



## Clinical trial results:

### Efficacy and Safety of Two Neoadjuvant Strategies With Bevacizumab in Locally Advanced Resectable Rectal Cancer: A Randomized, Non-Comparative Phase II Study

#### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2006-003472-35 |
| Trial protocol           | FR             |
| Global end of trial date | 23 March 2016  |

#### Results information

|                                |               |
|--------------------------------|---------------|
| Result version number          | v1 (current)  |
| This version publication date  | 29 April 2017 |
| First version publication date | 29 April 2017 |

#### Trial information

##### Trial identification

|                       |         |
|-----------------------|---------|
| Sponsor protocol code | ML19202 |
|-----------------------|---------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT00865189 |
| 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                       | 23 March 2016 |
| Is this the analysis of the primary completion data? | No            |

|                                  |               |
|----------------------------------|---------------|
| Global end of trial reached?     | Yes           |
| Global end of trial date         | 23 March 2016 |
| Was the trial ended prematurely? | No            |

Notes:

## General information about the trial

Main objective of the trial:

To assess the efficacy of two preoperative therapeutic strategies including bevacizumab in participants with newly diagnosed locally advanced rectal cancer.

Protection of trial subjects:

The study was conducted in accordance with the principles of the "Declaration of Helsinki" and International Conference on Harmonisation (ICH) Good Clinical Practice (GCP).

Background therapy: -

Evidence for comparator: -

|                                                           |                 |
|-----------------------------------------------------------|-----------------|
| Actual start date of recruitment                          | 23 October 2007 |
| Long term follow-up planned                               | Yes             |
| Long term follow-up rationale                             | Efficacy        |
| Long term follow-up duration                              | 5 Years         |
| Independent data monitoring committee (IDMC) involvement? | No              |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |            |
|--------------------------------------|------------|
| Country: Number of subjects enrolled | France: 91 |
| Worldwide total number of subjects   | 91         |
| EEA total number of subjects         | 91         |

Notes:

### Subjects enrolled per age group

|                                           |    |
|-------------------------------------------|----|
| In utero                                  | 0  |
| Preterm newborn - gestational age < 37 wk | 0  |
| Newborns (0-27 days)                      | 0  |
| Infants and toddlers (28 days-23 months)  | 0  |
| Children (2-11 years)                     | 0  |
| Adolescents (12-17 years)                 | 0  |
| Adults (18-64 years)                      | 62 |
| From 65 to 84 years                       | 29 |
| 85 years and over                         | 0  |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

A total of 92 participants with resectable rectal cancer were selected and 91 participants were randomized into the study. One participant was not randomized due to non-compliance with the inclusion/exclusion criteria.

### Period 1

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

### Arms

|                              |                                                                |
|------------------------------|----------------------------------------------------------------|
| Are arms mutually exclusive? | Yes                                                            |
| <b>Arm title</b>             | Arm A (Bevacizumab, Induction Chemotherapy, Chemoradiotherapy) |

Arm description:

In this arm, participants underwent 3 phases of treatment. During the Phase 1, participants received induction chemotherapy with 6 two-week cycles of bevacizumab + Folfox-4 (5-FU + oxaliplatin + folinic acid) for 12 weeks followed by a treatment-free interval of 3 to 4 weeks. The Phase 2 consisted of 7 weeks of bevacizumab + chemoradiotherapy (intravenous [IV] infusion of bevacizumab alone, 2 weeks before administration of the first cycle of chemoradiotherapy, then 5 one-week cycles of chemoradiotherapy [5-FU + radiotherapy], with administration of bevacizumab every two weeks [Cycles 1, 3 and 5]) followed by a treatment-free interval of 6 to 8 weeks. The Phase 3 was surgery involving a radical rectal excision using the total mesorectal excision (TME) technique.

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

Dosage and administration details:

Bevacizumab was administered at the fixed dose of 5 milligrams per kilogram (mg/kg) as an IV infusion over 30 to 90 minutes.

|                                        |                        |
|----------------------------------------|------------------------|
| Investigational medicinal product name | Folinic acid           |
| Investigational medicinal product code |                        |
| Other name                             | Leucovorin             |
| Pharmaceutical forms                   | Solution for injection |
| Routes of administration               | Intravenous use        |

Dosage and administration details:

Folinic acid was administered at a dose of 200 mg/m<sup>2</sup> as a 2-hour IV infusion.

|                                        |                                  |
|----------------------------------------|----------------------------------|
| Investigational medicinal product name | Oxaliplatin                      |
| Investigational medicinal product code |                                  |
| Other name                             | Eloxatine                        |
| Pharmaceutical forms                   | Powder for solution for infusion |
| Routes of administration               | Intravenous use                  |

Dosage and administration details:

Oxaliplatin was administered at a dose of 85 milligrams per square meter (mg/m<sup>2</sup>) as a 2-hour IV infusion.

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

**Dosage and administration details:**

5-fluorouracil was administered at a dose of 400 mg/m<sup>2</sup> as an IV bolus, then at a dose of 600 mg/m<sup>2</sup> as a continuous IV infusion for 22 hours in Phase 1, and was administered at a dose of 225 mg/m<sup>2</sup> as a 24-hour IV infusion, 5 days a week, for 5 weeks in Phase 2.

|                  |                                        |
|------------------|----------------------------------------|
| <b>Arm title</b> | Arm B (Bevacizumab, Chemoradiotherapy) |
|------------------|----------------------------------------|

**Arm description:**

In this arm, participants received the Phase 2 and Phase 3 treatments only. The phase 2 consisted of 7 weeks of bevacizumab + chemoradiotherapy (IV infusion of bevacizumab alone, 2 weeks before administration of the first cycle of chemoradiotherapy, then 5 one-week cycles of chemoradiotherapy [5-FU + radiotherapy], with administration of bevacizumab every two weeks [Cycles 1, 3 and 5]) followed by a treatment-free interval of 6 to 8 weeks. The phase 3 was surgery involving a radical rectal excision using the TME technique.

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

**Dosage and administration details:**

5-fluorouracil was administered at a dose of 400 mg/m<sup>2</sup> as an IV bolus, then at a dose of 600 mg/m<sup>2</sup> as a continuous infusion for 22 hours in Phase 1, and was administered at a dose of 225 mg/m<sup>2</sup> as a 24-hour infusion, 5 days a week, for 5 weeks in Phase 2.

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

**Dosage and administration details:**

Bevacizumab was administered at the fixed dose of 5 mg/kg as an IV infusion over 30 to 90 minutes.

| <b>Number of subjects in period 1</b> | <b>Arm A<br/>(Bevacizumab,<br/>Induction<br/>Chemotherapy,<br/>Chemoradiotherapy)</b> | <b>Arm B<br/>(Bevacizumab,<br/>Chemoradiotherapy)</b> |
|---------------------------------------|---------------------------------------------------------------------------------------|-------------------------------------------------------|
| Started                               | 46                                                                                    | 45                                                    |
| Completed                             | 34                                                                                    | 26                                                    |
| Not completed                         | 12                                                                                    | 19                                                    |
| Consent withdrawn by subject          | 1                                                                                     | -                                                     |
| Death                                 | 4                                                                                     | 11                                                    |
| Unspecified                           | 1                                                                                     | 2                                                     |
| Lost to follow-up                     | 6                                                                                     | 6                                                     |



## Baseline characteristics

### Reporting groups

|                       |                                                                |
|-----------------------|----------------------------------------------------------------|
| Reporting group title | Arm A (Bevacizumab, Induction Chemotherapy, Chemoradiotherapy) |
|-----------------------|----------------------------------------------------------------|

#### Reporting group description:

In this arm, participants underwent 3 phases of treatment. During the Phase 1, participants received induction chemotherapy with 6 two-week cycles of bevacizumab + Folfox-4 (5-FU + oxaliplatin + folinic acid) for 12 weeks followed by a treatment-free interval of 3 to 4 weeks. The Phase 2 consisted of 7 weeks of bevacizumab + chemoradiotherapy (intravenous [IV] infusion of bevacizumab alone, 2 weeks before administration of the first cycle of chemoradiotherapy, then 5 one-week cycles of chemoradiotherapy [5-FU + radiotherapy], with administration of bevacizumab every two weeks [Cycles 1, 3 and 5]) followed by a treatment-free interval of 6 to 8 weeks. The Phase 3 was surgery involving a radical rectal excision using the total mesorectal excision (TME) technique.

|                       |                                        |
|-----------------------|----------------------------------------|
| Reporting group title | Arm B (Bevacizumab, Chemoradiotherapy) |
|-----------------------|----------------------------------------|

#### Reporting group description:

In this arm, participants received the Phase 2 and Phase 3 treatments only. The phase 2 consisted of 7 weeks of bevacizumab + chemoradiotherapy (IV infusion of bevacizumab alone, 2 weeks before administration of the first cycle of chemoradiotherapy, then 5 one-week cycles of chemoradiotherapy [5-FU + radiotherapy], with administration of bevacizumab every two weeks [Cycles 1, 3 and 5]) followed by a treatment-free interval of 6 to 8 weeks. The phase 3 was surgery involving a radical rectal excision using the TME technique.

| Reporting group values                | Arm A<br>(Bevacizumab,<br>Induction<br>Chemotherapy,<br>Chemoradiotherapy) | Arm B<br>(Bevacizumab,<br>Chemoradiotherapy) | Total |
|---------------------------------------|----------------------------------------------------------------------------|----------------------------------------------|-------|
| Number of subjects                    | 46                                                                         | 45                                           | 91    |
| Age Categorical<br>Units: Subjects    |                                                                            |                                              |       |
| Adults (18-64 years)                  | 33                                                                         | 29                                           | 62    |
| From 65-84 years                      | 13                                                                         | 16                                           | 29    |
| Age Continuous<br>Units: years        |                                                                            |                                              |       |
| arithmetic mean                       | 60.38                                                                      | 60.71                                        |       |
| standard deviation                    | ± 8.99                                                                     | ± 9.88                                       | -     |
| Gender Categorical<br>Units: Subjects |                                                                            |                                              |       |
| Female                                | 15                                                                         | 15                                           | 30    |
| Male                                  | 31                                                                         | 30                                           | 61    |

## End points

### End points reporting groups

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------|
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | Arm A (Bevacizumab, Induction Chemotherapy, Chemoradiotherapy) |
| Reporting group description:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                                                |
| In this arm, participants underwent 3 phases of treatment. During the Phase 1, participants received induction chemotherapy with 6 two-week cycles of bevacizumab + Folfox-4 (5-FU + oxaliplatin + folinic acid) for 12 weeks followed by a treatment-free interval of 3 to 4 weeks. The Phase 2 consisted of 7 weeks of bevacizumab + chemoradiotherapy (intravenous [IV] infusion of bevacizumab alone, 2 weeks before administration of the first cycle of chemoradiotherapy, then 5 one-week cycles of chemoradiotherapy [5-FU + radiotherapy], with administration of bevacizumab every two weeks [Cycles 1, 3 and 5]) followed by a treatment-free interval of 6 to 8 weeks. The Phase 3 was surgery involving a radical rectal excision using the total mesorectal excision (TME) technique. |                                                                |
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | Arm B (Bevacizumab, Chemoradiotherapy)                         |
| Reporting group description:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                                                |
| In this arm, participants received the Phase 2 and Phase 3 treatments only. The phase 2 consisted of 7 weeks of bevacizumab + chemoradiotherapy (IV infusion of bevacizumab alone, 2 weeks before administration of the first cycle of chemoradiotherapy, then 5 one-week cycles of chemoradiotherapy [5-FU + radiotherapy], with administration of bevacizumab every two weeks [Cycles 1, 3 and 5]) followed by a treatment-free interval of 6 to 8 weeks. The phase 3 was surgery involving a radical rectal excision using the TME technique.                                                                                                                                                                                                                                                    |                                                                |

### Primary: Percentage of Participants With Tumor Sterilization Defined by ypT0-N0

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                       |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | Percentage of Participants With Tumor Sterilization Defined by ypT0-N0 <sup>[1]</sup> |
| End point description:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                                                       |
| Tumor sterilization was defined as the absence of residual tumor cells in the resected specimen including lymph nodes (ypT0-N0). The rate of sterilization of the tumoral specimen was assessed after surgery on the surgical specimen by local review. Analyses were performed for participants who have been operated as defined by the protocol (within the study and TME technique) and for all participants who have been operated. Reported is the percentage of participants with tumor sterilization. Intent to treat (ITT) population included all the randomized participants who received at least one dose of treatment. Here, number of participants analyzed = participants who were evaluable for this outcome. |                                                                                       |
| End point type                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | Primary                                                                               |
| End point timeframe:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                                                                       |
| After surgery (Arm A: approximately 28-31 weeks after initiation of treatment; Arm B: approximately 13-15 weeks after initiation of treatment)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                                                                       |

#### 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 not reported due to a limitation of EudraCT application as the application does not allow the capture of a statistical analysis performed within a group.

| End point values                  | Arm A<br>(Bevacizumab,<br>Induction<br>Chemotherapy,<br>Chemoradiothe<br>rapy) | Arm B<br>(Bevacizumab,<br>Chemoradiothe<br>rapy) |  |  |
|-----------------------------------|--------------------------------------------------------------------------------|--------------------------------------------------|--|--|
| Subject group type                | Reporting group                                                                | Reporting group                                  |  |  |
| Number of subjects analysed       | 42                                                                             | 44                                               |  |  |
| Units: percentage of participants |                                                                                |                                                  |  |  |
| number (confidence interval 95%)  | 23.8 (12.1 to 39.5)                                                            | 11.4 (3.8 to 24.6)                               |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Participants With Tumor Down-Staging (ypT0-pT2)

|                 |                                                               |
|-----------------|---------------------------------------------------------------|
| End point title | Percentage of Participants With Tumor Down-Staging (ypT0-pT2) |
|-----------------|---------------------------------------------------------------|

End point description:

A participant with a downstaging was defined as a participant with T3 (T describes the size of the original [primary] tumor) at inclusion and T2 or T1 or T0 after surgery, or with N+ (N describes lymph nodes involvement) at inclusion and N- after surgery and if T is equal at inclusion and after surgery. The clinical tumor-node-metastasis (cTNM) classification was used at inclusion and the pathological staging tumor and nodes (ypTN) classification after surgery. Reported is the percentage of participants with tumor downstaging of the surgical specimen according to the local review and centralized review. ITT population. Here, number of participants analyzed = participants who were evaluable for this outcome. "n" = participants who were evaluable for specified category.

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

End point timeframe:

After surgery (Arm A: approximately 28-31 weeks after initiation of treatment; Arm B: approximately 13-15 weeks after initiation of treatment)

| End point values                           | Arm A<br>(Bevacizumab,<br>Induction<br>Chemotherapy,<br>Chemoradiothe<br>rapy) | Arm B<br>(Bevacizumab,<br>Chemoradiothe<br>rapy) |  |  |
|--------------------------------------------|--------------------------------------------------------------------------------|--------------------------------------------------|--|--|
| Subject group type                         | Reporting group                                                                | Reporting group                                  |  |  |
| Number of subjects analysed                | 41                                                                             | 44                                               |  |  |
| Units: percentage of participants          |                                                                                |                                                  |  |  |
| number (confidence interval 95%)           |                                                                                |                                                  |  |  |
| Downstaging, local review (n=41, 44)       | 65.9 (51.3 to 80.4)                                                            | 54.5 (39.8 to 69.3)                              |  |  |
| Downstaging, centralized review (n=39, 43) | 64.1 (49 to 79.2)                                                              | 55.8 (41 to 70.7)                                |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Participants With Local and Distant Recurrences

|                 |                                                               |
|-----------------|---------------------------------------------------------------|
| End point title | Percentage of Participants With Local and Distant Recurrences |
|-----------------|---------------------------------------------------------------|

End point description:

The percentage of participants with a recurrence was described by type of recurrence (local and distant recurrence). ITT population.



|                                                                                                                                                |           |
|------------------------------------------------------------------------------------------------------------------------------------------------|-----------|
| End point type                                                                                                                                 | Secondary |
| End point timeframe:                                                                                                                           |           |
| After surgery (Arm A: approximately 28-31 weeks after initiation of treatment; Arm B: approximately 13-15 weeks after initiation of treatment) |           |

| End point values                       | Arm A<br>(Bevacizumab,<br>Induction<br>Chemotherapy,<br>Chemoradiothe<br>rapy) | Arm B<br>(Bevacizumab,<br>Chemoradiothe<br>rapy) |  |  |
|----------------------------------------|--------------------------------------------------------------------------------|--------------------------------------------------|--|--|
| Subject group type                     | Reporting group                                                                | Reporting group                                  |  |  |
| Number of subjects analysed            | 46                                                                             | 45                                               |  |  |
| Units: percentage of participants      |                                                                                |                                                  |  |  |
| number (confidence interval 95%)       |                                                                                |                                                  |  |  |
| Participants with a local recurrence   | 2.2 (0.1 to 11.5)                                                              | 6.7 (1.4 to 18.3)                                |  |  |
| Participants with a distant recurrence | 17.4 (7.8 to 31.4)                                                             | 13.3 (5.1 to 26.8)                               |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Participants With Second Cancer, Local or Regional Recurrence, Distant Metastasis, or Death

|                                      |                                                                                                           |
|--------------------------------------|-----------------------------------------------------------------------------------------------------------|
| End point title                      | Percentage of Participants With Second Cancer, Local or Regional Recurrence, Distant Metastasis, or Death |
| End point description:               |                                                                                                           |
| ITT population.                      |                                                                                                           |
| End point type                       | Secondary                                                                                                 |
| End point timeframe:                 |                                                                                                           |
| Baseline up to approximately 6 years |                                                                                                           |

| End point values                  | Arm A<br>(Bevacizumab,<br>Induction<br>Chemotherapy,<br>Chemoradiothe<br>rapy) | Arm B<br>(Bevacizumab,<br>Chemoradiothe<br>rapy) |  |  |
|-----------------------------------|--------------------------------------------------------------------------------|--------------------------------------------------|--|--|
| Subject group type                | Reporting group                                                                | Reporting group                                  |  |  |
| Number of subjects analysed       | 46                                                                             | 45                                               |  |  |
| Units: percentage of participants |                                                                                |                                                  |  |  |
| number (not applicable)           | 30.4                                                                           | 33.3                                             |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Disease-Free Survival (DFS)

|                 |                             |
|-----------------|-----------------------------|
| End point title | Disease-Free Survival (DFS) |
|-----------------|-----------------------------|

End point description:

The DFS was defined as the time from the first treatment intake to disease recurrence assessed (second primary cancer, local or distant recurrence, distant metastases) or death from any cause. The DFS was analyzed using Kaplan-Meier method. ITT population. Here, 9999 and 99999 indicates that median and upper limit of 95% CI, respectively, were not reached due to low number of DFS-events.

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

End point timeframe:

From first time of the treatment administration to the date of second cancer, local or regional recurrence, distant metastasis or death from any cause (up to approximately 6 years)

| End point values                 | Arm A<br>(Bevacizumab,<br>Induction<br>Chemotherapy,<br>Chemoradiothe<br>rapy) | Arm B<br>(Bevacizumab,<br>Chemoradiothe<br>rapy) |  |  |
|----------------------------------|--------------------------------------------------------------------------------|--------------------------------------------------|--|--|
| Subject group type               | Reporting group                                                                | Reporting group                                  |  |  |
| Number of subjects analysed      | 46                                                                             | 45                                               |  |  |
| Units: months                    |                                                                                |                                                  |  |  |
| median (confidence interval 95%) | 68.3 (68.3 to<br>99999)                                                        | 9999 (53 to<br>99999)                            |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Participants Who Died

|                 |                                     |
|-----------------|-------------------------------------|
| End point title | Percentage of Participants Who Died |
|-----------------|-------------------------------------|

End point description:

ITT population.

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

End point timeframe:

Baseline up to approximately 6 years

| End point values            | Arm A<br>(Bevacizumab,<br>Induction<br>Chemotherapy,<br>Chemoradiothe<br>rapy) | Arm B<br>(Bevacizumab,<br>Chemoradiothe<br>rapy) |  |  |
|-----------------------------|--------------------------------------------------------------------------------|--------------------------------------------------|--|--|
| Subject group type          | Reporting group                                                                | Reporting group                                  |  |  |
| Number of subjects analysed | 46                                                                             | 45                                               |  |  |

|                                   |     |      |  |  |
|-----------------------------------|-----|------|--|--|
| Units: percentage of participants |     |      |  |  |
| number (not applicable)           | 8.7 | 24.4 |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Overall Survival

|                 |                  |
|-----------------|------------------|
| End point title | Overall Survival |
|-----------------|------------------|

End point description:

The overall survival was defined as the time from the first treatment intake to death from any cause. ITT population. Here, 9999, 999 and 99999 indicates that median and 95% CI were not reached due to the low number of deaths.

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

End point timeframe:

From the first treatment administration to the date of death (up to approximately 6 years)

| End point values                 | Arm A<br>(Bevacizumab,<br>Induction<br>Chemotherapy,<br>Chemoradiothe<br>rapy) | Arm B<br>(Bevacizumab,<br>Chemoradiothe<br>rapy) |  |  |
|----------------------------------|--------------------------------------------------------------------------------|--------------------------------------------------|--|--|
| Subject group type               | Reporting group                                                                | Reporting group                                  |  |  |
| Number of subjects analysed      | 46                                                                             | 45                                               |  |  |
| Units: months                    |                                                                                |                                                  |  |  |
| median (confidence interval 95%) | 9999 (999 to 99999)                                                            | 9999 (999 to 99999)                              |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Cycles of Induction Chemotherapy

|                 |                                                           |
|-----------------|-----------------------------------------------------------|
| End point title | Number of Cycles of Induction Chemotherapy <sup>[2]</sup> |
|-----------------|-----------------------------------------------------------|

End point description:

ITT population. Only Arm A participants received induction treatment.

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

End point timeframe:

6 cycles (12 weeks; cycle length = 14 days)

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint is only applicable for Arm A

| End point values                     | Arm A<br>(Bevacizumab,<br>Induction<br>Chemotherapy,<br>Chemoradiothe<br>rapy) |  |  |  |
|--------------------------------------|--------------------------------------------------------------------------------|--|--|--|
| Subject group type                   | Reporting group                                                                |  |  |  |
| Number of subjects analysed          | 46                                                                             |  |  |  |
| Units: cycles                        |                                                                                |  |  |  |
| arithmetic mean (standard deviation) | 5.8 ( $\pm$ 0.7)                                                               |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Cycles of Chemotherapy

|                                                                            |                                  |
|----------------------------------------------------------------------------|----------------------------------|
| End point title                                                            | Number of Cycles of Chemotherapy |
| End point description:<br>ITT population.                                  |                                  |
| End point type                                                             | Secondary                        |
| End point timeframe:<br>Arm A: Week 16 to Week 23; Arm B: Week 1 to Week 7 |                                  |

| End point values                     | Arm A<br>(Bevacizumab,<br>Induction<br>Chemotherapy,<br>Chemoradiothe<br>rapy) | Arm B<br>(Bevacizumab,<br>Chemoradiothe<br>rapy) |  |  |
|--------------------------------------|--------------------------------------------------------------------------------|--------------------------------------------------|--|--|
| Subject group type                   | Reporting group                                                                | Reporting group                                  |  |  |
| Number of subjects analysed          | 46                                                                             | 45                                               |  |  |
| Units: cycles                        |                                                                                |                                                  |  |  |
| arithmetic mean (standard deviation) | 4.4 ( $\pm$ 1.5)                                                               | 4.8 ( $\pm$ 0.5)                                 |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Cycles of Radiotherapy

|                                                                            |                                  |
|----------------------------------------------------------------------------|----------------------------------|
| End point title                                                            | Number of Cycles of Radiotherapy |
| End point description:<br>ITT population.                                  |                                  |
| End point type                                                             | Secondary                        |
| End point timeframe:<br>Arm A: Week 16 to Week 23; Arm B: Week 1 to Week 7 |                                  |

| <b>End point values</b>              | Arm A<br>(Bevacizumab,<br>Induction<br>Chemotherapy,<br>Chemoradiothe<br>rapy) | Arm B<br>(Bevacizumab,<br>Chemoradiothe<br>rapy) |  |  |
|--------------------------------------|--------------------------------------------------------------------------------|--------------------------------------------------|--|--|
| Subject group type                   | Reporting group                                                                | Reporting group                                  |  |  |
| Number of subjects analysed          | 46                                                                             | 45                                               |  |  |
| Units: cycles                        |                                                                                |                                                  |  |  |
| arithmetic mean (standard deviation) | 4.5 (± 1.5)                                                                    | 5 (± 0)                                          |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Participants With Surgery

|                                                                                                                                                        |                                         |
|--------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------|
| End point title                                                                                                                                        | Percentage of Participants With Surgery |
| End point description:<br>The surgery involving a radical rectal excision using the TME technique. ITT population.                                     |                                         |
| End point type                                                                                                                                         | Secondary                               |
| End point timeframe:<br>Arm A: approximately 28-31 weeks after initiation of treatment; Arm B: approximately 13-15 weeks after initiation of treatment |                                         |

| <b>End point values</b>           | Arm A<br>(Bevacizumab,<br>Induction<br>Chemotherapy,<br>Chemoradiothe<br>rapy) | Arm B<br>(Bevacizumab,<br>Chemoradiothe<br>rapy) |  |  |
|-----------------------------------|--------------------------------------------------------------------------------|--------------------------------------------------|--|--|
| Subject group type                | Reporting group                                                                | Reporting group                                  |  |  |
| Number of subjects analysed       | 46                                                                             | 45                                               |  |  |
| Units: percentage of participants |                                                                                |                                                  |  |  |
| number (not applicable)           | 91.3                                                                           | 97.8                                             |  |  |

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Baseline up to approximately 6 years

Adverse event reporting additional description:

The safety population included all selected participants who received at least one dose of treatment and corresponded to the ITT population.

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 18.1 |
|--------------------|------|

### Reporting groups

|                       |                                        |
|-----------------------|----------------------------------------|
| Reporting group title | Arm B (Bevacizumab, Chemoradiotherapy) |
|-----------------------|----------------------------------------|

Reporting group description:

In this arm, participants received the Phase 2 and Phase 3 treatments only. The phase 2 consisted of 7 weeks of bevacizumab + chemoradiotherapy (IV infusion of bevacizumab alone, 2 weeks before administration of the first cycle of chemoradiotherapy, then 5 one-week cycles of chemoradiotherapy [5-FU + radiotherapy], with administration of bevacizumab every two weeks [Cycles 1, 3 and 5]) followed by a treatment-free interval of 6 to 8 weeks. The phase 3 was surgery involving a radical rectal excision using the TME technique.

|                       |                                                                |
|-----------------------|----------------------------------------------------------------|
| Reporting group title | Arm A (Bevacizumab, Induction Chemotherapy, Chemoradiotherapy) |
|-----------------------|----------------------------------------------------------------|

Reporting group description:

In this arm, participants underwent 3 phases of treatment. During the Phase 1, participants received induction chemotherapy with 6 two-week cycles of bevacizumab + Folfox-4 (5-FU + oxaliplatin + folinic acid) for 12 weeks followed by a treatment-free interval of 3 to 4 weeks. The Phase 2 consisted of 7 weeks of bevacizumab + chemoradiotherapy (intravenous [IV] infusion of bevacizumab alone, 2 weeks before administration of the first cycle of chemoradiotherapy, then 5 one-week cycles of chemoradiotherapy [5-FU + radiotherapy], with administration of bevacizumab every two weeks [Cycles 1, 3 and 5]) followed by a treatment-free interval of 6 to 8 weeks. The Phase 3 was surgery involving a radical rectal excision using the total mesorectal excision (TME) technique.

| Serious adverse events                            | Arm B<br>(Bevacizumab,<br>Chemoradiotherapy) | Arm A<br>(Bevacizumab,<br>Induction<br>Chemotherapy,<br>Chemoradiotherapy) |  |
|---------------------------------------------------|----------------------------------------------|----------------------------------------------------------------------------|--|
| Total subjects affected by serious adverse events |                                              |                                                                            |  |
| subjects affected / exposed                       | 18 / 45 (40.00%)                             | 21 / 46 (45.65%)                                                           |  |
| number of deaths (all causes)                     | 11                                           | 4                                                                          |  |
| number of deaths resulting from adverse events    |                                              |                                                                            |  |
| Vascular disorders                                |                                              |                                                                            |  |
| Phlebitis                                         |                                              |                                                                            |  |
| subjects affected / exposed                       | 1 / 45 (2.22%)                               | 1 / 46 (2.17%)                                                             |  |
| occurrences causally related to treatment / all   | 0 / 1                                        | 1 / 1                                                                      |  |
| deaths causally related to treatment / all        | 0 / 0                                        | 0 / 0                                                                      |  |
| Embolism venous                                   |                                              |                                                                            |  |

|                                                      |                |                |  |
|------------------------------------------------------|----------------|----------------|--|
| subjects affected / exposed                          | 1 / 45 (2.22%) | 0 / 46 (0.00%) |  |
| occurrences causally related to treatment / all      | 1 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          |  |
| Shock haemorrhagic                                   |                |                |  |
| subjects affected / exposed                          | 0 / 45 (0.00%) | 1 / 46 (2.17%) |  |
| occurrences causally related to treatment / all      | 0 / 0          | 1 / 1          |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          |  |
| Thrombophlebitis                                     |                |                |  |
| subjects affected / exposed                          | 0 / 45 (0.00%) | 1 / 46 (2.17%) |  |
| occurrences causally related to treatment / all      | 0 / 0          | 1 / 1          |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          |  |
| General disorders and administration site conditions |                |                |  |
| Catheter site pain                                   |                |                |  |
| subjects affected / exposed                          | 1 / 45 (2.22%) | 0 / 46 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          |  |
| Localised oedema                                     |                |                |  |
| subjects affected / exposed                          | 0 / 45 (0.00%) | 1 / 46 (2.17%) |  |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          |  |
| Complication associated with device                  |                |                |  |
| subjects affected / exposed                          | 1 / 45 (2.22%) | 0 / 46 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          |  |
| Reproductive system and breast disorders             |                |                |  |
| Female genital tract fistula                         |                |                |  |
| subjects affected / exposed                          | 1 / 45 (2.22%) | 1 / 46 (2.17%) |  |
| occurrences causally related to treatment / all      | 1 / 1          | 1 / 1          |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          |  |
| Perineal pain                                        |                |                |  |
| subjects affected / exposed                          | 0 / 45 (0.00%) | 1 / 46 (2.17%) |  |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          |  |

|                                                 |                |                |  |
|-------------------------------------------------|----------------|----------------|--|
| Rectoprostatic fistula                          |                |                |  |
| subjects affected / exposed                     | 0 / 45 (0.00%) | 1 / 46 (2.17%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Vaginal fistula                                 |                |                |  |
| subjects affected / exposed                     | 0 / 45 (0.00%) | 1 / 46 (2.17%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Respiratory, thoracic and mediastinal disorders |                |                |  |
| Pulmonary embolism                              |                |                |  |
| subjects affected / exposed                     | 0 / 45 (0.00%) | 1 / 46 (2.17%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Investigations                                  |                |                |  |
| Neutrophil count decreased                      |                |                |  |
| subjects affected / exposed                     | 0 / 45 (0.00%) | 1 / 46 (2.17%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Injury, poisoning and procedural complications  |                |                |  |
| Anastomotic fistula                             |                |                |  |
| subjects affected / exposed                     | 4 / 45 (8.89%) | 4 / 46 (8.70%) |  |
| occurrences causally related to treatment / all | 4 / 4          | 4 / 4          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Incisional hernia                               |                |                |  |
| subjects affected / exposed                     | 2 / 45 (4.44%) | 3 / 46 (6.52%) |  |
| occurrences causally related to treatment / all | 0 / 2          | 0 / 3          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Intestinal anastomosis complication             |                |                |  |
| subjects affected / exposed                     | 0 / 45 (0.00%) | 2 / 46 (4.35%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 2          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Wound complication                              |                |                |  |



|                                                 |                |                |  |
|-------------------------------------------------|----------------|----------------|--|
| subjects affected / exposed                     | 2 / 45 (4.44%) | 0 / 46 (0.00%) |  |
| occurrences causally related to treatment / all | 2 / 2          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Catheter site infection                         |                |                |  |
| subjects affected / exposed                     | 1 / 45 (2.22%) | 0 / 46 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Gastrointestinal anastomotic complication       |                |                |  |
| subjects affected / exposed                     | 0 / 45 (0.00%) | 1 / 46 (2.17%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Gastrointestinal stoma complication             |                |                |  |
| subjects affected / exposed                     | 1 / 45 (2.22%) | 0 / 46 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Wound dehiscence                                |                |                |  |
| subjects affected / exposed                     | 1 / 45 (2.22%) | 0 / 46 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Post procedural infection                       |                |                |  |
| subjects affected / exposed                     | 1 / 45 (2.22%) | 0 / 46 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Cardiac disorders                               |                |                |  |
| Sinus arrhythmia                                |                |                |  |
| subjects affected / exposed                     | 1 / 45 (2.22%) | 0 / 46 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Tachycardia                                     |                |                |  |
| subjects affected / exposed                     | 0 / 45 (0.00%) | 1 / 46 (2.17%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Nervous system disorders                        |                |                |  |

|                                                 |                |                |  |
|-------------------------------------------------|----------------|----------------|--|
| Ruptured cerebral aneurysm                      |                |                |  |
| subjects affected / exposed                     | 0 / 45 (0.00%) | 1 / 46 (2.17%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Wernicke's encephalopathy                       |                |                |  |
| subjects affected / exposed                     | 1 / 45 (2.22%) | 0 / 46 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Blood and lymphatic system disorders            |                |                |  |
| Febrile neutropenia                             |                |                |  |
| subjects affected / exposed                     | 0 / 45 (0.00%) | 2 / 46 (4.35%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 2          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Gastrointestinal disorders                      |                |                |  |
| Rectal haemorrhage                              |                |                |  |
| subjects affected / exposed                     | 2 / 45 (4.44%) | 1 / 46 (2.17%) |  |
| occurrences causally related to treatment / all | 1 / 2          | 1 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Intestinal obstruction                          |                |                |  |
| subjects affected / exposed                     | 1 / 45 (2.22%) | 1 / 46 (2.17%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Diarrhoea                                       |                |                |  |
| subjects affected / exposed                     | 1 / 45 (2.22%) | 1 / 46 (2.17%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Colitis ischaemic                               |                |                |  |
| subjects affected / exposed                     | 1 / 45 (2.22%) | 0 / 46 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Diverticulitis                                  |                |                |  |
| subjects affected / exposed                     | 0 / 45 (0.00%) | 1 / 46 (2.17%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |

|                                                 |                |                |  |
|-------------------------------------------------|----------------|----------------|--|
| Enteritis                                       |                |                |  |
| subjects affected / exposed                     | 0 / 45 (0.00%) | 1 / 46 (2.17%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Gastrointestinal perforation                    |                |                |  |
| subjects affected / exposed                     | 0 / 45 (0.00%) | 1 / 46 (2.17%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Intra-abdominal haematoma                       |                |                |  |
| subjects affected / exposed                     | 0 / 45 (0.00%) | 1 / 46 (2.17%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Intussusception                                 |                |                |  |
| subjects affected / exposed                     | 1 / 45 (2.22%) | 0 / 46 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Subileus                                        |                |                |  |
| subjects affected / exposed                     | 1 / 45 (2.22%) | 0 / 46 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Hepatobiliary disorders                         |                |                |  |
| Cholecystitis acute                             |                |                |  |
| subjects affected / exposed                     | 1 / 45 (2.22%) | 0 / 46 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Renal and urinary disorders                     |                |                |  |
| Urinary retention                               |                |                |  |
| subjects affected / exposed                     | 2 / 45 (4.44%) | 0 / 46 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Acute kidney injury                             |                |                |  |
| subjects affected / exposed                     | 0 / 45 (0.00%) | 1 / 46 (2.17%) |  |
| 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 |                |                |  |
| Osteonecrosis                                   |                |                |  |
| subjects affected / exposed                     | 0 / 45 (0.00%) | 1 / 46 (2.17%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Infections and infestations                     |                |                |  |
| Postoperative abscess                           |                |                |  |
| subjects affected / exposed                     | 2 / 45 (4.44%) | 0 / 46 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 2          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Abdominal wall abscess                          |                |                |  |
| subjects affected / exposed                     | 1 / 45 (2.22%) | 0 / 46 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Infection                                       |                |                |  |
| subjects affected / exposed                     | 0 / 45 (0.00%) | 1 / 46 (2.17%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Gastroenteritis                                 |                |                |  |
| subjects affected / exposed                     | 0 / 45 (0.00%) | 1 / 46 (2.17%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Intervertebral discitis                         |                |                |  |
| subjects affected / exposed                     | 1 / 45 (2.22%) | 0 / 46 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Perineal abscess                                |                |                |  |
| subjects affected / exposed                     | 1 / 45 (2.22%) | 0 / 46 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Pelvic abscess                                  |                |                |  |
| subjects affected / exposed                     | 0 / 45 (0.00%) | 1 / 46 (2.17%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |

|                                                 |                |                |  |
|-------------------------------------------------|----------------|----------------|--|
| Pilonidal cyst                                  |                |                |  |
| subjects affected / exposed                     | 1 / 45 (2.22%) | 0 / 46 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Sepsis                                          |                |                |  |
| subjects affected / exposed                     | 0 / 45 (0.00%) | 1 / 46 (2.17%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Septic shock                                    |                |                |  |
| subjects affected / exposed                     | 0 / 45 (0.00%) | 1 / 46 (2.17%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Metabolism and nutrition disorders              |                |                |  |
| Dehydration                                     |                |                |  |
| subjects affected / exposed                     | 2 / 45 (4.44%) | 1 / 46 (2.17%) |  |
| occurrences causally related to treatment / all | 0 / 3          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |

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

| <b>Non-serious adverse events</b>                     | Arm B<br>(Bevacizumab,<br>Chemoradiotherapy) | Arm A<br>(Bevacizumab,<br>Induction<br>Chemotherapy,<br>Chemoradiotherapy) |  |
|-------------------------------------------------------|----------------------------------------------|----------------------------------------------------------------------------|--|
| Total subjects affected by non-serious adverse events |                                              |                                                                            |  |
| subjects affected / exposed                           | 44 / 45 (97.78%)                             | 46 / 46 (100.00%)                                                          |  |
| Vascular disorders                                    |                                              |                                                                            |  |
| Hypertension                                          |                                              |                                                                            |  |
| subjects affected / exposed                           | 7 / 45 (15.56%)                              | 11 / 46 (23.91%)                                                           |  |
| occurrences (all)                                     | 10                                           | 13                                                                         |  |
| General disorders and administration site conditions  |                                              |                                                                            |  |
| Asthenia                                              |                                              |                                                                            |  |
| subjects affected / exposed                           | 6 / 45 (13.33%)                              | 17 / 46 (36.96%)                                                           |  |
| occurrences (all)                                     | 7                                            | 32                                                                         |  |
| Mucosal inflammation                                  |                                              |                                                                            |  |

|                                                                                                                           |                      |                        |  |
|---------------------------------------------------------------------------------------------------------------------------|----------------------|------------------------|--|
| subjects affected / exposed<br>occurrences (all)                                                                          | 4 / 45 (8.89%)<br>4  | 7 / 46 (15.22%)<br>8   |  |
| Fatigue<br>subjects affected / exposed<br>occurrences (all)                                                               | 2 / 45 (4.44%)<br>2  | 4 / 46 (8.70%)<br>9    |  |
| Pyrexia<br>subjects affected / exposed<br>occurrences (all)                                                               | 0 / 45 (0.00%)<br>0  | 3 / 46 (6.52%)<br>3    |  |
| Reproductive system and breast disorders<br>Erectile dysfunction<br>subjects affected / exposed<br>occurrences (all)      | 1 / 45 (2.22%)<br>1  | 3 / 46 (6.52%)<br>3    |  |
| Respiratory, thoracic and mediastinal disorders<br>Epistaxis<br>subjects affected / exposed<br>occurrences (all)          | 2 / 45 (4.44%)<br>2  | 15 / 46 (32.61%)<br>17 |  |
| Investigations<br>Neutrophil count decreased<br>subjects affected / exposed<br>occurrences (all)                          | 1 / 45 (2.22%)<br>1  | 12 / 46 (26.09%)<br>16 |  |
| Blood potassium decreased<br>subjects affected / exposed<br>occurrences (all)                                             | 1 / 45 (2.22%)<br>1  | 5 / 46 (10.87%)<br>6   |  |
| Weight decreased<br>subjects affected / exposed<br>occurrences (all)                                                      | 2 / 45 (4.44%)<br>2  | 3 / 46 (6.52%)<br>3    |  |
| Injury, poisoning and procedural complications<br>Anastomotic fistula<br>subjects affected / exposed<br>occurrences (all) | 2 / 45 (4.44%)<br>2  | 3 / 46 (6.52%)<br>3    |  |
| Wound dehiscence<br>subjects affected / exposed<br>occurrences (all)                                                      | 5 / 45 (11.11%)<br>6 | 2 / 46 (4.35%)<br>2    |  |
| Wound complication                                                                                                        |                      |                        |  |

|                                                                                                       |                        |                        |  |
|-------------------------------------------------------------------------------------------------------|------------------------|------------------------|--|
| subjects affected / exposed<br>occurrences (all)                                                      | 1 / 45 (2.22%)<br>1    | 4 / 46 (8.70%)<br>4    |  |
| Radiation skin injury<br>subjects affected / exposed<br>occurrences (all)                             | 1 / 45 (2.22%)<br>1    | 3 / 46 (6.52%)<br>3    |  |
| Nervous system disorders<br>Neuropathy peripheral<br>subjects affected / exposed<br>occurrences (all) | 0 / 45 (0.00%)<br>0    | 22 / 46 (47.83%)<br>30 |  |
| Paraesthesia<br>subjects affected / exposed<br>occurrences (all)                                      | 2 / 45 (4.44%)<br>2    | 11 / 46 (23.91%)<br>16 |  |
| Headache<br>subjects affected / exposed<br>occurrences (all)                                          | 2 / 45 (4.44%)<br>2    | 7 / 46 (15.22%)<br>8   |  |
| Dysaesthesia<br>subjects affected / exposed<br>occurrences (all)                                      | 0 / 45 (0.00%)<br>0    | 4 / 46 (8.70%)<br>5    |  |
| Gastrointestinal disorders<br>Diarrhoea<br>subjects affected / exposed<br>occurrences (all)           | 24 / 45 (53.33%)<br>28 | 25 / 46 (54.35%)<br>35 |  |
| Proctitis<br>subjects affected / exposed<br>occurrences (all)                                         | 18 / 45 (40.00%)<br>19 | 21 / 46 (45.65%)<br>23 |  |
| Nausea<br>subjects affected / exposed<br>occurrences (all)                                            | 7 / 45 (15.56%)<br>7   | 24 / 46 (52.17%)<br>38 |  |
| Constipation<br>subjects affected / exposed<br>occurrences (all)                                      | 3 / 45 (6.67%)<br>3    | 15 / 46 (32.61%)<br>16 |  |
| Abdominal pain<br>subjects affected / exposed<br>occurrences (all)                                    | 5 / 45 (11.11%)<br>5   | 7 / 46 (15.22%)<br>10  |  |
| Rectal haemorrhage                                                                                    |                        |                        |  |

|                                             |                 |                 |  |
|---------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                 | 2 / 45 (4.44%)  | 9 / 46 (19.57%) |  |
| occurrences (all)                           | 2               | 10              |  |
| Abdominal pain upper                        |                 |                 |  |
| subjects affected / exposed                 | 4 / 45 (8.89%)  | 5 / 46 (10.87%) |  |
| occurrences (all)                           | 4               | 5               |  |
| Anorectal discomfort                        |                 |                 |  |
| subjects affected / exposed                 | 7 / 45 (15.56%) | 1 / 46 (2.17%)  |  |
| occurrences (all)                           | 7               | 1               |  |
| Proctalgia                                  |                 |                 |  |
| subjects affected / exposed                 | 3 / 45 (6.67%)  | 4 / 46 (8.70%)  |  |
| occurrences (all)                           | 3               | 4               |  |
| Haemorrhoids                                |                 |                 |  |
| subjects affected / exposed                 | 2 / 45 (4.44%)  | 4 / 46 (8.70%)  |  |
| occurrences (all)                           | 2               | 4               |  |
| Vomiting                                    |                 |                 |  |
| subjects affected / exposed                 | 0 / 45 (0.00%)  | 6 / 46 (13.04%) |  |
| occurrences (all)                           | 0               | 6               |  |
| Rectal tenesmus                             |                 |                 |  |
| subjects affected / exposed                 | 3 / 45 (6.67%)  | 1 / 46 (2.17%)  |  |
| occurrences (all)                           | 3               | 1               |  |
| Stomatitis                                  |                 |                 |  |
| subjects affected / exposed                 | 1 / 45 (2.22%)  | 3 / 46 (6.52%)  |  |
| occurrences (all)                           | 1               | 3               |  |
| Abdominal pain lower                        |                 |                 |  |
| subjects affected / exposed                 | 3 / 45 (6.67%)  | 0 / 46 (0.00%)  |  |
| occurrences (all)                           | 3               | 0               |  |
| Gingivitis                                  |                 |                 |  |
| subjects affected / exposed                 | 0 / 45 (0.00%)  | 3 / 46 (6.52%)  |  |
| occurrences (all)                           | 0               | 4               |  |
| Skin and subcutaneous tissue disorders      |                 |                 |  |
| Palmar-plantar erythrodysaesthesia syndrome |                 |                 |  |
| subjects affected / exposed                 | 0 / 45 (0.00%)  | 4 / 46 (8.70%)  |  |
| occurrences (all)                           | 0               | 5               |  |
| Alopecia                                    |                 |                 |  |



|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 45 (0.00%)   | 3 / 46 (6.52%)   |  |
| occurrences (all)                               | 0                | 3                |  |
| Pruritus                                        |                  |                  |  |
| subjects affected / exposed                     | 0 / 45 (0.00%)   | 3 / 46 (6.52%)   |  |
| occurrences (all)                               | 0                | 3                |  |
| Renal and urinary disorders                     |                  |                  |  |
| Proteinuria                                     |                  |                  |  |
| subjects affected / exposed                     | 13 / 45 (28.89%) | 20 / 46 (43.48%) |  |
| occurrences (all)                               | 18               | 31               |  |
| Dysuria                                         |                  |                  |  |
| subjects affected / exposed                     | 10 / 45 (22.22%) | 12 / 46 (26.09%) |  |
| occurrences (all)                               | 10               | 12               |  |
| Pollakiuria                                     |                  |                  |  |
| subjects affected / exposed                     | 3 / 45 (6.67%)   | 2 / 46 (4.35%)   |  |
| occurrences (all)                               | 3                | 2                |  |
| Musculoskeletal and connective tissue disorders |                  |                  |  |
| Muscle spasms                                   |                  |                  |  |
| subjects affected / exposed                     | 0 / 45 (0.00%)   | 3 / 46 (6.52%)   |  |
| occurrences (all)                               | 0                | 4                |  |
| Infections and infestations                     |                  |                  |  |
| Urinary tract infection                         |                  |                  |  |
| subjects affected / exposed                     | 4 / 45 (8.89%)   | 2 / 46 (4.35%)   |  |
| occurrences (all)                               | 4                | 2                |  |
| Metabolism and nutrition disorders              |                  |                  |  |
| Decreased appetite                              |                  |                  |  |
| subjects affected / exposed                     | 3 / 45 (6.67%)   | 6 / 46 (13.04%)  |  |
| occurrences (all)                               | 3                | 6                |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date              | Amendment                                                                                                                                                                                                                                                                                                                                                                                                              |
|-------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 25 June 2007      | The following changes were implemented: Minor modifications allowing to clarify some points and adding supplemental information in the inclusion and exclusion criteria, the follow-up of targeted events, the participant's follow-up period in case of emergence of toxicity, modifications in the protocol and the participant's information form for the ancillary study, and update of the list of Investigators. |
| 02 June 2008      | This amendment was implemented to update and clarify some exclusion criteria related to study treatments and disease, include the safety data of bevacizumab updated on November 2007. The last updates being incorporate in the protocol and the participant's consent form.                                                                                                                                          |
| 08 September 2015 | This amendment was implemented to change the secondary efficacy endpoint "progression-free survival" by "disease-free survival".                                                                                                                                                                                                                                                                                       |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported