<br>treatment / all                          | 0 / 0           | 0 / 0           |  |  |
| Ear infection<br>alternative assessment type:<br>Systematic            |                 |                 |  |  |
| subjects affected / exposed                                            | 1 / 238 (0.42%) | 0 / 245 (0.00%) |  |  |
| occurrences causally related to<br>treatment / all                     | 1 / 1           | 0 / 0           |  |  |
| deaths causally related to<br>treatment / all                          | 0 / 0           | 0 / 0           |  |  |
| Enterocolitis infectious<br>alternative assessment type:<br>Systematic |                 |                 |  |  |
| subjects affected / exposed                                            | 1 / 238 (0.42%) | 0 / 245 (0.00%) |  |  |
| occurrences causally related to<br>treatment / all                     | 1 / 1           | 0 / 0           |  |  |
| deaths causally related to<br>treatment / all                          | 0 / 0           | 0 / 0           |  |  |
| Erysipelas<br>alternative assessment type:<br>Systematic               |                 |                 |  |  |
| subjects affected / exposed                                            | 1 / 238 (0.42%) | 0 / 245 (0.00%) |  |  |
| occurrences causally related to<br>treatment / all                     | 1 / 1           | 0 / 0           |  |  |
| deaths causally related to<br>treatment / all                          | 0 / 0           | 0 / 0           |  |  |
| Herpes zoster<br>alternative assessment type:<br>Systematic            |                 |                 |  |  |
| subjects affected / exposed                                            | 1 / 238 (0.42%) | 0 / 245 (0.00%) |  |  |
| occurrences causally related to<br>treatment / all                     | 1 / 1           | 0 / 0           |  |  |
| deaths causally related to<br>treatment / all                          | 0 / 0           | 0 / 0           |  |  |
| Injection site infection<br>alternative assessment type:<br>Systematic |                 |                 |  |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 238 (0.42%) | 0 / 245 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Osteomyelitis                                   |                 |                 |  |
| alternative assessment type: Systematic         |                 |                 |  |
| subjects affected / exposed                     | 0 / 238 (0.00%) | 1 / 245 (0.41%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Peritonitis bacterial                           |                 |                 |  |
| alternative assessment type: Systematic         |                 |                 |  |
| subjects affected / exposed                     | 0 / 238 (0.00%) | 1 / 245 (0.41%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pseudomembranous colitis                        |                 |                 |  |
| alternative assessment type: Systematic         |                 |                 |  |
| subjects affected / exposed                     | 0 / 238 (0.00%) | 1 / 245 (0.41%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Sepsis                                          |                 |                 |  |
| alternative assessment type: Systematic         |                 |                 |  |
| subjects affected / exposed                     | 0 / 238 (0.00%) | 2 / 245 (0.82%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Tooth infection                                 |                 |                 |  |
| alternative assessment type: Systematic         |                 |                 |  |
| subjects affected / exposed                     | 0 / 238 (0.00%) | 1 / 245 (0.41%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Urinary tract infection                         |                 |                 |  |
| alternative assessment type: Systematic         |                 |                 |  |
| subjects affected / exposed                     | 0 / 238 (0.00%) | 1 / 245 (0.41%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

|                                                    |                 |                 |  |
|----------------------------------------------------|-----------------|-----------------|--|
| Urosepsis                                          |                 |                 |  |
| alternative assessment type:<br>Systematic         |                 |                 |  |
| subjects affected / exposed                        | 0 / 238 (0.00%) | 1 / 245 (0.41%) |  |
| occurrences causally related to<br>treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to<br>treatment / all      | 0 / 0           | 0 / 0           |  |
| Wound infection                                    |                 |                 |  |
| alternative assessment type:<br>Systematic         |                 |                 |  |
| subjects affected / exposed                        | 0 / 238 (0.00%) | 1 / 245 (0.41%) |  |
| occurrences causally related to<br>treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to<br>treatment / all      | 0 / 0           | 0 / 0           |  |
| Metabolism and nutrition disorders                 |                 |                 |  |
| Hyponatraemia                                      |                 |                 |  |
| alternative assessment type:<br>Systematic         |                 |                 |  |
| subjects affected / exposed                        | 1 / 238 (0.42%) | 2 / 245 (0.82%) |  |
| occurrences causally related to<br>treatment / all | 1 / 1           | 0 / 2           |  |
| deaths causally related to<br>treatment / all      | 0 / 0           | 0 / 0           |  |
| Hypercalcaemia                                     |                 |                 |  |
| alternative assessment type:<br>Systematic         |                 |                 |  |
| subjects affected / exposed                        | 1 / 238 (0.42%) | 1 / 245 (0.41%) |  |
| occurrences causally related to<br>treatment / all | 1 / 1           | 0 / 1           |  |
| deaths causally related to<br>treatment / all      | 0 / 0           | 0 / 0           |  |
| Hypocalcaemia                                      |                 |                 |  |
| alternative assessment type:<br>Systematic         |                 |                 |  |
| subjects affected / exposed                        | 0 / 238 (0.00%) | 1 / 245 (0.41%) |  |
| occurrences causally related to<br>treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to<br>treatment / all      | 0 / 0           | 0 / 0           |  |
| Hypoglycaemia                                      |                 |                 |  |
| alternative assessment type:<br>Systematic         |                 |                 |  |
| subjects affected / exposed                        | 0 / 238 (0.00%) | 1 / 245 (0.41%) |  |
| occurrences causally related to<br>treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to<br>treatment / all      | 0 / 0           | 0 / 0           |  |

| <b>Non-serious adverse events</b>                     | CT Arm             | CT+BV Arm          |  |
|-------------------------------------------------------|--------------------|--------------------|--|
| Total subjects affected by non-serious adverse events |                    |                    |  |
| subjects affected / exposed                           | 181 / 238 (76.05%) | 218 / 245 (88.98%) |  |
| Vascular disorders                                    |                    |                    |  |
| Hypertension                                          |                    |                    |  |
| alternative assessment type: Systematic               |                    |                    |  |
| subjects affected / exposed                           | 55 / 238 (23.11%)  | 90 / 245 (36.73%)  |  |
| occurrences (all)                                     | 91                 | 181                |  |
| Haemorrhage                                           |                    |                    |  |
| alternative assessment type: Systematic               |                    |                    |  |
| subjects affected / exposed                           | 7 / 238 (2.94%)    | 29 / 245 (11.84%)  |  |
| occurrences (all)                                     | 7                  | 51                 |  |
| Nervous system disorders                              |                    |                    |  |
| Peripheral sensory neuropathy                         |                    |                    |  |
| subjects affected / exposed                           | 10 / 238 (4.20%)   | 15 / 245 (6.12%)   |  |
| occurrences (all)                                     | 12                 | 15                 |  |
| Blood and lymphatic system disorders                  |                    |                    |  |
| Neutropenia                                           |                    |                    |  |
| alternative assessment type: Systematic               |                    |                    |  |
| subjects affected / exposed                           | 55 / 238 (23.11%)  | 64 / 245 (26.12%)  |  |
| occurrences (all)                                     | 112                | 158                |  |
| Leukopenia                                            |                    |                    |  |
| alternative assessment type: Systematic               |                    |                    |  |
| subjects affected / exposed                           | 18 / 238 (7.56%)   | 30 / 245 (12.24%)  |  |
| occurrences (all)                                     | 30                 | 71                 |  |
| Anaemia                                               |                    |                    |  |
| alternative assessment type: Systematic               |                    |                    |  |
| subjects affected / exposed                           | 13 / 238 (5.46%)   | 22 / 245 (8.98%)   |  |
| occurrences (all)                                     | 19                 | 29                 |  |
| Thrombocytopenia                                      |                    |                    |  |
| subjects affected / exposed                           | 4 / 238 (1.68%)    | 16 / 245 (6.53%)   |  |
| occurrences (all)                                     | 8                  | 30                 |  |
| General disorders and administration site conditions  |                    |                    |  |
| Fatigue                                               |                    |                    |  |
| alternative assessment type: Systematic               |                    |                    |  |

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                          |                                                                                                                                                                             |  |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--|
| <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Mucosal inflammation</p> <p>alternative assessment type: Systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Asthenia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Pyrexia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>                                                                                                                                                                                                                           | <p>33 / 238 (13.87%)</p> <p>39</p> <p>9 / 238 (3.78%)</p> <p>9</p> <p>5 / 238 (2.10%)</p> <p>5</p> <p>11 / 238 (4.62%)</p> <p>17</p>                                     | <p>49 / 245 (20.00%)</p> <p>67</p> <p>26 / 245 (10.61%)</p> <p>38</p> <p>14 / 245 (5.71%)</p> <p>16</p> <p>14 / 245 (5.71%)</p> <p>18</p>                                   |  |
| <p>Gastrointestinal disorders</p> <p>Diarrhoea</p> <p>alternative assessment type: Systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Nausea</p> <p>alternative assessment type: Systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Vomiting</p> <p>alternative assessment type: Systematic</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Abdominal pain</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Constipation</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>27 / 238 (11.34%)</p> <p>35</p> <p>31 / 238 (13.03%)</p> <p>35</p> <p>22 / 238 (9.24%)</p> <p>28</p> <p>3 / 238 (1.26%)</p> <p>4</p> <p>9 / 238 (3.78%)</p> <p>13</p> | <p>35 / 245 (14.29%)</p> <p>44</p> <p>33 / 245 (13.47%)</p> <p>45</p> <p>16 / 245 (6.53%)</p> <p>20</p> <p>15 / 245 (6.12%)</p> <p>18</p> <p>13 / 245 (5.31%)</p> <p>14</p> |  |
| <p>Respiratory, thoracic and mediastinal disorders</p> <p>epistaxis</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                 | <p>3 / 238 (1.26%)</p> <p>3</p>                                                                                                                                          | <p>18 / 245 (7.35%)</p> <p>19</p>                                                                                                                                           |  |

|                                                                                                                                              |                          |                           |  |
|----------------------------------------------------------------------------------------------------------------------------------------------|--------------------------|---------------------------|--|
| Skin and subcutaneous tissue disorders<br>Palmar-plantar erythrodysaesthesia<br>syndrome<br>subjects affected / exposed<br>occurrences (all) | 58 / 238 (24.37%)<br>76  | 72 / 245 (29.39%)<br>103  |  |
| Renal and urinary disorders<br>Proteinuria<br>subjects affected / exposed<br>occurrences (all)                                               | 70 / 238 (29.41%)<br>103 | 133 / 245 (54.29%)<br>247 |  |
| Infections and infestations<br>Urinary tract infection<br>subjects affected / exposed<br>occurrences (all)                                   | 2 / 238 (0.84%)<br>2     | 16 / 245 (6.53%)<br>16    |  |
| Metabolism and nutrition disorders<br>Decreased appetite<br>subjects affected / exposed<br>occurrences (all)                                 | 4 / 238 (1.68%)<br>4     | 21 / 245 (8.57%)<br>23    |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date              | Amendment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|-------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 14 January 2011   | <ul style="list-style-type: none"> <li>• Exclusion criteria regarding participants not using effective contraception were updated to specify time limits (during the study and for 6 months after the last bevacizumab administration).</li> <li>• Time limit for reporting pregnancies after the completion of bevacizumab was updated from 90 days to 6 months.</li> <li>• AEs to be collected were updated from all AEs to all SAEs and/or Grade 3-5 AEs and all adverse event of special interest (AESI).</li> <li>• AESI were added; all grades of AESI were to be reported; any treatment for AESI was to be captured.</li> <li>• Clinically significant laboratory test results to be captured in the electronic CRF (eCRF) were specified as Grade 3-5 only.</li> <li>• Specification added that information on anti-cancer treatments given post third-line progression should be collected.</li> <li>• Clarification added that second-line progression, and not toxicity, would result in third-line treatment.</li> <li>• Clarification added that in the CT Arm after second-line disease progression participants had to receive third-line standard of care chemotherapy.</li> <li>• Clarification added that tumor assessment would only be performed post-study treatment in the absence of confirmation of disease progression.</li> <li>• Clarification added that plasma (not serum) assays would be used for genetic analysis and that 2 x 2.5 mL blood instead of 6 mL blood samples would be collected for RCR sampling.</li> <li>• Clarification added that chemotherapy at the investigator's discretion must be approved.</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| 03 September 2013 | <ul style="list-style-type: none"> <li>• List of reasons for participants finishing treatment in second-line was updated to include 'maximum cumulative dose of anthracycline.'</li> <li>• Clarification added regarding the treatment options available to participants who discontinued chemotherapy due to toxicity during second- and third-line treatment.</li> <li>• End of study and length of study were defined and aligned and the different analysis time points were differentiated.</li> <li>• Post-trial provision of care with bevacizumab was clarified.</li> <li>• Clarification added that both second- and third-line chemotherapy options permitted for this study must be one of those listed in the protocol.</li> <li>• In response to queries from countries where the local SmPC was not aligned with the protocol-defined chemotherapy dose, chemotherapy dosing was allowed as per local label (on approval from the study sponsor team or its representative).</li> <li>• The vinorelbine dose was updated to include the 60 mg/m<sup>2</sup>/week induction dose to be consistent with the starting dose stated in the SmPC.</li> <li>• To avoid any misinterpretation by investigators, it was clarified that cross-over from the CT Arm to CT+BV Arm was not permitted after second-line therapy.</li> <li>• Further to a request of the steering committee, eribulin was included as a chemotherapy option for third-line treatment only.</li> <li>• Randomization was defined as the baseline for tumor assessments.</li> <li>• It is standard clinical practice to use endocrine therapy in combination with chemotherapy. Therefore in cases of bevacizumab toxicity where the patient continued with chemotherapy only (CT+BV Arm), the use of endocrine therapy in combination with chemotherapy was permitted.</li> <li>• In line with updated European Commission guidelines, the reporting period for SAEs was amended from 'within 1 working day' to 'within 24 hours'. Text updated to provide the correct information regarding SAE reporting after database lock.</li> <li>• Additional information was added to explain why bevacizumab should not be used during pregnancy.</li> </ul> |

Notes:

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## **Interruptions (globally)**

Were there any global interruptions to the trial? No

## **Limitations and caveats**

None reported