



## Clinical trial results:

### Selecting Treatment in Colorectal Cancer: Capecitabine or 5-fluorouracil Selection to be Combined With Oxaliplatin or Irinotecan as First-line Chemotherapy in Advanced Colorectal Cancer (SETICC)

#### Summary

|                          |                  |
|--------------------------|------------------|
| EudraCT number           | 2009-012562-31   |
| Trial protocol           | ES               |
| Global end of trial date | 07 November 2013 |

#### Results information

|                                |                 |
|--------------------------------|-----------------|
| Result version number          | v1 (current)    |
| This version publication date  | 26 January 2020 |
| First version publication date | 26 January 2020 |

#### Trial information

##### Trial identification

|                       |           |
|-----------------------|-----------|
| Sponsor protocol code | TTD-09-01 |
|-----------------------|-----------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT01071655 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | Grupo de Tratamiento de los Tumores Digestivos (TTD)   |
| Sponsor organisation address | Plaza de Castilla, 3, 8º D- 1., Madrid, Spain, 28046   |
| Public contact               | Inmaculada Ruiz Mena, Grupo de Tratamiento de los Tumores Digestivos (TTD), 0034 913788275, ttd@ttdgroup.org |
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Notes:

#### Paediatric regulatory details

|  |    |
|--|----|
| Is trial part of an agreed paediatric investigation plan (PIP)       | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

## Results analysis stage

|  |                  |
|--|------------------|
| Analysis stage                                       | Final            |
| Date of interim/final analysis                       | 30 April 2014    |
| Is this the analysis of the primary completion data? | Yes              |
| Primary completion date                              | 07 November 2013 |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 07 November 2013 |
| Was the trial ended prematurely?                     | No               |

Notes:

## General information about the trial

Main objective of the trial:

The aim of the present study was to examine whether assigning first-line chemotherapy based on relevant germline polymorphisms would improve outcomes compared with treating all patients with a standard regimen.

The primary end point was progression-free survival (PFS). Secondary end points included overall survival (OS), overall response rate (ORR; assessed using RECIST Version 1.1), proportion of patients whose disease became resectable, adverse events, and evaluation of KRAS exon 2 mutation status as a molecular prognostic marker.

Protection of trial subjects:

Treatment was assigned depending on TYMS-3'UTR 6 bp ins/del and ERCC1-118C/T polymorphisms. Investigators were informed of treatments by automatically generated e-mails. Polymorphisms were determined for patients assigned to the control group, but these results were not needed before treatment commenced. The investigator still received an automatically generated e-mail. Treatment continued until disease progression, unacceptable toxicity, or patient withdrawal.

Background therapy:

Patients assigned to the control group received bevacizumab 7.5 mg/kg on day 1 with XELOX.

Evidence for comparator:

Our previous study suggested that patients harboring the TYMS-30 untranslated region (UTR) 6 bp ins/ins and ERCC1-118C/T or C/C genotypes might benefit from combining oxaliplatin with capecitabine rather than 5-FU.

|   |                  |
|---|------------------|
| Actual start date of recruitment                          | 15 February 2010 |
| Long term follow-up planned                               | No               |
| Independent data monitoring committee (IDMC) involvement? | No               |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |            |
|--------------------------------------|------------|
| Country: Number of subjects enrolled | Spain: 195 |
| Worldwide total number of subjects   | 195        |
| EEA total number of subjects         | 195        |

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)                     | 105 |
| From 65 to 84 years                      | 88  |
| 85 years and over                        | 2   |

## Subject disposition

### Recruitment

Recruitment details:

Of 202 patients enrolled, 195 were treated/randomized. There were 7 screening failures (withdrawn consent, n=1; criteria violation, n=6). This was a national study with all patients being included at 31 Spanish sites.

### Pre-assignment

Screening details:

Adult patients ( $\geq 18$  years) with histologically confirmed colon or rectal adenocarcinoma with measurable metastatic disease, ECOG performance status 0–2, and adequate renal function. Key exclusion criteria: prior systemic treatment of metastatic disease; concomitant CVD; CNS disease, uncontrolled hypertension, bleeding diathesis, or coagulopathy.

### Period 1

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

Blinding implementation details:

Not applicable.

### Arms

|                              |                               |
|------------------------------|-------------------------------|
| Are arms mutually exclusive? | Yes                           |
| <b>Arm title</b>             | Control Group (A) (Bev+XELOX) |

Arm description:

Patients were randomized 1 : 2 to the control (A) or experimental (B) group. Patients assigned to the control group received bevacizumab 7.5 mg/kg on day 1 with XELOX (capecitabine 1000 mg/m<sup>2</sup>/12 h days 1-14, and oxaliplatin 130 mg/m<sup>2</sup> on day 1). One cycle corresponds to 3 weeks of treatment.

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

Dosage and administration details:

Bevacizumab 7.5 mg/kg on day 1.

|  |              |
|--|--------------|
| Investigational medicinal product name | Capecitabine |
| Investigational medicinal product code |              |
| Other name                             |              |
| Pharmaceutical forms                   | Tablet       |
| Routes of administration               | Oral use     |

Dosage and administration details:

Capecitabine 1000 mg/m<sup>2</sup>/12 h on days 1-14

|  |                 |
|--|-----------------|
| Investigational medicinal product name | Oxaliplatin     |
| Investigational medicinal product code |                 |
| Other name                             |                 |
| Pharmaceutical forms                   | Infusion        |
| Routes of administration               | Intravenous use |

Dosage and administration details:

Oxaliplatin 130 mg/m<sup>2</sup> on day 1

|                  |                        |
|------------------|------------------------|
| <b>Arm title</b> | Experimental Group (B) |
|------------------|------------------------|

**Arm description:**

Patients were randomized 1 : 2 to the control (A) or experimental (B) group. Patients assigned to the experimental group received different schedules according to the number of TYMS-3'UTR 6 bp ins/del and ERCC1-118C/T favorable genotypes:

- 1) Patients with no favorable genotypes (FG) (Bev+XELIRI);
- 2) Patients with one FG: TS 3'UTR +6bp/+6bp and ERCC1-118 T/T (Bev+XELOX); TS 3'UTR +6bp/-6bp and ERCC1-118 C/T or C/C (Bev+FUIRI);
- 3) Patients with two FG (Bev+FUOX).

|  |              |
|--|--------------|
| Arm type                               | Experimental |
| Investigational medicinal product name | Bev+XELIRI   |
| Investigational medicinal product code |              |
| Other name                             |              |
| Pharmaceutical forms                   | Tablet       |
| Routes of administration               | Oral use     |

**Dosage and administration details:**

Bevacizumab 7.5 mg/kg on day 1 with XELIRI (capecitabine 800 mg/m<sup>2</sup>/12 h days 1-14, and irinotecan 200 mg/m<sup>2</sup> on day 1). One cycle corresponds to 3 weeks of treatment.

|  |           |
|--|-----------|
| Investigational medicinal product name | Bev+XELOX |
| Investigational medicinal product code |           |
| Other name                             |           |
| Pharmaceutical forms                   | Tablet    |
| Routes of administration               | Oral use  |

**Dosage and administration details:**

Bevacizumab 7.5 mg/kg on day 1 with XELOX (capecitabine 1000 mg/m<sup>2</sup>/12 h days 1-14, and oxaliplatin 130 mg/m<sup>2</sup> on day 1). One cycle corresponds to 3 weeks of treatment.

|  |                 |
|--|-----------------|
| Investigational medicinal product name | Bev+FUIRI       |
| Investigational medicinal product code |                 |
| Other name                             |                 |
| Pharmaceutical forms                   | Infusion        |
| Routes of administration               | Intravenous use |

**Dosage and administration details:**

Bevacizumab 5 mg/kg (days 1, 15 and 29) with FUIRI (5-FU 2.250 mg/m<sup>2</sup> in 48h-continuous infusion and irinotecan 80 mg/m<sup>2</sup> on days 1, 8, 15, 22, 29 and 36). One cycle corresponds to 6 weeks of treatment.

|  |                 |
|--|-----------------|
| Investigational medicinal product name | Bev+FUOX        |
| Investigational medicinal product code |                 |
| Other name                             |                 |
| Pharmaceutical forms                   | Infusion        |
| Routes of administration               | Intravenous use |

**Dosage and administration details:**

Bevacizumab 5 mg/kg (days 1, 15 and 29) with FUOX (5-FU 2.250 mg/m<sup>2</sup> in 48h-continuous infusion on days 1, 8, 15, 22, 29 and 36; and oxaliplatin 85 mg/m<sup>2</sup> on days 1, 15 and 29). One cycle corresponds to 6 weeks of treatment.

| <b>Number of subjects in period 1</b> | <b>Control Group (A)<br/>(Bev+XELOX)</b> | <b>Experimental Group<br/>(B)</b> |
|---------------------------------------|--|-----------------------------------|
| Started                               | 65                                       | 130                               |
| Completed                             | 61                                       | 119                               |
| Not completed                         | 4  | 11                                |
| Adverse event, serious fatal          | 4  | 3                                 |
| Consent withdrawn by subject          | -  | 4                                 |

|                    |   |   |
|--------------------|---|---|
| Protocol deviation | - | 4 |
|--------------------|---|---|

## Baseline characteristics

### Reporting groups

|                       |                               |
|-----------------------|-------------------------------|
| Reporting group title | Control Group (A) (Bev+XELOX) |
|-----------------------|-------------------------------|

Reporting group description:

Patients were randomized 1 : 2 to the control (A) or experimental (B) group. Patients assigned to the control group received bevacizumab 7.5 mg/kg on day 1 with XELOX (capecitabine 1000 mg/m<sup>2</sup>/12 h days 1-14, and oxaliplatin 130 mg/m<sup>2</sup> on day 1). One cycle corresponds to 3 weeks of treatment.

|                       |                        |
|-----------------------|------------------------|
| Reporting group title | Experimental Group (B) |
|-----------------------|------------------------|

Reporting group description:

Patients were randomized 1 : 2 to the control (A) or experimental (B) group. Patients assigned to the experimental group received different schedules according to the number of TYMS-3'UTR 6 bp ins/del and ERCC1-118C/T favorable genotypes:

- 1) Patients with no favorable genotypes (FG) (Bev+XELIRI);
- 2) Patients with one FG: TS 3'UTR +6bp/+6bp and ERCC1-118 T/T (Bev+XELOX); TS 3'UTR +6bp/-6bp and ERCC1-118 C/T or C/C (Bev+FUORI);
- 3) Patients with two FG (Bev+FUOX).

| Reporting group values  | Control Group (A)<br>(Bev+XELOX) | Experimental Group<br>(B) | Total |
|---|----------------------------------|---------------------------|-------|
| Number of subjects  | 65                               | 130                       | 195   |
| Age categorical<br>Units: Subjects  |                                  |                           |       |
| In utero  |                                  |                           | 0     |
| Preterm newborn infants<br>(gestational age < 37 wks)                     |                                  |                           | 0     |
| Newborns (0-27 days)  |                                  |                           | 0     |
| Infants and toddlers (28 days-23<br>months)                               |                                  |                           | 0     |
| Children (2-11 years)   |                                  |                           | 0     |
| Adolescents (12-17 years)   |                                  |                           | 0     |
| Adults (18-64 years)  |                                  |                           | 0     |
| From 65-84 years  |                                  |                           | 0     |
| 85 years and over   |                                  |                           | 0     |
| Age continuous  |                                  |                           |       |
| Age in years has been calculated the date of signing the informed consent |                                  |                           |       |
| Units: years  |                                  |                           |       |
| arithmetic mean   | 64.4                             | 63.4                      |       |
| standard deviation  | ± 10.1                           | ± 10.4                    | -     |
| Gender categorical<br>Units: Subjects                                     |                                  |                           |       |
| Female  | 30                               | 48                        | 78    |
| Male  | 35                               | 82                        | 117   |
| ECOG performance status<br>Units: Subjects                                |                                  |                           |       |
| ECOG 0  | 29                               | 50                        | 79    |
| ECOG 1  | 34                               | 79                        | 113   |
| ECOG 2  | 2                                | 1                         | 3     |
| Tumor location<br>Units: Subjects   |                                  |                           |       |
| Colon   | 41                               | 80                        | 121   |
| Rectum  | 18                               | 38                        | 56    |

|   |        |        |     |
|---|--------|--------|-----|
| Both  | 6      | 12     | 18  |
| No. of affected organs  |        |        |     |
| Units: Subjects   |        |        |     |
| 1 organ   | 25     | 55     | 80  |
| 2 organs  | 21     | 52     | 73  |
| >2 organs   | 19     | 23     | 42  |
| Surgery for primary tumor   |        |        |     |
| Units: Subjects   |        |        |     |
| Yes   | 34     | 73     | 107 |
| No  | 31     | 57     | 88  |
| Prior adjuvant radiotherapy   |        |        |     |
| With or without prior radiotherapy  |        |        |     |
| Units: Subjects   |        |        |     |
| Yes   | 3      | 7      | 10  |
| No  | 62     | 123    | 185 |
| KRAS mutation   |        |        |     |
| Units: Subjects   |        |        |     |
| Wild-type   | 31     | 64     | 95  |
| Mutated   | 27     | 42     | 69  |
| Not available   | 7      | 24     | 31  |
| Relevant prior and concomitant pathologies  |        |        |     |
| Units: Subjects   |        |        |     |
| No  | 5      | 15     | 20  |
| Yes   | 60     | 115    | 175 |
| Prior adjuvant chemotherapy   |        |        |     |
| Units: Subjects   |        |        |     |
| Yes   | 9      | 15     | 24  |
| No  | 56     | 115    | 171 |
| Weight  |        |        |     |
| Units: kilogram(s)  |        |        |     |
| arithmetic mean   | 71.4   | 71.3   |     |
| standard deviation  | ± 12.2 | ± 14.8 | -   |
| Height  |        |        |     |
| Units: centimeters  |        |        |     |
| arithmetic mean   | 163.8  | 164.2  |     |
| standard deviation  | ± 8.6  | ± 10.2 | -   |
| Body surface  |        |        |     |
| Units: square meter   |        |        |     |
| arithmetic mean   | 1.8    | 1.8    |     |
| standard deviation  | ± 0.2  | ± 0.2  | -   |
| Duration of disease   |        |        |     |
| Time since diagnosis of primary disease until the date of signing the informed consent. |        |        |     |
| Units: months   |        |        |     |
| arithmetic mean   | 10.1   | 5.7    |     |
| standard deviation  | ± 27.2 | ± 11.5 | -   |



## End points

### End points reporting groups

|  |                               |
|--|-------------------------------|
| Reporting group title  | Control Group (A) (Bev+XELOX) |
| Reporting group description:<br>Patients were randomized 1 : 2 to the control (A) or experimental (B) group. Patients assigned to the control group received bevacizumab 7.5 mg/kg on day 1 with XELOX (capecitabine 1000 mg/m <sup>2</sup> /12 h days 1-14, and oxaliplatin 130 mg/m <sup>2</sup> on day 1). One cycle corresponds to 3 weeks of treatment.   |                               |
| Reporting group title  | Experimental Group (B)        |
| Reporting group description:<br>Patients were randomized 1 : 2 to the control (A) or experimental (B) group. Patients assigned to the experimental group received different schedules according to the number of TYMS-3'UTR 6 bp ins/del and ERCC1-118C/T favorable genotypes:<br><br>1) Patients with no favorable genotypes (FG) (Bev+XELIRI);<br>2) Patients with one FG: TS 3'UTR +6bp/+6bp and ERCC1-118 T/T (Bev+XELOX); TS 3'UTR +6bp/-6bp and ERCC1-118 C/T or C/C (Bev+FUIRI);<br>3) Patients with two FG (Bev+FUOX). |                               |

### Primary: Progression-free survival

|   |                           |
|---|---------------------------|
| End point title   | Progression-free survival |
| End point description:<br>Time elapsed from the randomization date until the patient progression or death for any reason (the first that occurred). |                           |
| End point type  | Primary                   |
| End point timeframe:<br>Until patient progression or death for any reason (the first that occurred)   |                           |

| End point values                 | Control Group (A) (Bev+XELOX) | Experimental Group (B) |  |  |
|----------------------------------|-------------------------------|------------------------|--|--|
| Subject group type               | Reporting group               | Reporting group        |  |  |
| Number of subjects analysed      | 65                            | 130                    |  |  |
| Units: months                    |                               |                        |  |  |
| median (confidence interval 95%) | 9.4 (6.8 to 12.1)             | 10.1 (8.5 to 11.6)     |  |  |

|                            |                                   |
|----------------------------|-----------------------------------|
| Attachments (see zip file) | Progression-free survival/PFS.PNG |
|----------------------------|-----------------------------------|

### Statistical analyses

|                            |  |
|----------------------------|--|
| Statistical analysis title | Hazard ratio   |
| Comparison groups          | Control Group (A) (Bev+XELOX) v Experimental Group (B) |

|   |                   |
|---|-------------------|
| Number of subjects included in analysis | 195               |
| Analysis specification                  | Pre-specified     |
| Analysis type                           | superiority       |
| P-value                                 | = 0.745           |
| Method                                  | Regression, Cox   |
| Parameter estimate                      | Hazard ratio (HR) |
| Point estimate                          | 0.942             |
| Confidence interval                     |                   |
| level                                   | 95 %              |
| sides                                   | 2-sided           |
| lower limit                             | 0.657             |
| upper limit                             | 1.351             |

## Secondary: Overall survival

|   |                  |
|---|------------------|
| End point title   | Overall survival |
| End point description:  |                  |
| Time elapsed from the randomization date until the patient death. In other patients the last control was considered the last follow-up available. |                  |
| End point type  | Secondary        |
| End point timeframe:  |                  |
| Until patient death or the last follow-up available.  |                  |

| End point values                 | Control Group (A)<br>(Bev+XELOX) | Experimental Group (B) |  |  |
|----------------------------------|----------------------------------|------------------------|--|--|
| Subject group type               | Reporting group                  | Reporting group        |  |  |
| Number of subjects analysed      | 65                               | 130                    |  |  |
| Units: months                    |                                  |                        |  |  |
| median (confidence interval 95%) | 16.5 (13.7 to 19.4)              | 19.1 (15.5 to 22.7)    |  |  |

|                                   |                         |
|-----------------------------------|-------------------------|
| <b>Attachments (see zip file)</b> | Overall survival/OS.PNG |
|-----------------------------------|-------------------------|

## Statistical analyses

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | Hazard ratio   |
| Comparison groups                       | Control Group (A) (Bev+XELOX) v Experimental Group (B) |
| Number of subjects included in analysis | 195  |
| Analysis specification                  | Pre-specified  |
| Analysis type                           | superiority  |
| P-value                                 | = 0.798  |
| Method                                  | Regression, Cox  |
| Parameter estimate                      | Hazard ratio (HR)                                      |
| Point estimate                          | 0.956  |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | 0.678   |
| upper limit         | 1.348   |

### Secondary: Complete response (CR)

|   |                        |
|---|------------------------|
| End point title                             | Complete response (CR) |
| End point description:                      |                        |
| End point type                              | Secondary              |
| End point timeframe:                        |                        |
| From treatment start to the decision to end |                        |

| End point values            | Control Group (A)<br>(Bev+XELOX) | Experimental Group (B) |  |  |
|-----------------------------|----------------------------------|------------------------|--|--|
| Subject group type          | Reporting group                  | Reporting group        |  |  |
| Number of subjects analysed | 55 <sup>[1]</sup>                | 106 <sup>[2]</sup>     |  |  |
| Units: Subjects             | 2                                | 4                      |  |  |

Notes:

[1] - Patients of the control group that were evaluable for response.

[2] - Patients of the experimental group that were evaluable for response.

### Statistical analyses

No statistical analyses for this end point

### Secondary: Partial response (PR)

|   |                       |
|---|-----------------------|
| End point title                             | Partial response (PR) |
| End point description:                      |                       |
| End point type                              | Secondary             |
| End point timeframe:                        |                       |
| From treatment start to the decision to end |                       |

| End point values            | Control Group (A)<br>(Bev+XELOX) | Experimental Group (B) |  |  |
|-----------------------------|----------------------------------|------------------------|--|--|
| Subject group type          | Reporting group                  | Reporting group        |  |  |
| Number of subjects analysed | 55 <sup>[3]</sup>                | 106 <sup>[4]</sup>     |  |  |
| Units: Subjects             | 24                               | 65                     |  |  |

Notes:

[3] - Patients of the control group that were evaluable for response.

[4] - Patients of the experimental group that were evaluable for response.

## Statistical analyses

No statistical analyses for this end point

### Secondary: Stable disease

|                 |                |
|-----------------|----------------|
| End point title | Stable disease |
|-----------------|----------------|

End point description:

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

End point timeframe:

From treatment start to the decision to end

| End point values            | Control Group (A)<br>(Bev+XELOX) | Experimental Group (B) |  |  |
|-----------------------------|----------------------------------|------------------------|--|--|
| Subject group type          | Reporting group                  | Reporting group        |  |  |
| Number of subjects analysed | 55 <sup>[5]</sup>                | 106 <sup>[6]</sup>     |  |  |
| Units: Subjects             | 22                               | 30                     |  |  |

Notes:

[5] - Patients of the control group that were evaluable for response.

[6] - Patients of the experimental group that were evaluable for response.

## Statistical analyses

No statistical analyses for this end point

### Secondary: Progressive disease

|                 |                     |
|-----------------|---------------------|
| End point title | Progressive disease |
|-----------------|---------------------|

End point description:

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

End point timeframe:

From treatment start to the decision to end

| End point values            | Control Group (A)<br>(Bev+XELOX) | Experimental Group (B) |  |  |
|-----------------------------|----------------------------------|------------------------|--|--|
| Subject group type          | Reporting group                  | Reporting group        |  |  |
| Number of subjects analysed | 55 <sup>[7]</sup>                | 106 <sup>[8]</sup>     |  |  |
| Units: Subjects             | 7                                | 7                      |  |  |

Notes:

[7] - Patients of the control group that were evaluable for response.

[8] - Patients of the experimental group that were evaluable for response.

## Statistical analyses

No statistical analyses for this end point

## Secondary: Overall response rate (ORR) (PR+CR)

|  |                                     |
|--|-------------------------------------|
| End point title  | Overall response rate (ORR) (PR+CR) |
| End point description:<br>Partial response (PR) + Complete response (CR). It was assessed using RECIST Version 1.1 |                                     |
| End point type   | Secondary                           |
| End point timeframe:<br>From treatment start to the decision to end  |                                     |

| End point values            | Control Group (A)<br>(Bev+XELOX) | Experimental Group (B) |  |  |
|-----------------------------|----------------------------------|------------------------|--|--|
| Subject group type          | Reporting group                  | Reporting group        |  |  |
| Number of subjects analysed | 55 <sup>[9]</sup>                | 106 <sup>[10]</sup>    |  |  |
| Units: Subjects             | 26                               | 69                     |  |  |

Notes:

[9] - Patients of the control group that were evaluable for response.

[10] - Patients of the experimental group that were evaluable for response.

## Statistical analyses

|   |  |
|---|--|
| Statistical analysis title              | Fisher exact   |
| Comparison groups                       | Control Group (A) (Bev+XELOX) v Experimental Group (B) |
| Number of subjects included in analysis | 161  |
| Analysis specification                  | Pre-specified  |
| Analysis type                           | equivalence  |
| P-value                                 | = 0.042  |
| Method                                  | Fisher exact   |

## Secondary: Disease-control rate (CR+PR+SD)

|  |                                 |
|--|---------------------------------|
| End point title  | Disease-control rate (CR+PR+SD) |
| End point description:<br>Complete response (CR) + Partial response (PR) + Stable disease (SD) |                                 |
| End point type   | Secondary                       |

End point timeframe:

From treatment start to the decision to end

| End point values            | Control Group (A)<br>(Bev+XELOX) | Experimental Group (B) |  |  |
|-----------------------------|----------------------------------|------------------------|--|--|
| Subject group type          | Reporting group                  | Reporting group        |  |  |
| Number of subjects analysed | 55 <sup>[11]</sup>               | 106 <sup>[12]</sup>    |  |  |
| Units: Subjects             | 48                               | 99                     |  |  |

Notes:

[11] - Patients of the control group that were evaluable for response.

[12] - Patients of the experimental group that were evaluable for response.

### Statistical analyses

| Statistical analysis title              | Fisher exact   |
|---|--|
| Comparison groups                       | Control Group (A) (Bev+XELOX) v Experimental Group (B) |
| Number of subjects included in analysis | 161  |
| Analysis specification                  | Pre-specified  |
| Analysis type                           | equivalence  |
| P-value                                 | = 0.24   |
| Method                                  | Fisher exact   |

### Secondary: R0 surgery

|                           |            |
|---------------------------|------------|
| End point title           | R0 surgery |
| End point description:    |            |
| End point type            | Secondary  |
| End point timeframe:      |            |
| During or after the study |            |

| End point values            | Control Group (A)<br>(Bev+XELOX) | Experimental Group (B) |  |  |
|-----------------------------|----------------------------------|------------------------|--|--|
| Subject group type          | Reporting group                  | Reporting group        |  |  |
| Number of subjects analysed | 16 <sup>[13]</sup>               | 21 <sup>[14]</sup>     |  |  |
| Units: Subjects             | 7                                | 18                     |  |  |

Notes:

[13] - 16 patients of the control group with surgical resection

[14] - 21 patients of the experimental group with surgical resection

### Statistical analyses

| Statistical analysis title | Fisher exact   |
|----------------------------|--|
| Comparison groups          | Control Group (A) (Bev+XELOX) v Experimental Group (B) |

|   |               |
|---|---------------|
| Number of subjects included in analysis | 37            |
| Analysis specification                  | Pre-specified |
| Analysis type                           | equivalence   |
| P-value                                 | = 0.018       |
| Method                                  | Fisher exact  |

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Throughout the study period.

Adverse event reporting additional description:

An adverse event is reported once per patient and treatment period with the highest severity grade according to NCI-CTCAE version 3.

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

### Dictionary used

|                    |        |
|--------------------|--------|
| Dictionary name    | MedDRA |
| Dictionary version | 16.0   |

### Reporting groups

|                       |                             |
|-----------------------|-----------------------------|
| Reporting group title | Group A - Safety population |
|-----------------------|-----------------------------|

Reporting group description:

Patients who have received at least one administration of study drug in Group A: BVZ+XELOX (Bevacizumab + capecitabine + oxaliplatin).

|                       |                                      |
|-----------------------|--------------------------------------|
| Reporting group title | Group B (global) - Safety population |
|-----------------------|--------------------------------------|

Reporting group description:

Patients who have received at least one administration of study drug in Group B (global). Reported for all Group B subgroups in total (BVZ+XELOX/XELIRI/FUOX/FUIRI).

| Serious adverse events                            | Group A - Safety population | Group B (global) - Safety population |  |
|---|-----------------------------|--------------------------------------|--|
| Total subjects affected by serious adverse events |                             |                                      |  |
| subjects affected / exposed                       | 27 / 61 (44.26%)            | 61 / 119 (51.26%)                    |  |
| number of deaths (all causes)                     | 49                          | 97                                   |  |
| number of deaths resulting from adverse events    | 3                           | 11                                   |  |
| Vascular disorders                                |                             |                                      |  |
| Acute pulmonary edema                             |                             |                                      |  |
| subjects affected / exposed                       | 1 / 61 (1.64%)              | 0 / 119 (0.00%)                      |  |
| occurrences causally related to treatment / all   | 1 / 1                       | 0 / 0                                |  |
| deaths causally related to treatment / all        | 0 / 0                       | 0 / 0                                |  |
| Brain vascular accident                           |                             |                                      |  |
| subjects affected / exposed                       | 0 / 61 (0.00%)              | 1 / 119 (0.84%)                      |  |
| occurrences causally related to treatment / all   | 0 / 0                       | 1 / 1                                |  |
| deaths causally related to treatment / all        | 0 / 0                       | 0 / 0                                |  |
| Deep vein thrombosis                              |                             |                                      |  |



|   |                |                 |  |
|---|----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 61 (1.64%) | 2 / 119 (1.68%) |  |
| occurrences causally related to treatment / all | 1 / 1          | 2 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Hematoma  |                |                 |  |
| subjects affected / exposed                     | 0 / 61 (0.00%) | 2 / 119 (1.68%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Pulmonary thromboembolism                       |                |                 |  |
| subjects affected / exposed                     | 2 / 61 (3.28%) | 8 / 119 (6.72%) |  |
| occurrences causally related to treatment / all | 2 / 2          | 7 / 8           |  |
| deaths causally related to treatment / all      | 0 / 0          | 3 / 3           |  |
| Vein thrombosis                                 |                |                 |  |
| subjects affected / exposed                     | 0 / 61 (0.00%) | 1 / 119 (0.84%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Cardiac disorders                               |                |                 |  |
| Foot ischemia                                   |                |                 |  |
| subjects affected / exposed                     | 0 / 61 (0.00%) | 1 / 119 (0.84%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Heart failure                                   |                |                 |  |
| subjects affected / exposed                     | 0 / 61 (0.00%) | 1 / 119 (0.84%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Hypovolemic shock                               |                |                 |  |
| subjects affected / exposed                     | 0 / 61 (0.00%) | 2 / 119 (1.68%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 2 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Vasospastic angina                              |                |                 |  |
| subjects affected / exposed                     | 1 / 61 (1.64%) | 0 / 119 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Nervous system disorders                        |                |                 |  |

|  |                |                 |  |
|--|----------------|-----------------|--|
| Cognitive impairment                                 |                |                 |  |
| subjects affected / exposed                          | 0 / 61 (0.00%) | 1 / 119 (0.84%) |  |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0           |  |
| Confusion  |                |                 |  |
| subjects affected / exposed                          | 1 / 61 (1.64%) | 0 / 119 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1          | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0           |  |
| Hypoxia  |                |                 |  |
| subjects affected / exposed                          | 0 / 61 (0.00%) | 1 / 119 (0.84%) |  |
| occurrences causally related to treatment / all      | 0 / 0          | 1 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0           |  |
| Vertiginous syndrome                                 |                |                 |  |
| subjects affected / exposed                          | 0 / 61 (0.00%) | 1 / 119 (0.84%) |  |
| 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 |                |                 |  |
| Abdominal pain                                       |                |                 |  |
| subjects affected / exposed                          | 0 / 61 (0.00%) | 3 / 119 (2.52%) |  |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 4           |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0           |  |
| Anal pain  |                |                 |  |
| subjects affected / exposed                          | 0 / 61 (0.00%) | 1 / 119 (0.84%) |  |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0           |  |
| Disease progression                                  |                |                 |  |
| subjects affected / exposed                          | 1 / 61 (1.64%) | 0 / 119 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1          | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0           |  |
| Epigastralgia  |                |                 |  |
| subjects affected / exposed                          | 1 / 61 (1.64%) | 0 / 119 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1          | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0           |  |

|   |                |                 |  |
|---|----------------|-----------------|--|
| Fever   |                |                 |  |
| subjects affected / exposed                     | 3 / 61 (4.92%) | 2 / 119 (1.68%) |  |
| occurrences causally related to treatment / all | 2 / 3          | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| General deterioration                           |                |                 |  |
| subjects affected / exposed                     | 0 / 61 (0.00%) | 3 / 119 (2.52%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Lumbar pain                                     |                |                 |  |
| subjects affected / exposed                     | 2 / 61 (3.28%) | 1 / 119 (0.84%) |  |
| occurrences causally related to treatment / all | 0 / 2          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Multiple myeloma                                |                |                 |  |
| subjects affected / exposed                     | 0 / 61 (0.00%) | 1 / 119 (0.84%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Pain  |                |                 |  |
| subjects affected / exposed                     | 0 / 61 (0.00%) | 1 / 119 (0.84%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Sudden death                                    |                |                 |  |
| subjects affected / exposed                     | 1 / 61 (1.64%) | 2 / 119 (1.68%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 1          | 0 / 2           |  |
| Blood and lymphatic system disorders            |                |                 |  |
| Aplasia   |                |                 |  |
| subjects affected / exposed                     | 0 / 61 (0.00%) | 1 / 119 (0.84%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Neutropenia                                     |                |                 |  |
| subjects affected / exposed                     | 1 / 61 (1.64%) | 4 / 119 (3.36%) |  |
| occurrences causally related to treatment / all | 1 / 1          | 4 / 4           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Rectal bleeding                                 |                |                 |  |

|   |                 |                   |  |
|---|-----------------|-------------------|--|
| subjects affected / exposed                     | 1 / 61 (1.64%)  | 1 / 119 (0.84%)   |  |
| occurrences causally related to treatment / all | 1 / 1           | 1 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0             |  |
| Thrombocitopenia                                |                 |                   |  |
| subjects affected / exposed                     | 1 / 61 (1.64%)  | 3 / 119 (2.52%)   |  |
| occurrences causally related to treatment / all | 1 / 1           | 3 / 4             |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0             |  |
| Upper gastrointestinal bleeding                 |                 |                   |  |
| subjects affected / exposed                     | 1 / 61 (1.64%)  | 0 / 119 (0.00%)   |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0             |  |
| Gastrointestinal disorders                      |                 |                   |  |
| Abscess perianal                                |                 |                   |  |
| subjects affected / exposed                     | 0 / 61 (0.00%)  | 1 / 119 (0.84%)   |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0             |  |
| Bowel obstruction                               |                 |                   |  |
| subjects affected / exposed                     | 7 / 61 (11.48%) | 5 / 119 (4.20%)   |  |
| occurrences causally related to treatment / all | 0 / 7           | 3 / 7             |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0             |  |
| Colitis   |                 |                   |  |
| subjects affected / exposed                     | 1 / 61 (1.64%)  | 0 / 119 (0.00%)   |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0             |  |
| Diarrhoea                                       |                 |                   |  |
| subjects affected / exposed                     | 1 / 61 (1.64%)  | 12 / 119 (10.08%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 14 / 14           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0             |  |
| Enteritis                                       |                 |                   |  |
| subjects affected / exposed                     | 0 / 61 (0.00%)  | 1 / 119 (0.84%)   |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0             |  |
| Gastrointestinal bleeding                       |                 |                   |  |

|   |                |                 |  |
|---|----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 61 (0.00%) | 1 / 119 (0.84%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 1 / 1           |  |
| Gastrointestinal perforation                    |                |                 |  |
| subjects affected / exposed                     | 1 / 61 (1.64%) | 1 / 119 (0.84%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Gastrointestinal toxicity                       |                |                 |  |
| subjects affected / exposed                     | 1 / 61 (1.64%) | 4 / 119 (3.36%) |  |
| occurrences causally related to treatment / all | 1 / 1          | 3 / 4           |  |
| deaths causally related to treatment / all      | 0 / 0          | 1 / 1           |  |
| Hematemesis                                     |                |                 |  |
| subjects affected / exposed                     | 0 / 61 (0.00%) | 1 / 119 (0.84%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Mucositis oral                                  |                |                 |  |
| subjects affected / exposed                     | 0 / 61 (0.00%) | 2 / 119 (1.68%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 2 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Obstruction of bile duct anastomotic            |                |                 |  |
| subjects affected / exposed                     | 1 / 61 (1.64%) | 0 / 119 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Parasigmoid abscess                             |                |                 |  |
| subjects affected / exposed                     | 0 / 61 (0.00%) | 1 / 119 (0.84%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Toxic duodenitis                                |                |                 |  |
| subjects affected / exposed                     | 0 / 61 (0.00%) | 1 / 119 (0.84%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Vomiting  |                |                 |  |

|   |                |                 |  |
|---|----------------|-----------------|--|
| subjects affected / exposed                     | 3 / 61 (4.92%) | 2 / 119 (1.68%) |  |
| occurrences causally related to treatment / all | 3 / 3          | 1 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Intestinal ischaemia                            |                |                 |  |
| subjects affected / exposed                     | 0 / 61 (0.00%) | 1 / 119 (0.84%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Respiratory, thoracic and mediastinal disorders |                |                 |  |
| Dyspnoea  |                |                 |  |
| subjects affected / exposed                     | 0 / 61 (0.00%) | 1 / 119 (0.84%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Respiratory failure                             |                |                 |  |
| subjects affected / exposed                     | 1 / 61 (1.64%) | 0 / 119 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0           |  |
| deaths causally related to treatment / all      | 1 / 1          | 0 / 0           |  |
| Hepatobiliary disorders                         |                |                 |  |
| Hepatic veno occlusive disease                  |                |                 |  |
| subjects affected / exposed                     | 1 / 61 (1.64%) | 0 / 119 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Toxic hepatitis                                 |                |                 |  |
| subjects affected / exposed                     | 0 / 61 (0.00%) | 1 / 119 (0.84%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Tumor fistulization                             |                |                 |  |
| subjects affected / exposed                     | 1 / 61 (1.64%) | 0 / 119 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Renal and urinary disorders                     |                |                 |  |
| Renal failure                                   |                |                 |  |
| subjects affected / exposed                     | 1 / 61 (1.64%) | 2 / 119 (1.68%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 1 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0          | 1 / 1           |  |

|   |                                  |                                   |  |
|---|----------------------------------|-----------------------------------|--|
| Infections and infestations<br>Bacterial meningitis<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all | 0 / 61 (0.00%)<br>0 / 0<br>0 / 0 | 1 / 119 (0.84%)<br>1 / 1<br>1 / 1 |  |
| Catheter infection<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all                                  | 0 / 61 (0.00%)<br>0 / 0<br>0 / 0 | 1 / 119 (0.84%)<br>0 / 1<br>0 / 0 |  |
| Deep infection of intestinal fistula<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all                | 1 / 61 (1.64%)<br>0 / 1<br>0 / 0 | 0 / 119 (0.00%)<br>0 / 0<br>0 / 0 |  |
| Febrile neutropenia<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all                                 | 0 / 61 (0.00%)<br>0 / 0<br>0 / 0 | 4 / 119 (3.36%)<br>5 / 5<br>1 / 1 |  |
| Fournier Gangrene<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all                                   | 0 / 61 (0.00%)<br>0 / 0<br>0 / 0 | 2 / 119 (1.68%)<br>0 / 2<br>0 / 0 |  |
| Peristomal abscess<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all                                  | 1 / 61 (1.64%)<br>1 / 1<br>0 / 0 | 0 / 119 (0.00%)<br>0 / 0<br>0 / 0 |  |
| Peritonitis<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all   | 1 / 61 (1.64%)<br>0 / 1<br>0 / 0 | 1 / 119 (0.84%)<br>0 / 1<br>0 / 0 |  |
| Pneumonia<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all   | 0 / 61 (0.00%)<br>0 / 0<br>0 / 0 | 2 / 119 (1.68%)<br>0 / 2<br>0 / 0 |  |
| Respiratory infection   |                                  |                                   |  |

|   |                |                 |  |
|---|----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 61 (0.00%) | 1 / 119 (0.84%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Surgical wound infection                        |                |                 |  |
| subjects affected / exposed                     | 1 / 61 (1.64%) | 1 / 119 (0.84%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Urinary tract infection                         |                |                 |  |
| subjects affected / exposed                     | 0 / 61 (0.00%) | 1 / 119 (0.84%) |  |
| 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 / 61 (0.00%) | 1 / 119 (0.84%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Metabolism and nutrition disorders              |                |                 |  |
| Hyperglycemia                                   |                |                 |  |
| subjects affected / exposed                     | 0 / 61 (0.00%) | 1 / 119 (0.84%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Hypocapnia                                      |                |                 |  |
| subjects affected / exposed                     | 0 / 61 (0.00%) | 1 / 119 (0.84%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Obstructive ictericia                           |                |                 |  |
| subjects affected / exposed                     | 0 / 61 (0.00%) | 1 / 119 (0.84%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 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>                     | Group A - Safety population | Group B (global) - Safety population |  |
|---|-----------------------------|--------------------------------------|--|
| Total subjects affected by non-serious adverse events |                             |                                      |  |
| subjects affected / exposed                           | 61 / 61 (100.00%)           | 118 / 119 (99.16%)                   |  |
| Cardiac disorders                                     |                             |                                      |  |
| Hypertension  |                             |                                      |  |
| subjects affected / exposed                           | 14 / 61 (22.95%)            | 23 / 119 (19.33%)                    |  |
| occurrences (all)                                     | 20                          | 24                                   |  |
| Nervous system disorders                              |                             |                                      |  |
| Dysaesthesia  |                             |                                      |  |
| subjects affected / exposed                           | 22 / 61 (36.07%)            | 13 / 119 (10.92%)                    |  |
| occurrences (all)                                     | 53                          | 18                                   |  |
| Neuropathy  |                             |                                      |  |
| subjects affected / exposed                           | 39 / 61 (63.93%)            | 36 / 119 (30.25%)                    |  |
| occurrences (all)                                     | 102                         | 57                                   |  |
| Neurotoxicity   |                             |                                      |  |
| subjects affected / exposed                           | 9 / 61 (14.75%)             | 8 / 119 (6.72%)                      |  |
| occurrences (all)                                     | 25                          | 19                                   |  |
| Anxiety   |                             |                                      |  |
| subjects affected / exposed                           | 3 / 61 (4.92%)              | 7 / 119 (5.88%)                      |  |
| occurrences (all)                                     | 3                           | 8                                    |  |
| Dizziness   |                             |                                      |  |
| subjects affected / exposed                           | 2 / 61 (3.28%)              | 10 / 119 (8.40%)                     |  |
| occurrences (all)                                     | 2                           | 14                                   |  |
| Blood and lymphatic system disorders                  |                             |                                      |  |
| Anaemia   |                             |                                      |  |
| subjects affected / exposed                           | 13 / 61 (21.31%)            | 30 / 119 (25.21%)                    |  |
| occurrences (all)                                     | 21                          | 54                                   |  |
| Neutropenia   |                             |                                      |  |
| subjects affected / exposed                           | 14 / 61 (22.95%)            | 27 / 119 (22.69%)                    |  |
| occurrences (all)                                     | 40                          | 72                                   |  |
| Thrombocytopenia                                      |                             |                                      |  |
| subjects affected / exposed                           | 15 / 61 (24.59%)            | 10 / 119 (8.40%)                     |  |
| occurrences (all)                                     | 28                          | 13                                   |  |
| Epistaxis   |                             |                                      |  |
| subjects affected / exposed                           | 12 / 61 (19.67%)            | 32 / 119 (26.89%)                    |  |
| occurrences (all)                                     | 19                          | 46                                   |  |
| Rectal bleeding                                       |                             |                                      |  |

|  |                  |                   |  |
|--|------------------|-------------------|--|
| subjects affected / exposed                          | 7 / 61 (11.48%)  | 15 / 119 (12.61%) |  |
| occurrences (all)                                    | 7                | 17                |  |
| Oedema   |                  |                   |  |
| subjects affected / exposed                          | 7 / 61 (11.48%)  | 8 / 119 (6.72%)   |  |
| occurrences (all)                                    | 7                | 8                 |  |
| Leukopenia   |                  |                   |  |
| subjects affected / exposed                          | 3 / 61 (4.92%)   | 8 / 119 (6.72%)   |  |
| occurrences (all)                                    | 3                | 19                |  |
| General disorders and administration site conditions |                  |                   |  |
| Asthenia   |                  |                   |  |
| subjects affected / exposed                          | 46 / 61 (75.41%) | 90 / 119 (75.63%) |  |
| occurrences (all)                                    | 117              | 280               |  |
| Common cold  |                  |                   |  |
| subjects affected / exposed                          | 6 / 61 (9.84%)   | 9 / 119 (7.56%)   |  |
| occurrences (all)                                    | 8                | 11                |  |
| Fever  |                  |                   |  |
| subjects affected / exposed                          | 12 / 61 (19.67%) | 27 / 119 (22.69%) |  |
| occurrences (all)                                    | 16               | 33                |  |
| Weight decreased                                     |                  |                   |  |
| subjects affected / exposed                          | 5 / 61 (8.20%)   | 3 / 119 (2.52%)   |  |
| occurrences (all)                                    | 5                | 5                 |  |
| Abdominal pain                                       |                  |                   |  |
| subjects affected / exposed                          | 24 / 61 (39.34%) | 42 / 119 (35.29%) |  |
| occurrences (all)                                    | 38               | 54                |  |
| Anal pain  |                  |                   |  |
| subjects affected / exposed                          | 4 / 61 (6.56%)   | 6 / 119 (5.04%)   |  |
| occurrences (all)                                    | 5                | 9                 |  |
| Insomnia   |                  |                   |  |
| subjects affected / exposed                          | 3 / 61 (4.92%)   | 10 / 119 (8.40%)  |  |
| occurrences (all)                                    | 3                | 10                |  |
| Back pain  |                  |                   |  |
| subjects affected / exposed                          | 1 / 61 (1.64%)   | 6 / 119 (5.04%)   |  |
| occurrences (all)                                    | 2                | 7                 |  |
| Lumbar pain  |                  |                   |  |

|                             |                  |                   |  |
|-----------------------------|------------------|-------------------|--|
| subjects affected / exposed | 3 / 61 (4.92%)   | 6 / 119 (5.04%)   |  |
| occurrences (all)           | 4                | 7                 |  |
| Pain                        |                  |                   |  |
| subjects affected / exposed | 2 / 61 (3.28%)   | 6 / 119 (5.04%)   |  |
| occurrences (all)           | 2                | 7                 |  |
| Gastrointestinal disorders  |                  |                   |  |
| Anorexia nervosa            |                  |                   |  |
| subjects affected / exposed | 16 / 61 (26.23%) | 32 / 119 (26.89%) |  |
| occurrences (all)           | 32               | 53                |  |
| Bowel obstruction           |                  |                   |  |
| subjects affected / exposed | 6 / 61 (9.84%)   | 3 / 119 (2.52%)   |  |
| occurrences (all)           | 6                | 3                 |  |
| Constipation                |                  |                   |  |
| subjects affected / exposed | 19 / 61 (31.15%) | 30 / 119 (25.21%) |  |
| occurrences (all)           | 30               | 46                |  |
| Diarrhoea                   |                  |                   |  |
| subjects affected / exposed | 43 / 61 (70.49%) | 99 / 119 (83.19%) |  |
| occurrences (all)           | 93               | 358               |  |
| Dysgeusia                   |                  |                   |  |
| subjects affected / exposed | 10 / 61 (16.39%) | 18 / 119 (15.13%) |  |
| occurrences (all)           | 15               | 28                |  |
| Hyporexia                   |                  |                   |  |
| subjects affected / exposed | 7 / 61 (11.48%)  | 16 / 119 (13.45%) |  |
| occurrences (all)           | 11               | 24                |  |
| Mucositis                   |                  |                   |  |
| subjects affected / exposed | 23 / 61 (37.70%) | 55 / 119 (46.22%) |  |
| occurrences (all)           | 42               | 97                |  |
| Nausea                      |                  |                   |  |
| subjects affected / exposed | 28 / 61 (45.90%) | 56 / 119 (47.06%) |  |
| occurrences (all)           | 54               | 109               |  |
| Vomiting                    |                  |                   |  |
| subjects affected / exposed | 29 / 61 (47.54%) | 51 / 119 (42.86%) |  |
| occurrences (all)           | 67               | 130               |  |
| Xerostomy                   |                  |                   |  |
| subjects affected / exposed | 5 / 61 (8.20%)   | 6 / 119 (5.04%)   |  |
| occurrences (all)           | 6                | 7                 |  |

|  |                        |                         |  |
|--|------------------------|-------------------------|--|
| Gingivitis<br>subjects affected / exposed<br>occurrences (all)   | 3 / 61 (4.92%)<br>3    | 7 / 119 (5.88%)<br>10   |  |
| Tenesmus<br>subjects affected / exposed<br>occurrences (all)   | 1 / 61 (1.64%)<br>1    | 6 / 119 (5.04%)<br>6    |  |
| Respiratory, thoracic and mediastinal disorders<br>Cough<br>subjects affected / exposed<br>occurrences (all)     | 4 / 61 (6.56%)<br>5    | 11 / 119 (9.24%)<br>18  |  |
| Dyspnoea<br>subjects affected / exposed<br>occurrences (all)   | 4 / 61 (6.56%)<br>6    | 8 / 119 (6.72%)<br>9    |  |
| Skin and subcutaneous tissue disorders<br>Hand-foot syndrome<br>subjects affected / exposed<br>occurrences (all) | 28 / 61 (45.90%)<br>52 | 34 / 119 (28.57%)<br>71 |  |
| Hyperpigmentation<br>subjects affected / exposed<br>occurrences (all)  | 6 / 61 (9.84%)<br>8    | 8 / 119 (6.72%)<br>9    |  |
| Pruritus<br>subjects affected / exposed<br>occurrences (all)   | 4 / 61 (6.56%)<br>5    | 9 / 119 (7.56%)<br>9    |  |
| Alopecia<br>subjects affected / exposed<br>occurrences (all)   | 2 / 61 (3.28%)<br>2    | 25 / 119 (21.01%)<br>31 |  |
| Infections and infestations<br>Respiratory infection<br>subjects affected / exposed<br>occurrences (all)         | 4 / 61 (6.56%)<br>4    | 7 / 119 (5.88%)<br>10   |  |
| Urinary tract infection<br>subjects affected / exposed<br>occurrences (all)                                      | 5 / 61 (8.20%)<br>8    | 12 / 119 (10.08%)<br>17 |  |
| Metabolism and nutrition disorders<br>Hypokalaemia   |                        |                         |  |

|                             |                |                 |  |
|-----------------------------|----------------|-----------------|--|
| subjects affected / exposed | 1 / 61 (1.64%) | 9 / 119 (7.56%) |  |
| occurrences (all)           | 1              | 14              |  |
| Hyperglycaemia              |                |                 |  |
| subjects affected / exposed | 0 / 61 (0.00%) | 8 / 119 (6.72%) |  |
| occurrences (all)           | 0              | 14              |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment  |
|------------------|--|
| 17 July 2009     | Taking into account the suggestions of the research ethics committee to approve the study.   |
| 02 October 2009  | Through this amendment 8 new centers have been added: H.San Juan Reus, C.H. Zamora, H. Josep Trueta, H.G.U. Gregorio Marañón, IDOC Corachan, H. Granollers, H. Guadalajara, H. Virgen Arrixaca.  |
| 23 October 2009  | Correction of a typographic error regarding the administration regimens of the two drugs administered every 2 weeks (Bevacizumab and Oxaliplatin): arms of treatment with FUORI and FUOX.  |
| 03 November 2009 | Through this amendment one new center has been added (H. Puerta Hierro)  |
| 01 March 2010    | Through this amendment some parts of the protocol have been modified /clarified, the biological study has been included and two new centers have been added: ICO and H. Doce de Octubre. Moreover, Dra Sandra Merino Varela replaced Dr Julen Fernandez as the Principal Investigator in H. Sant Joan de Reus. |
| 01 April 2011    | Through this amendment Dra Montserrat Gay Pastor replaced Miquel Nogué Aliguer as the Principal Investigator in Consorci Hospitalari de Vic.   |
| 17 January 2013  | Through this amendment Dra Clara Montagut Viladot replaced Dr Manuel Gallén Castillo as the Principal Investigator in Hospital del Mar.  |
| 27 May 2013      | Through this amendment Dr José Luis Manzano Mozo replaced Dr Albert Abad Esteve as the Principal Investigator in Hospital Germans Trias i Pujol.   |
| 16 July 2013     | Through this amendment Dr Luis Robles Díaz replaced Dra Cristina Grávalos Castro as the Principal Investigator in Hospital Universitario 12 de Octubre.  |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Serum samples were not analyzed for cell-free tumor DNA. This technique may allow identification of variability in response due to the tumor genome, complementary to information provided by examination of germline polymorphisms.

Notes:

### Online references

<http://www.ncbi.nlm.nih.gov/pubmed/29145602>