



## Clinical trial results:

### Induction FOLFOX with or without Aflibercept followed by chemoradiation in High Risk Locally Advanced Rectal Cancer. Phase II randomized, multicenter, open label trial

#### Summary

|                          |                  |
|--------------------------|------------------|
| EudraCT number           | 2014-002063-14   |
| Trial protocol           | ES               |
| Global end of trial date | 04 February 2020 |

#### Results information

|                                   |   |
|-----------------------------------|---|
| Result version number             | v1 (current)  |
| This version publication date     | 26 March 2021   |
| First version publication date    | 26 March 2021   |
| Summary attachment (see zip file) | RIA ICH3 Synopsis (RIA CLINICAL STUDY REPORT EUDRACT.pdf) |

#### Trial information

##### Trial identification

|                       |             |
|-----------------------|-------------|
| Sponsor protocol code | GEMCAD-1402 |
|-----------------------|-------------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT02340949 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | Grupo Español Multidisciplinar en Cáncer Digestivo (GEMCAD)     |
| Sponsor organisation address | Pau Alsina, 64-68.Esc.B, entlo. 5ª, Barcelona, Spain,           |
| Public contact               | Federico Nepote, MFAR Clinical Research, investigacion@mfar.net |
| Scientific contact           | Federico Nepote, MFAR Clinical Research, investigacion@mfar.net |

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                       | 31 January 2021  |
| Is this the analysis of the primary completion data? | Yes              |
| Primary completion date                              | 15 July 2019     |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 04 February 2020 |
| Was the trial ended prematurely?                     | No               |

Notes:

## General information about the trial

Main objective of the trial:

To evaluate the efficacy of induction therapy with mFOLFOX6 +/- aflibercept followed by CT/RT in terms of pathological Complete Responses (pCR)

Protection of trial subjects:

The protocol, through the schedule of visits and procedures, establishes measures to ensure the minimal risk to patients enrolled in the study.

Background therapy: -

Evidence for comparator: -

|   |                 |
|---|-----------------|
| Actual start date of recruitment                          | 31 October 2014 |
| 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: 180 |
| Worldwide total number of subjects   | 180        |
| EEA total number of subjects         | 180        |

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)                      | 180 |
| From 65 to 84 years                       | 0   |
| 85 years and over                         | 0   |

## Subject disposition

### Recruitment

Recruitment details:

Locally advanced high-risk rectum adenocarcinoma patients were recruited in 22 centers in Spain

### Pre-assignment

Screening details:

Random assignment of treatment will be stratified by T3 versus T4 stage for all patients. Patients will be allocated in a 2:1 ratio to the experimental or active comparator arms respectively.

### Period 1

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

### Arms

|                              |                       |
|------------------------------|-----------------------|
| Are arms mutually exclusive? | Yes                   |
| <b>Arm title</b>             | mFOLFOX6 + Afibercept |

Arm description:

- mFOLFOX-6 scheme: 5-Fluoruracil [5-FU], oxaliplatin and leucovorin will be administered intravenously once every 14 days according to mFOLFOX-6 scheme:

Day 1: Oxaliplatin 85 mg/m<sup>2</sup> IV infusion in 250-500 mL and leucovorin 200 mg/m<sup>2</sup> IV, both over two hours, followed by 5-FU 400 mg/m<sup>2</sup> IV bolus and a 46 h infusion of 5-FU 2400 mg/m<sup>2</sup>.

- Afibercept, will be administered intravenously (I.V.) at doses of 4 mg/Kg on Day 1 every 14 days. Afibercept will be supplied to sites by the study Sponsor as 4 ml vials at a concentration of 25 mg/ml. Treatment will continue until six cycles are administered unless unacceptable toxicity or progression occurs.

Afibercept: Administered I.V. at doses of 4 mg/Kg on Day 1 every 14 days. It will be supplied to sites by Sponsor as 4 ml vials at a concentration of 25 mg/ml

5-Fluoruracil: Once every 14 days. Day 1: 400 mg/m<sup>2</sup> I.V. bolus and a 46 h infusion of 5-FU 2400 mg/m<sup>2</sup>

Oxaliplatin: Once every 14 days. Day 1: 85 mg/m<sup>2</sup> I.V. infusión in 250-500 mL, ove

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

Dosage and administration details:

Afibercept, will be administered intravenously (I.V.) at doses of 4 mg/Kg on Day 1 every 14 days.

|  |  |
|--|--|
| Investigational medicinal product name | FOLFOX6 regimen                                  |
| Investigational medicinal product code |  |
| Other name                             | 5-Fluoruracil [5-FU], oxaliplatin and leucovorin |
| Pharmaceutical forms                   | Concentrate for solution for infusion            |
| Routes of administration               | Intravenous use                                  |

Dosage and administration details:

5-Fluoruracil [5-FU], oxaliplatin and leucovorin will be administered intravenously once every 14 days according to mFOLFOX-6 scheme:

Day 1: Oxaliplatin 85 mg/m<sup>2</sup> IV infusion in 250-500 mL and leucovorin 200 mg/m<sup>2</sup> IV, both over two hours, followed by 5-FU 400 mg/m<sup>2</sup> IV bolus and a 46 h infusion of 5-FU 2400 mg/m<sup>2</sup>.

|                  |          |
|------------------|----------|
| <b>Arm title</b> | mFOLFOX6 |
|------------------|----------|

Arm description:

- mFOLFOX-6 scheme: 5-Fluoruracil [5-FU], oxaliplatin and leucovorin will be administered intravenously once every 14 days according to mFOLFOX-6 scheme:

Day 1: Oxaliplatin 85 mg/m<sup>2</sup> IV infusion in 250-500 mL and leucovorin 200 mg/m<sup>2</sup> IV, both over two hours, followed by 5-FU 400 mg/m<sup>2</sup> IV bolus and a 46 h infusion of 5-FU 2400 mg/m<sup>2</sup>.

Treatment will continue until six cycles are administered unless unacceptable toxicity or progression occurs.

5-Fluoruracil: Once every 14 days. Day 1: 400 mg/m<sup>2</sup> I.V. bolus and a 46 h infusion of 5-FU 2400 mg/m<sup>2</sup>

Oxaliplatin: Once every 14 days. Day 1: 85 mg/m<sup>2</sup> I.V. infusión in 250-500 mL, over two hours, followed by 5-FU

Leucovorin: Once every 14 days. Day 1: 200 mg/m<sup>2</sup> I.V., over two hours, followed by 5-FU

|  |  |
|--|--|
| Arm type                               | Active comparator                                |
| Investigational medicinal product name | FOLFOX6 regimen                                  |
| Investigational medicinal product code |  |
| Other name                             | 5-Fluoruracil [5-FU], oxaliplatin and leucovorin |
| Pharmaceutical forms                   | Concentrate for solution for infusion            |
| Routes of administration               | Intravenous use                                  |

Dosage and administration details:

5-Fluoruracil [5-FU], oxaliplatin and leucovorin will be administered intravenously once every 14 days according to mFOLFOX-6 scheme:

Day 1: Oxaliplatin 85 mg/m<sup>2</sup> IV infusion in 250-500 mL and leucovorin 200 mg/m<sup>2</sup> IV, both over two hours, followed by 5-FU 400 mg/m<sup>2</sup> IV bolus and a 46 h infusion of 5-FU 2400 mg/m<sup>2</sup>.

| Number of subjects in period 1 | mFOLFOX6 + Aflibercept | mFOLFOX6 |
|--------------------------------|------------------------|----------|
| Started                        | 115                    | 65       |
| Completed                      | 115                    | 65       |

## Period 2

|                              |                        |
|------------------------------|------------------------|
| Period 2 title               | Study treatment period |
| Is this the baseline period? | No                     |
| Allocation method            | Not applicable         |
| Blinding used                | Not blinded            |

Blinding implementation details:

No blinding

## Arms

|                              |                        |
|------------------------------|------------------------|
| Are arms mutually exclusive? | Yes                    |
| Arm title                    | mFOLFOX6 + Aflibercept |

Arm description:

- mFOLFOX-6 scheme: 5-Fluoruracil [5-FU], oxaliplatin and leucovorin will be administered intravenously once every 14 days according to mFOLFOX-6 scheme:

Day 1: Oxaliplatin 85 mg/m<sup>2</sup> IV infusion in 250-500 mL and leucovorin 200 mg/m<sup>2</sup> IV, both over two hours, followed by 5-FU 400 mg/m<sup>2</sup> IV bolus and a 46 h infusion of 5-FU 2400 mg/m<sup>2</sup>.

- Aflibercept, will be administered intravenously (I.V.) at doses of 4 mg/Kg on Day 1 every 14 days. Aflibercept will be supplied to sites by the study Sponsor as 4 ml vials at a concentration of 25 mg/ml. Treatment will continue until six cycles are administered unless unacceptable toxicity or progression occurs.

Aflibercept: Administered I.V. at doses of 4 mg/Kg on Day 1 every 14 days. It will be supplied to sites by Sponsor as 4 ml vials at a concentration of 25 mg/ml

5-Fluoruracil: Once every 14 days. Day 1: 400 mg/m<sup>2</sup> I.V. bolus and a 46 h infusion of 5-FU 2400

mg/m<sup>2</sup>

Oxaliplatin: Once every 14 days. Day 1: 85 mg/m<sup>2</sup> I.V. infusión in 250-500 mL, ove

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

Dosage and administration details:

Aflibercept, will be administered intravenously (I.V.) at doses of 4 mg/Kg on Day 1 every 14 days.

|  |  |
|--|--|
| Investigational medicinal product name | FOLFOX6 regimen                                  |
| Investigational medicinal product code |  |
| Other name                             | 5-Fluoruracil [5-FU], oxaliplatin and leucovorin |
| Pharmaceutical forms                   | Concentrate for solution for infusion            |
| Routes of administration               | Intravenous use                                  |

Dosage and administration details:

5-Fluoruracil [5-FU], oxaliplatin and leucovorin will be administered intravenously once every 14 days according to mFOLFOX-6 scheme:

Day 1: Oxaliplatin 85 mg/m<sup>2</sup> IV infusion in 250-500 mL and leucovorin 200 mg/m<sup>2</sup> IV, both over two hours, followed by 5-FU 400 mg/m<sup>2</sup> IV bolus and a 46 h infusion of 5-FU 2400 mg/m<sup>2</sup>.

|                  |          |
|------------------|----------|
| <b>Arm title</b> | mFOLFOX6 |
|------------------|----------|

Arm description:

- mFOLFOX-6 scheme: 5-Fluoruracil [5-FU], oxaliplatin and leucovorin will be administered intravenously once every 14 days according to mFOLFOX-6 scheme:

Day 1: Oxaliplatin 85 mg/m<sup>2</sup> IV infusion in 250-500 mL and leucovorin 200 mg/m<sup>2</sup> IV, both over two hours, followed by 5-FU 400 mg/m<sup>2</sup> IV bolus and a 46 h infusion of 5-FU 2400 mg/m<sup>2</sup>.

Treatment will continue until six cycles are administered unless unacceptable toxicity or progression occurs.

5-Fluoruracil: Once every 14 days. Day 1: 400 mg/m<sup>2</sup> I.V. bolus and a 46 h infusion of 5-FU 2400 mg/m<sup>2</sup>

Oxaliplatin: Once every 14 days. Day 1: 85 mg/m<sup>2</sup> I.V. infusión in 250-500 mL, over two hours, followed by 5-FU

Leucovorin: Once every 14 days. Day 1: 200 mg/m<sup>2</sup> I.V., over two hours, followed by 5-FU

|  |  |
|--|--|
| Arm type                               | Active comparator                                |
| Investigational medicinal product name | FOLFOX6 regimen                                  |
| Investigational medicinal product code |  |
| Other name                             | 5-Fluoruracil [5-FU], oxaliplatin and leucovorin |
| Pharmaceutical forms                   | Concentrate for solution for infusion            |
| Routes of administration               | Intravenous use                                  |

Dosage and administration details:

5-Fluoruracil [5-FU], oxaliplatin and leucovorin will be administered intravenously once every 14 days according to mFOLFOX-6 scheme:

Day 1: Oxaliplatin 85 mg/m<sup>2</sup> IV infusion in 250-500 mL and leucovorin 200 mg/m<sup>2</sup> IV, both over two hours, followed by 5-FU 400 mg/m<sup>2</sup> IV bolus and a 46 h infusion of 5-FU 2400 mg/m<sup>2</sup>.

| <b>Number of subjects in period 2</b> | mFOLFOX6 + Aflibercept | mFOLFOX6 |
|---------------------------------------|------------------------|----------|
| Started                               | 115                    | 65       |
| Completed treatment as per protocol   | 99                     | 61       |
| Completed                             | 99                     | 61       |
| Not completed                         | 16                     | 4        |
| Adverse event, serious fatal          | 3                      | -        |

|                              |   |   |
|------------------------------|---|---|
| Consent withdrawn by subject | 2 | - |
| Physician decision           | 1 | - |
| Adverse event, non-fatal     | 4 | 2 |
| Lack of efficacy             | 6 | 2 |

## Baseline characteristics

### Reporting groups

|                       |                        |
|-----------------------|------------------------|
| Reporting group title | mFOLFOX6 + Aflibercept |
|-----------------------|------------------------|

Reporting group description:

- mFOLFOX-6 scheme: 5-Fluoruracil [5-FU], oxaliplatin and leucovorin will be administered intravenously once every 14 days according to mFOLFOX-6 scheme:

Day 1: Oxaliplatin 85 mg/m<sup>2</sup> IV infusion in 250-500 mL and leucovorin 200 mg/m<sup>2</sup> IV, both over two hours, followed by 5-FU 400 mg/m<sup>2</sup> IV bolus and a 46 h infusion of 5-FU 2400 mg/m<sup>2</sup>.

- Aflibercept, will be administered intravenously (I.V.) at doses of 4 mg/Kg on Day 1 every 14 days. Aflibercept will be supplied to sites by the study Sponsor as 4 ml vials at a concentration of 25 mg/ml. Treatment will continue until six cycles are administered unless unacceptable toxicity or progression occurs.

Aflibercept: Administered I.V. at doses of 4 mg/Kg on Day 1 every 14 days. It will be supplied to sites by Sponsor as 4 ml vials at a concentration of 25 mg/ml

5-Fluoruracil: Once every 14 days. Day 1: 400 mg/m<sup>2</sup> I.V. bolus and a 46 h infusion of 5-FU 2400 mg/m<sup>2</sup>

Oxaliplatin: Once every 14 days. Day 1: 85 mg/m<sup>2</sup> I.V. infusión in 250-500 mL, ove

|                       |          |
|-----------------------|----------|
| Reporting group title | mFOLFOX6 |
|-----------------------|----------|

Reporting group description:

- mFOLFOX-6 scheme: 5-Fluoruracil [5-FU], oxaliplatin and leucovorin will be administered intravenously once every 14 days according to mFOLFOX-6 scheme:

Day 1: Oxaliplatin 85 mg/m<sup>2</sup> IV infusion in 250-500 mL and leucovorin 200 mg/m<sup>2</sup> IV, both over two hours, followed by 5-FU 400 mg/m<sup>2</sup> IV bolus and a 46 h infusion of 5-FU 2400 mg/m<sup>2</sup>.

Treatment will continue until six cycles are administered unless unacceptable toxicity or progression occurs.

5-Fluoruracil: Once every 14 days. Day 1: 400 mg/m<sup>2</sup> I.V. bolus and a 46 h infusion of 5-FU 2400 mg/m<sup>2</sup>

Oxaliplatin: Once every 14 days. Day 1: 85 mg/m<sup>2</sup> I.V. infusión in 250-500 mL, over two hours, followed by 5-FU

Leucovorin: Once every 14 days. Day 1: 200 mg/m<sup>2</sup> I.V., over two hours, followed by 5-FU

| Reporting group values                             | mFOLFOX6 + Aflibercept | mFOLFOX6 | Total |
|--|------------------------|----------|-------|
| Number of subjects                                 | 115                    | 65       | 180   |
| Age categorical                                    |                        |          |       |
| Units: Subjects                                    |                        |          |       |
| In utero   |                        |          | 0     |
| Preterm newborn infants (gestational age < 37 wks) |                        |          | 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)                               |                        |          | 0     |
| From 65-84 years                                   |                        |          | 0     |
| 85 years and over                                  |                        |          | 0     |
| Age continuous                                     |                        |          |       |
| Units: years                                       |                        |          |       |
| arithmetic mean                                    | 58.4                   | 62.2     |       |
| standard deviation                                 | ± 10.4                 | ± 9.2    | -     |
| Gender categorical                                 |                        |          |       |
| Units: Subjects                                    |                        |          |       |
| Female   | 38                     | 26       | 64    |
| Male   | 77                     | 39       | 116   |

|  |     |    |     |
|--|-----|----|-----|
| Clinical stage Tumor-nodes-metastasis (TNM)  |     |    |     |
| TNM clinical stage. The T refers to the size and extent of the main tumor. The main tumor is usually called the primary tumor. The higher the number after the T, the larger the tumor or the more it has grown into nearby tissues. The range is from T0 to T4. T's may be further divided to provide more detail, such as T3a and T3b.                           |     |    |     |
| Units: Subjects  |     |    |     |
| Mising   | 1   | 1  | 2   |
| mrT2   | 1   | 0  | 1   |
| mrT3   | 17  | 12 | 29  |
| mrT3B  | 8   | 8  | 16  |
| mrT3A  | 1   | 0  | 1   |
| mrT3C  | 47  | 22 | 69  |
| mrT3D  | 7   | 4  | 11  |
| mrT4   | 9   | 6  | 15  |
| mrT4A  | 16  | 7  | 23  |
| mrT4B  | 8   | 5  | 13  |
| Clinical Stage TNM Nodes (n2)  |     |    |     |
| Used to describe regional lymph node involvement of the tumor. Lymph nodes function as biologic filters, as fluid from body tissues are absorbed into lymphatic capillaries and flows to the lymph nodes.[1] N0 indicates no regional nodal spread, while N1-N3 indicates some degree of nodal spread, with a progressively distal spread from N1 to N3.           |     |    |     |
| Units: Subjects  |     |    |     |
| N2   | 115 | 65 | 180 |
| Location   |     |    |     |
| Location of primary tumor in the rectum  |     |    |     |
| Units: Subjects  |     |    |     |
| Distal   | 30  | 18 | 48  |
| Middle   | 84  | 46 | 130 |
| Missing  | 1   | 1  | 2   |
| Histology  |     |    |     |
| Type of tumor cell composition found by histopathology analysis.   |     |    |     |
| Units: Subjects  |     |    |     |
| Adenocarcinoma   | 115 | 65 | 180 |
| Other  | 0   | 0  | 0   |
| Mesorectal Fascia (FMR)  |     |    |     |
| Distance from tumor to mesorectal fascia grouped in two categories depending on the distances: close (distance <=1 mm) or distal (NR).   |     |    |     |
| Units: Subjects  |     |    |     |
| FMR + (distance <=1 mm)  | 68  | 37 | 105 |
| NR   | 47  | 28 | 75  |
| EMVI score   |     |    |     |
| Extramural vascular invasion (EMVI) is the direct invasion of a blood vessel (usually a vein) by a tumor. In rectal cancer, this can occur on a macroscopic level and be detected on staging MRI. It is a significant prognostic factor, being a predictor of haematogenous spread. Score range from 0 to 4. Higher score means higher risk of distant metastasis. |     |    |     |
| Units: Subjects  |     |    |     |
| Score 0/1/2  | 60  | 34 | 94  |
| Score 3/4  | 55  | 31 | 86  |



## End points

### End points reporting groups

|  |                        |
|--|------------------------|
| Reporting group title  | mFOLFOX6 + Aflibercept |
| Reporting group description:   |                        |
| <p>- mFOLFOX-6 scheme: 5-Fluoruracil [5-FU], oxaliplatin and leucovorin will be administered intravenously once every 14 days according to mFOLFOX-6 scheme:</p> <p>Day 1: Oxaliplatin 85 mg/m<sup>2</sup> IV infusion in 250-500 mL and leucovorin 200 mg/m<sup>2</sup> IV, both over two hours, followed by 5-FU 400 mg/m<sup>2</sup> IV bolus and a 46 h infusion of 5-FU 2400 mg/m<sup>2</sup>.</p> <p>- Aflibercept, will be administered intravenously (I.V.) at doses of 4 mg/Kg on Day 1 every 14 days. Aflibercept will be supplied to sites by the study Sponsor as 4 ml vials at a concentration of 25 mg/ml. Treatment will continue until six cycles are administered unless unacceptable toxicity or progression occurs.</p> <p>Aflibercept: Administered I.V. at doses of 4 mg/Kg on Day 1 every 14 days. It will be supplied to sites by Sponsor as 4 ml vials at a concentration of 25 mg/ml</p> <p>5-Fluoruracil: Once every 14 days. Day 1: 400 mg/m<sup>2</sup> I.V. bolus and a 46 h infusion of 5-FU 2400 mg/m<sup>2</sup></p> <p>Oxaliplatin: Once every 14 days. Day 1: 85 mg/m<sup>2</sup> I.V. infusión in 250-500 mL, ove</p> |                        |
| Reporting group title  | mFOLFOX6               |
| Reporting group description:   |                        |
| <p>- mFOLFOX-6 scheme: 5-Fluoruracil [5-FU], oxaliplatin and leucovorin will be administered intravenously once every 14 days according to mFOLFOX-6 scheme:</p> <p>Day 1: Oxaliplatin 85 mg/m<sup>2</sup> IV infusion in 250-500 mL and leucovorin 200 mg/m<sup>2</sup> IV, both over two hours, followed by 5-FU 400 mg/m<sup>2</sup> IV bolus and a 46 h infusion of 5-FU 2400 mg/m<sup>2</sup>.</p> <p>Treatment will continue until six cycles are administered unless unacceptable toxicity or progression occurs.</p> <p>5-Fluoruracil: Once every 14 days. Day 1: 400 mg/m<sup>2</sup> I.V. bolus and a 46 h infusion of 5-FU 2400 mg/m<sup>2</sup></p> <p>Oxaliplatin: Once every 14 days. Day 1: 85 mg/m<sup>2</sup> I.V. infusión in 250-500 mL, over two hours, followed by 5-FU</p> <p>Leucovorin: Once every 14 days. Day 1: 200 mg/m<sup>2</sup> I.V., over two hours, followed by 5-FU</p>   |                        |
| Reporting group title  | mFOLFOX6 + Aflibercept |
| Reporting group description:   |                        |
| <p>- mFOLFOX-6 scheme: 5-Fluoruracil [5-FU], oxaliplatin and leucovorin will be administered intravenously once every 14 days according to mFOLFOX-6 scheme:</p> <p>Day 1: Oxaliplatin 85 mg/m<sup>2</sup> IV infusion in 250-500 mL and leucovorin 200 mg/m<sup>2</sup> IV, both over two hours, followed by 5-FU 400 mg/m<sup>2</sup> IV bolus and a 46 h infusion of 5-FU 2400 mg/m<sup>2</sup>.</p> <p>- Aflibercept, will be administered intravenously (I.V.) at doses of 4 mg/Kg on Day 1 every 14 days. Aflibercept will be supplied to sites by the study Sponsor as 4 ml vials at a concentration of 25 mg/ml. Treatment will continue until six cycles are administered unless unacceptable toxicity or progression occurs.</p> <p>Aflibercept: Administered I.V. at doses of 4 mg/Kg on Day 1 every 14 days. It will be supplied to sites by Sponsor as 4 ml vials at a concentration of 25 mg/ml</p> <p>5-Fluoruracil: Once every 14 days. Day 1: 400 mg/m<sup>2</sup> I.V. bolus and a 46 h infusion of 5-FU 2400 mg/m<sup>2</sup></p> <p>Oxaliplatin: Once every 14 days. Day 1: 85 mg/m<sup>2</sup> I.V. infusión in 250-500 mL, ove</p> |                        |
| Reporting group title  | mFOLFOX6               |
| Reporting group description:   |                        |
| <p>- mFOLFOX-6 scheme: 5-Fluoruracil [5-FU], oxaliplatin and leucovorin will be administered intravenously once every 14 days according to mFOLFOX-6 scheme:</p> <p>Day 1: Oxaliplatin 85 mg/m<sup>2</sup> IV infusion in 250-500 mL and leucovorin 200 mg/m<sup>2</sup> IV, both over two hours, followed by 5-FU 400 mg/m<sup>2</sup> IV bolus and a 46 h infusion of 5-FU 2400 mg/m<sup>2</sup>.</p> <p>Treatment will continue until six cycles are administered unless unacceptable toxicity or progression occurs.</p> <p>5-Fluoruracil: Once every 14 days. Day 1: 400 mg/m<sup>2</sup> I.V. bolus and a 46 h infusion of 5-FU 2400 mg/m<sup>2</sup></p> <p>Oxaliplatin: Once every 14 days. Day 1: 85 mg/m<sup>2</sup> I.V. infusión in 250-500 mL, over two hours, followed by 5-FU</p> <p>Leucovorin: Once every 14 days. Day 1: 200 mg/m<sup>2</sup> I.V., over two hours, followed by 5-FU</p>   |                        |

**Primary: Number of Patients Achieving pCR**

|                 |                                  |
|-----------------|----------------------------------|
| End point title | Number of Patients Achieving pCR |
|-----------------|----------------------------------|

End point description:

To analyze the number of patients achieving pCR after induction therapy with mFOLFOX6 +/- aflibercept followed by CT/RT. pCR will be defined as the absence of viable tumor cells in the primary tumor and in the lymph nodes (ypT0N0)

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

End point timeframe:

Until 2 years and 2 months

| End point values            | mFOLFOX6 + Aflibercept | mFOLFOX6        |  |  |
|-----------------------------|------------------------|-----------------|--|--|
| Subject group type          | Reporting group        | Reporting group |  |  |
| Number of subjects analysed | 115                    | 65              |  |  |
| Units: Patients             |                        |                 |  |  |
| Yes                         | 25                     | 9               |  |  |
| No                          | 90                     | 56              |  |  |

**Statistical analyses**

|   |                                   |
|---|-----------------------------------|
| Statistical analysis title              | Chi square test                   |
| Comparison groups                       | mFOLFOX6 v mFOLFOX6 + Aflibercept |
| Number of subjects included in analysis | 180                               |
| Analysis specification                  | Pre-specified                     |
| Analysis type                           | non-inferiority                   |
| P-value                                 | = 0.1938                          |
| Method                                  | Chi-squared                       |

**Secondary: Efficacy: R0 Resection**

|                 |                        |
|-----------------|------------------------|
| End point title | Efficacy: R0 Resection |
|-----------------|------------------------|

End point description:

To determine R0 resection rates. Number of patients achieving a R0, optimal surgical outcome.

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

End point timeframe:

Until 2 years and 2 months

| End point values            | mFOLFOX6 +<br>Aflibercept | mFOLFOX6        |  |  |
|-----------------------------|---------------------------|-----------------|--|--|
| Subject group type          | Reporting group           | Reporting group |  |  |
| Number of subjects analysed | 115                       | 65              |  |  |
| Units: Patients             |                           |                 |  |  |
| Yes                         | 101                       | 60              |  |  |
| No                          | 2                         | 2               |  |  |
| Not Available               | 12                        | 3               |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: TRG; residual tumor after preoperative therapy

|   |  |
|---|--|
| End point title   | TRG; residual tumor after preoperative therapy |
| End point description:<br>TRG; residual tumor after preoperative therapy will be semiquantitatively evaluated according to the 5-point regression grading scale established by Mandard. |  |
| End point type  | Secondary                                      |
| End point timeframe:<br>Until 2 years and 2 months  |  |

| End point values            | mFOLFOX6 +<br>Aflibercept | mFOLFOX6        |  |  |
|-----------------------------|---------------------------|-----------------|--|--|
| Subject group type          | Reporting group           | Reporting group |  |  |
| Number of subjects analysed | 115                       | 65              |  |  |
| Units: Patients             |                           |                 |  |  |
| Yes                         | 59                        | 30              |  |  |
| No                          | 56                        | 35              |  |  |
| Not available               | 0                         | 0               |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: CRM ≤ 1

|  |           |
|--|-----------|
| End point title  | CRM ≤ 1   |
| End point description:<br>CRM will be defined as tumor ≤ 1 mm from the resection margin. Number of patients with CRM ≤ 1 |           |
| End point type   | Secondary |
| End point timeframe:<br>Until 2 years and 2 months   |           |

| End point values            | mFOLFOX6 +<br>Aflibercept | mFOLFOX6        |  |  |
|-----------------------------|---------------------------|-----------------|--|--|
| Subject group type          | Reporting group           | Reporting group |  |  |
| Number of subjects analysed | 115                       | 65              |  |  |
| Units: Patients             |                           |                 |  |  |
| Yes                         | 3                         | 3               |  |  |
| No                          | 96                        | 56              |  |  |
| Not available               | 16                        | 6               |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: To evaluate the relationship between MRI changes with outcome.

|   |  |
|---|--|
| End point title   | To evaluate the relationship between MRI changes with outcome. |
| End point description:  |  |
| T Downstaging: defined as a lower pathologic T stage compared to pre-treatment mrT stage. |  |
| End point type  | Secondary  |
| End point timeframe:  |  |
| Until 2 years and 2 months  |  |

| End point values            | mFOLFOX6 +<br>Aflibercept | mFOLFOX6        |  |  |
|-----------------------------|---------------------------|-----------------|--|--|
| Subject group type          | Reporting group           | Reporting group |  |  |
| Number of subjects analysed | 115                       | 65              |  |  |
| Units: Patients             |                           |                 |  |  |
| Yes                         | 68                        | 46              |  |  |
| No                          | 47                        | 19              |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Safety and Tolerability of mFOLFOX6 +/- Aflibercept Followed Chemoradiation

|  |   |
|--|---|
| End point title  | Safety and Tolerability of mFOLFOX6 +/- Aflibercept Followed Chemoradiation |
| End point description:   |   |
| The safety and tolerability of the study therapy will be assessed by means of AEs and changes in laboratory data. AEs will be coded and evaluated using the NCI-CTCAE v4.0 toxicity criteria (if NCI-CTCAE are not applicable, MedDRA will be used). |   |

|                            |           |
|----------------------------|-----------|
| End point type             | Secondary |
| End point timeframe:       |           |
| Until 2 years and 2 months |           |

| End point values                                   | mFOLFOX6 +<br>Aflibercept | mFOLFOX6          |  |  |
|--|---------------------------|-------------------|--|--|
| Subject group type                                 | Reporting group           | Reporting group   |  |  |
| Number of subjects analysed                        | 115 <sup>[1]</sup>        | 65 <sup>[2]</sup> |  |  |
| Units: Patients                                    |                           |                   |  |  |
| At least one AE                                    | 115                       | 65                |  |  |
| At least one Grade 3-4 AE                          | 83                        | 31                |  |  |
| At least one AE that lead to treatment discontinua | 20                        | 4                 |  |  |
| At least one AE that lead to death                 | 3                         | 0                 |  |  |
| At least one Serious Adverse Event (SAE)           | 45                        | 16                |  |  |
| At least one treatment-related AE                  | 105                       | 59                |  |  |
| At least one treatment-related AE Grade 3-4        | 64                        | 17                |  |  |
| At least one treatment-related AE that led to deat | 0                         | 0                 |  |  |
| At least one treatment-related AE that led to perm | 17                        | 3                 |  |  |
| At least one treatment-related Serious Adverse Eve | 25                        | 3                 |  |  |

Notes:

[1] - Each row is independent (one patient may suffer more than one event on the row list)

[2] - Each row is independent (one patient may suffer more than one event on the row list)

## Statistical analyses

No statistical analyses for this end point

## Secondary: To Determine the Rate of 30 Days Surgical Complications (Assessed by Means of AEs Reported)

|   |   |
|---|---|
| End point title   | To Determine the Rate of 30 Days Surgical Complications (Assessed by Means of AEs Reported) |
| End point description:  |   |
| Surgical complications will be assessed by means of AEs reported during 30 days post surgery. |   |
| End point type  | Secondary   |
| End point timeframe:  |   |
| Until 2 years and 2 months  |   |

| End point values            | mFOLFOX6 + Afibercept | mFOLFOX6          |  |  |
|-----------------------------|-----------------------|-------------------|--|--|
| Subject group type          | Reporting group       | Reporting group   |  |  |
| Number of subjects analysed | 115 <sup>[3]</sup>    | 65 <sup>[4]</sup> |  |  |
| Units: Patients             |                       |                   |  |  |
| Postoperative AEs           | 3                     | 1                 |  |  |
| Postoperative AEs Grade 3-4 | 2                     | 0                 |  |  |
| Complications               | 60                    | 30                |  |  |
| Anastomosis fistula         | 4                     | 1                 |  |  |
| wound infection             | 5                     | 5                 |  |  |
| intraabdominal infection    | 10                    | 1                 |  |  |
| Stoma complications         | 2                     | 0                 |  |  |
| Reoperation                 | 9                     | 5                 |  |  |

Notes:

[3] - Each row is independent (one patient may suffer more than one event and count in several rows)

[4] - Each row is independent (one patient may suffer more than one event and count in several rows)

### Statistical analyses

No statistical analyses for this end point

### Secondary: To Evaluate the 3 Years Local Recurrence and DFS

|                        |  |
|------------------------|--|
| End point title        | To Evaluate the 3 Years Local Recurrence and DFS   |
| End point description: | To determine the rate of local recurrence and DFS at 3-years after completing the Study treatment. |
| End point type         | Secondary  |
| End point timeframe:   | Until 5 years and two months   |

| End point values                          | mFOLFOX6 + Afibercept | mFOLFOX6            |  |  |
|---|-----------------------|---------------------|--|--|
| Subject group type                        | Reporting group       | Reporting group     |  |  |
| Number of subjects analysed               | 115                   | 65                  |  |  |
| Units: Percentage of patients             |                       |                     |  |  |
| arithmetic mean (confidence interval 95%) | 75.2 (66.1 to 82.2)   | 81.5 (69.8 to 89.1) |  |  |

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Throughout the study. Approximately 3 years

Adverse event reporting additional description:

For the statistical tables, adverse events have been coded according to the Medical Dictionary of Regulatory Activities (MedDRA 20.1) system. Their intensity has been coded by (NCI-CTCAE) v4.0 toxicity criteria.

Grade 3 or higher AEs were reported as serious. All the grade 1 and 2 as non serious.

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 20.1 |
|--------------------|------|

### Reporting groups

|                       |                        |
|-----------------------|------------------------|
| Reporting group title | mFOLFOX6 + Aflibercept |
|-----------------------|------------------------|

Reporting group description:

- mFOLFOX-6 scheme: 5-Fluoruracil [5-FU], oxaliplatin and leucovorin will be administered intravenously once every 14 days according to mFOLFOX-6 scheme:

Day 1: Oxaliplatin 85 mg/m<sup>2</sup> IV infusion in 250-500 mL and leucovorin 200 mg/m<sup>2</sup> IV, both over two hours, followed by 5-FU 400 mg/m<sup>2</sup> IV bolus and a 46 h infusion of 5-FU 2400 mg/m<sup>2</sup>.

- Aflibercept, will be administered intravenously (I.V.) at doses of 4 mg/Kg on Day 1 every 14 days. Aflibercept will be supplied to sites by the study Sponsor as 4 ml vials at a concentration of 25 mg/ml. Treatment will continue until six cycles are administered unless unacceptable toxicity or progression occurs.

Aflibercept: Administered I.V. at doses of 4 mg/Kg on Day 1 every 14 days. It will be supplied to sites by Sponsor as 4 ml vials at a concentration of 25 mg/ml

5-Fluoruracil: Once every 14 days. Day 1: 400 mg/m<sup>2</sup> I.V. bolus and a 46 h infusion of 5-FU 2400 mg/m<sup>2</sup>

Oxaliplatin: Once every 14 days. Day 1: 85 mg/m<sup>2</sup> I.V. infusión in 250-500 mL, ove

|                       |          |
|-----------------------|----------|
| Reporting group title | mFOLFOX6 |
|-----------------------|----------|

Reporting group description:

- mFOLFOX-6 scheme: 5-Fluoruracil [5-FU], oxaliplatin and leucovorin will be administered intravenously once every 14 days according to mFOLFOX-6 scheme:

Day 1: Oxaliplatin 85 mg/m<sup>2</sup> IV infusion in 250-500 mL and leucovorin 200 mg/m<sup>2</sup> IV, both over two hours, followed by 5-FU 400 mg/m<sup>2</sup> IV bolus and a 46 h infusion of 5-FU 2400 mg/m<sup>2</sup>.

Treatment will continue until six cycles are administered unless unacceptable toxicity or progression occurs.

5-Fluoruracil: Once every 14 days. Day 1: 400 mg/m<sup>2</sup> I.V. bolus and a 46 h infusion of 5-FU 2400 mg/m<sup>2</sup>

Oxaliplatin: Once every 14 days. Day 1: 85 mg/m<sup>2</sup> I.V. infusión in 250-500 mL, over two hours, followed by 5-FU

Leucovorin: Once every 14 days. Day 1: 200 mg/m<sup>2</sup> I.V., over two hours, followed by 5-FU

| Serious adverse events                            | mFOLFOX6 + Aflibercept | mFOLFOX6         |  |
|---|------------------------|------------------|--|
| Total subjects affected by serious adverse events |                        |                  |  |
| subjects affected / exposed                       | 45 / 115 (39.13%)      | 16 / 65 (24.62%) |  |
| number of deaths (all causes)                     | 12                     | 7                |  |
| number of deaths resulting from adverse events    |                        |                  |  |
| Vascular disorders                                |                        |                  |  |
| Hypertension                                      |                        |                  |  |

|  |                 |                |  |
|--|-----------------|----------------|--|
| subjects affected / exposed                          | 0 / 115 (0.00%) | 1 / 65 (1.54%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 1 / 1          |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0          |  |
| Nervous system disorders                             |                 |                |  |
| Peripheral neuropathy                                |                 |                |  |
| subjects affected / exposed                          | 2 / 115 (1.74%) | 1 / 65 (1.54%) |  |
| occurrences causally related to treatment / all      | 2 / 2           | 1 / 1          |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0          |  |
| General disorders and administration site conditions |                 |                |  |
| Asthenia   |                 |                |  |
| subjects affected / exposed                          | 2 / 115 (1.74%) | 0 / 65 (0.00%) |  |
| occurrences causally related to treatment / all      | 2 / 2           | 0 / 0          |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0          |  |
| Nausea   |                 |                |  |
| subjects affected / exposed                          | 4 / 115 (3.48%) | 0 / 65 (0.00%) |  |
| occurrences causally related to treatment / all      | 4 / 4           | 0 / 0          |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0          |  |
| Abdominal pain                                       |                 |                |  |
| subjects affected / exposed                          | 1 / 115 (0.87%) | 0 / 65 (0.00%) |  |
| occurrences causally related to treatment / all      | 1 / 1           | 0 / 0          |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0          |  |
| Dysphonia  |                 |                |  |
| subjects affected / exposed                          | 1 / 115 (0.87%) | 0 / 65 (0.00%) |  |
| occurrences causally related to treatment / all      | 1 / 1           | 0 / 0          |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0          |  |
| Pyrexia  |                 |                |  |
| subjects affected / exposed                          | 1 / 115 (0.87%) | 0 / 65 (0.00%) |  |
| occurrences causally related to treatment / all      | 1 / 1           | 0 / 0          |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0          |  |
| Fatigue  |                 |                |  |
| subjects affected / exposed                          | 1 / 115 (0.87%) | 0 / 65 (0.00%) |  |
| occurrences causally related to treatment / all      | 1 / 1           | 0 / 0          |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0          |  |



|   |                   |                |  |
|---|-------------------|----------------|--|
| Blood and lymphatic system disorders            |                   |                |  |
| Neutropenia                                     |                   |                |  |
| subjects affected / exposed                     | 34 / 115 (29.57%) | 2 / 65 (3.08%) |  |
| occurrences causally related to treatment / all | 34 / 34           | 2 / 2          |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          |  |
| Thrombocytopenia                                |                   |                |  |
| subjects affected / exposed                     | 1 / 115 (0.87%)   | 2 / 65 (3.08%) |  |
| occurrences causally related to treatment / all | 1 / 1             | 2 / 2          |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          |  |
| Anaemia   |                   |                |  |
| subjects affected / exposed                     | 1 / 115 (0.87%)   | 1 / 65 (1.54%) |  |
| occurrences causally related to treatment / all | 1 / 1             | 1 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          |  |
| Gastrointestinal disorders                      |                   |                |  |
| Diarrhoea                                       |                   |                |  |
| subjects affected / exposed                     | 8 / 115 (6.96%)   | 4 / 65 (6.15%) |  |
| occurrences causally related to treatment / all | 8 / 8             | 4 / 4          |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          |  |
| Proctalgia                                      |                   |                |  |
| subjects affected / exposed                     | 1 / 115 (0.87%)   | 1 / 65 (1.54%) |  |
| occurrences causally related to treatment / all | 1 / 1             | 1 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          |  |
| Rectal haemorrhage                              |                   |                |  |
| subjects affected / exposed                     | 2 / 115 (1.74%)   | 0 / 65 (0.00%) |  |
| occurrences causally related to treatment / all | 2 / 2             | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          |  |
| Mucosal inflammation                            |                   |                |  |
| subjects affected / exposed                     | 4 / 115 (3.48%)   | 0 / 65 (0.00%) |  |
| occurrences causally related to treatment / all | 4 / 4             | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0          |  |
| Skin and subcutaneous tissue disorders          |                   |                |  |
| Palmar-plantar erythrodysaesthesia syndrome     |                   |                |  |

|   |                 |                |  |
|---|-----------------|----------------|--|
| subjects affected / exposed                     | 3 / 115 (2.61%) | 0 / 65 (0.00%) |  |
| occurrences causally related to treatment / all | 3 / 3           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| <b>Infections and infestations</b>              |                 |                |  |
| Stomatitis                                      |                 |                |  |
| subjects affected / exposed                     | 0 / 115 (0.00%) | 1 / 65 (1.54%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |

Frequency threshold for reporting non-serious adverse events: 0 %

| <b>Non-serious adverse events</b>                           | mFOLFOX6 +<br>Aflibercept | mFOLFOX6          |  |
|---|---------------------------|-------------------|--|
| Total subjects affected by non-serious adverse events       |                           |                   |  |
| subjects affected / exposed                                 | 115 / 115<br>(100.00%)    | 65 / 65 (100.00%) |  |
| <b>Vascular disorders</b>                                   |                           |                   |  |
| Hypertension  |                           |                   |  |
| subjects affected / exposed                                 | 22 / 115 (19.13%)         | 3 / 65 (4.62%)    |  |
| occurrences (all)   | 22                        | 3                 |  |
| Epistaxis   |                           |                   |  |
| subjects affected / exposed                                 | 17 / 115 (14.78%)         | 1 / 65 (1.54%)    |  |
| occurrences (all)   | 17                        | 1                 |  |
| <b>Nervous system disorders</b>                             |                           |                   |  |
| Peripheral neuropathy                                       |                           |                   |  |
| subjects affected / exposed                                 | 48 / 115 (41.74%)         | 30 / 65 (46.15%)  |  |
| occurrences (all)   | 48                        | 30                |  |
| Dysaesthesia  |                           |                   |  |
| subjects affected / exposed                                 | 15 / 115 (13.04%)         | 10 / 65 (15.38%)  |  |
| occurrences (all)   | 15                        | 10                |  |
| Paraesthesia  |                           |                   |  |
| subjects affected / exposed                                 | 11 / 115 (9.57%)          | 11 / 65 (16.92%)  |  |
| occurrences (all)   | 11                        | 11                |  |
| <b>General disorders and administration site conditions</b> |                           |                   |  |
| Asthenia  |                           |                   |  |
| subjects affected / exposed                                 | 65 / 115 (56.52%)         | 38 / 65 (58.46%)  |  |
| occurrences (all)   | 65                        | 38                |  |

|                                      |                   |                  |  |
|--------------------------------------|-------------------|------------------|--|
| Nausea                               |                   |                  |  |
| subjects affected / exposed          | 37 / 115 (32.17%) | 23 / 65 (35.38%) |  |
| occurrences (all)                    | 37                | 23               |  |
| Abdominal pain                       |                   |                  |  |
| subjects affected / exposed          | 16 / 115 (13.91%) | 5 / 65 (7.69%)   |  |
| occurrences (all)                    | 16                | 5                |  |
| Dysphonia                            |                   |                  |  |
| subjects affected / exposed          | 19 / 115 (16.52%) | 1 / 65 (1.54%)   |  |
| occurrences (all)                    | 19                | 1                |  |
| Pyrexia                              |                   |                  |  |
| subjects affected / exposed          | 14 / 115 (12.17%) | 4 / 65 (6.15%)   |  |
| occurrences (all)                    | 14                | 4                |  |
| Dysgeusia                            |                   |                  |  |
| subjects affected / exposed          | 11 / 115 (9.57%)  | 8 / 65 (12.31%)  |  |
| occurrences (all)                    | 11                | 8                |  |
| Musculoskeletal pain                 |                   |                  |  |
| subjects affected / exposed          | 11 / 115 (9.57%)  | 7 / 65 (10.77%)  |  |
| occurrences (all)                    | 11                | 7                |  |
| Aphonia                              |                   |                  |  |
| subjects affected / exposed          | 14 / 115 (12.17%) | 0 / 65 (0.00%)   |  |
| occurrences (all)                    | 14                | 0                |  |
| Abdominal pain upper                 |                   |                  |  |
| subjects affected / exposed          | 10 / 115 (8.70%)  | 3 / 65 (4.62%)   |  |
| occurrences (all)                    | 10                | 3                |  |
| Fatigue                              |                   |                  |  |
| subjects affected / exposed          | 7 / 115 (6.09%)   | 5 / 65 (7.69%)   |  |
| occurrences (all)                    | 7                 | 5                |  |
| Headache                             |                   |                  |  |
| subjects affected / exposed          | 8 / 115 (6.96%)   | 1 / 65 (1.54%)   |  |
| occurrences (all)                    | 8                 | 1                |  |
| Blood and lymphatic system disorders |                   |                  |  |
| Neutropenia                          |                   |                  |  |
| subjects affected / exposed          | 14 / 115 (12.17%) | 4 / 65 (6.15%)   |  |
| occurrences (all)                    | 14                | 4                |  |
| Thrombocytopenia                     |                   |                  |  |

|  |                         |                        |  |
|--|-------------------------|------------------------|--|
| subjects affected / exposed<br>occurrences (all)                         | 9 / 115 (7.83%)<br>9    | 7 / 65 (10.77%)<br>7   |  |
| Anaemia<br>subjects affected / exposed<br>occurrences (all)              | 6 / 115 (5.22%)<br>6    | 7 / 65 (10.77%)<br>7   |  |
| Gastrointestinal disorders   |                         |                        |  |
| Diarrhoea<br>subjects affected / exposed<br>occurrences (all)            | 42 / 115 (36.52%)<br>42 | 22 / 65 (33.85%)<br>22 |  |
| Mucosal inflammation<br>subjects affected / exposed<br>occurrences (all) | 48 / 115 (41.74%)<br>48 | 14 / 65 (21.54%)<br>14 |  |
| Vomiting<br>subjects affected / exposed<br>occurrences (all)             | 21 / 115 (18.26%)<br>21 | 13 / 65 (20.00%)<br>13 |  |
| Decreased appetite<br>subjects affected / exposed<br>occurrences (all)   | 25 / 115 (21.74%)<br>25 | 9 / 65 (13.85%)<br>9   |  |
| Constipation<br>subjects affected / exposed<br>occurrences (all)         | 13 / 115 (11.30%)<br>13 | 9 / 65 (13.85%)<br>9   |  |
| Proctalgia<br>subjects affected / exposed<br>occurrences (all)           | 11 / 115 (9.57%)<br>11  | 6 / 65 (9.23%)<br>6    |  |
| Rectal haemorrhage<br>subjects affected / exposed<br>occurrences (all)   | 14 / 115 (12.17%)<br>14 | 3 / 65 (4.62%)<br>3    |  |
| Anal inflammation<br>subjects affected / exposed<br>occurrences (all)    | 10 / 115 (8.70%)<br>10  | 0 / 65 (0.00%)<br>0    |  |
| Rectal tenesmus<br>subjects affected / exposed<br>occurrences (all)      | 8 / 115 (6.96%)<br>8    | 1 / 65 (1.54%)<br>1    |  |
| Skin and subcutaneous tissue disorders                                   |                         |                        |  |
| Palmar-plantar erythrodysaesthesia<br>syndrome                           |                         |                        |  |

|  |                         |                      |  |
|--|-------------------------|----------------------|--|
| subjects affected / exposed<br>occurrences (all) | 13 / 115 (11.30%)<br>13 | 8 / 65 (12.31%)<br>8 |  |
| Infections and infestations                      |                         |                      |  |
| Stomatitis                                       |                         |                      |  |
| subjects affected / exposed                      | 14 / 115 (12.17%)       | 3 / 65 (4.62%)       |  |
| occurrences (all)                                | 14                      | 3                    |  |
| Cystitis   |                         |                      |  |
| subjects affected / exposed                      | 9 / 115 (7.83%)         | 7 / 65 (10.77%)      |  |
| occurrences (all)                                | 9                       | 7                    |  |

## **More information**

### **Substantial protocol amendments (globally)**

Were there any global substantial amendments to the protocol? No

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### **Interruptions (globally)**

Were there any global interruptions to the trial? No

### **Limitations and caveats**

None reported