



## Clinical trial results:

### **MAVERICC (Marker Evaluation for Avastin Research in CRC): A Randomized Phase II Study of Bevacizumab+mFOLFOX6 Vs. Bevacizumab+FOLFIRI With Biomarker Stratification in Patients With Previously Untreated Metastatic Colorectal Cancer**

#### **Summary**

EudraCT number	2011-004755-39
Trial protocol	IE EE PT
Global end of trial date	02 July 2015

#### **Results information**

Result version number	v1 (current)
This version publication date	16 July 2016
First version publication date	16 July 2016

#### **Trial information**

##### **Trial identification**

Sponsor protocol code	ML25710
-----------------------	---------

##### **Additional study identifiers**

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01374425
WHO universal trial number (UTN)	-

Notes:

##### **Sponsors**

Sponsor organisation name	F. Hoffmann-La Roche AG
Sponsor organisation address	Grenzacherstrasse 124, Basel, Switzerland, CH-4070
Public contact	Roche Trial Information Hotline, F. Hoffmann-La Roche AG, +41 61 6878333, global.trial_information@roche.com
Scientific contact	Roche Trial Information Hotline, F. Hoffmann-La Roche AG, +41 61 6878333, global.trial_information@roche.com

Notes:

##### **Paediatric regulatory details**

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

Notes:

## Results analysis stage

Analysis stage	Final
Date of interim/final analysis	27 January 2016
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	02 July 2015
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

This was a randomized, open-label, multicenter, Phase II study with primary objectives to assess whether expression of select chemotherapy markers is associated with progression-free survival (PFS) in participants treated with bevacizumab plus leucovorin, 5-fluorouracil, and oxaliplatin (mFOLFOX6) or bevacizumab plus leucovorin, 5-fluorouracil, and irinotecan (FOLFIRI). The study population consisted of participants with first-line metastatic colorectal cancer (mCRC).

Protection of trial subjects:

The Investigator has ensured that this study was conducted in full conformance with the principles of the Declaration of Helsinki or with the laws and regulations of the country in which the research was conducted, whichever affords the greater protection to the individual. The study must have fully adhered to the principles outlined in the Guideline for Good Clinical Practice International Council for Harmonisation (ICH) Tripartite Guideline (January 1997) or with local law if it affords greater protection to the participant. In other countries where the Guideline for Good Clinical Practice exists, Roche and the investigators have strictly ensured adherence to the stated provisions.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	21 August 2011
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	Norway: 2
Country: Number of subjects enrolled	Portugal: 18
Country: Number of subjects enrolled	Estonia: 8
Country: Number of subjects enrolled	Ireland: 11
Country: Number of subjects enrolled	Canada: 11
Country: Number of subjects enrolled	Switzerland: 8
Country: Number of subjects enrolled	United States: 318
Worldwide total number of subjects	376
EEA total number of subjects	39

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)	236
From 65 to 84 years	139
85 years and over	1

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

The trial included a 21-day Screening period during which participants provided information for demographics, medical history and cancer/treatment history and completed urinalysis collection.

### Period 1

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

### Arms

Are arms mutually exclusive?	No
<b>Arm title</b>	Bevacizumab + mFOLFOX6

Arm description:

Participants with untreated mCRC who were candidates for first-line therapy received bevacizumab plus mFOLFOX6 until disease progression or unacceptable toxicity. Bevacizumab was given as 5 milligrams per kilogram (mg/kg), leucovorin as 400 milligrams per meter-squared (mg/m<sup>2</sup>), oxaliplatin as 85 mg/m<sup>2</sup>, and 5-fluorouracil as 400 mg/m<sup>2</sup> bolus followed by 2400 mg/m<sup>2</sup> continuous 46-hour infusion. All treatments were administered via intravenous (IV) infusion and started on Day 1 of each 2-week cycle. Participants could be transitioned to oral capecitabine in the event of unacceptable toxicity to oxaliplatin and given as 850 or 1000 mg/m<sup>2</sup> twice a day on Days 1 to 14, with bevacizumab continued in 3-week cycles.

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

Dosage and administration details:

Bevacizumab was given as 5 mg/kg IV infusion on Day 1 of each 2-week cycle. For participants who discontinued from oxaliplatin or irinotecan due to unacceptable toxicity, bevacizumab was given in 3-week cycles with capecitabine.

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

Dosage and administration details:

Leucovorin was given as 400 mg/m<sup>2</sup> via IV infusion on Day 1 of each 2-week cycle.

Investigational medicinal product name	5-Fluorouracil
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

5-Fluorouracil was given as 400 mg/m<sup>2</sup> bolus followed by 2400 mg/m<sup>2</sup> continuous 46-hour infusion started on Day 1 of each 2-week cycle.

Investigational medicinal product name	Oxaliplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use
Dosage and administration details:	
Oxaliplatin was given as 85 mg/m <sup>2</sup> via IV infusion on Day 1 of each 2-week cycle.	
Investigational medicinal product name	Capecitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
Capecitabine was given as 850 or 1000 mg/m <sup>2</sup> twice a day on Days 1 to 14 of each 3-week cycle.	
<b>Arm title</b>	Bevacizumab + FOLFIRI
Arm description:	
Participants with untreated mCRC who were candidates for first-line therapy received bevacizumab plus FOLFIRI until disease progression or unacceptable toxicity. Bevacizumab was given as 5 mg/kg, leucovorin as 400 mg/m <sup>2</sup> , irinotecan as 180 mg/m <sup>2</sup> , and 5-fluorouracil as 400 mg/m <sup>2</sup> bolus followed by 2400 mg/m <sup>2</sup> continuous 46-hour infusion. All treatments were administered via IV infusion and started on Day 1 of each 2-week cycle. Participants could be transitioned to oral capecitabine in the event of unacceptable toxicity to irinotecan and given as 850 or 1000 mg/m <sup>2</sup> twice a day on Days 1 to 14, with bevacizumab continued in 3-week cycles.	
Arm type	Experimental
Investigational medicinal product name	Bevacizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use
Dosage and administration details:	
Bevacizumab was given as 5 mg/kg IV infusion on Day 1 of each 2-week cycle. For participants who discontinued from oxaliplatin or irinotecan due to unacceptable toxicity, bevacizumab was given in 3-week cycles with capecitabine.	
Investigational medicinal product name	Leucovorin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use
Dosage and administration details:	
Leucovorin was given as 400 mg/m <sup>2</sup> via IV infusion on Day 1 of each 2-week cycle.	
Investigational medicinal product name	5-Fluorouracil
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use
Dosage and administration details:	
5-Fluorouracil was given as 400 mg/m <sup>2</sup> bolus followed by 2400 mg/m <sup>2</sup> continuous 46-hour infusion started on Day 1 of each 2-week cycle.	
Investigational medicinal product name	Irinotecan
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

**Dosage and administration details:**

Irinotecan was given as 180 mg/m<sup>2</sup> via IV infusion on Day 1 of each 2-week cycle.

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

**Dosage and administration details:**

Capecitabine was given as 850 or 1000 mg/m<sup>2</sup> twice a day on Days 1 to 14 of each 3-week cycle.

<b>Arm title</b>	Bevacizumab + mFOLFOX/FOLFIRI
------------------	-------------------------------

**Arm description:**

Participants with untreated mCRC who were candidates for first-line therapy received bevacizumab plus mFOLFOX6 or bevacizumab plus FOLFIRI until disease progression or unacceptable toxicity. Depending on the regimen to which the participant was randomized, bevacizumab was given as 5 mg/kg, leucovorin as 400 mg/m<sup>2</sup>, oxaliplatin as 85 mg/m<sup>2</sup>, irinotecan as 180 mg/m<sup>2</sup>, and 5-fluorouracil as 400 mg/m<sup>2</sup> bolus followed by 2400 mg/m<sup>2</sup> continuous 46-hour infusion. All treatments were administered via IV infusion and started on Day 1 of each 2-week cycle. Participants could be transitioned to oral capecitabine in the event of unacceptable toxicity to oxaliplatin or irinotecan and given as 850 or 1000 mg/m<sup>2</sup> twice a day on Days 1 to 14, with bevacizumab continued in 3-week cycles.

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

**Dosage and administration details:**

Bevacizumab was given as 5 mg/kg IV infusion on Day 1 of each 2-week cycle. For participants who discontinued from oxaliplatin or irinotecan due to unacceptable toxicity, bevacizumab was given in 3-week cycles with capecitabine.

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

**Dosage and administration details:**

Leucovorin was given as 400 mg/m<sup>2</sup> via IV infusion on Day 1 of each 2-week cycle.

Investigational medicinal product name	5-Fluorouracil
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

**Dosage and administration details:**

5-Fluorouracil was given as 400 mg/m<sup>2</sup> bolus followed by 2400 mg/m<sup>2</sup> continuous 46-hour infusion started on Day 1 of each 2-week cycle.

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

**Dosage and administration details:**

Oxaliplatin was given as 85 mg/m<sup>2</sup> via IV infusion on Day 1 of each 2-week cycle.

Investigational medicinal product name	Irinotecan
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use
Dosage and administration details:	
Irinotecan was given as 180 mg/m <sup>2</sup> via IV infusion on Day 1 of each 2-week cycle.	
Investigational medicinal product name	Capecitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Capecitabine was given as 850 or 1000 mg/m<sup>2</sup> twice a day on Days 1 to 14 of each 3-week cycle.

<b>Number of subjects in period 1</b>	Bevacizumab + mFOLFOX6	Bevacizumab + FOLFIRI	Bevacizumab + mFOLFOX/FOLFIRI
Started	188	188	376
Completed	0	0	0
Not completed	188	188	376
Death (adverse event)	2	4	6
Consent withdrawn by subject	6	7	13
Radiographic disease progression	86	81	167
Protocol violation	2	3	5
Not specified	41	43	84
Death (progression of disease)	1	-	1
Refused treatment	10	24	34
Clinical disease progression	9	6	15
Adverse event	29	18	47
Lost to follow-up	2	1	3
Sponsor decision	-	1	1

## Baseline characteristics

### Reporting groups

Reporting group title	Bevacizumab + mFOLFOX6
-----------------------	------------------------

Reporting group description:

Participants with untreated mCRC who were candidates for first-line therapy received bevacizumab plus mFOLFOX6 until disease progression or unacceptable toxicity. Bevacizumab was given as 5 milligrams per kilogram (mg/kg), leucovorin as 400 milligrams per meter-squared (mg/m<sup>2</sup>), oxaliplatin as 85 mg/m<sup>2</sup>, and 5-fluorouracil as 400 mg/m<sup>2</sup> bolus followed by 2400 mg/m<sup>2</sup> continuous 46-hour infusion. All treatments were administered via intravenous (IV) infusion and started on Day 1 of each 2-week cycle. Participants could be transitioned to oral capecitabine in the event of unacceptable toxicity to oxaliplatin and given as 850 or 1000 mg/m<sup>2</sup> twice a day on Days 1 to 14, with bevacizumab continued in 3-week cycles.

Reporting group title	Bevacizumab + FOLFIRI
-----------------------	-----------------------

Reporting group description:

Participants with untreated mCRC who were candidates for first-line therapy received bevacizumab plus FOLFIRI until disease progression or unacceptable toxicity. Bevacizumab was given as 5 mg/kg, leucovorin as 400 mg/m<sup>2</sup>, irinotecan as 180 mg/m<sup>2</sup>, and 5-fluorouracil as 400 mg/m<sup>2</sup> bolus followed by 2400 mg/m<sup>2</sup> continuous 46-hour infusion. All treatments were administered via IV infusion and started on Day 1 of each 2-week cycle. Participants could be transitioned to oral capecitabine in the event of unacceptable toxicity to irinotecan and given as 850 or 1000 mg/m<sup>2</sup> twice a day on Days 1 to 14, with bevacizumab continued in 3-week cycles.

Reporting group title	Bevacizumab + mFOLFOX/FOLFIRI
-----------------------	-------------------------------

Reporting group description:

Participants with untreated mCRC who were candidates for first-line therapy received bevacizumab plus mFOLFOX6 or bevacizumab plus FOLFIRI until disease progression or unacceptable toxicity. Depending on the regimen to which the participant was randomized, bevacizumab was given as 5 mg/kg, leucovorin as 400 mg/m<sup>2</sup>, oxaliplatin as 85 mg/m<sup>2</sup>, irinotecan as 180 mg/m<sup>2</sup>, and 5-fluorouracil as 400 mg/m<sup>2</sup> bolus followed by 2400 mg/m<sup>2</sup> continuous 46-hour infusion. All treatments were administered via IV infusion and started on Day 1 of each 2-week cycle. Participants could be transitioned to oral capecitabine in the event of unacceptable toxicity to oxaliplatin or irinotecan and given as 850 or 1000 mg/m<sup>2</sup> twice a day on Days 1 to 14, with bevacizumab continued in 3-week cycles.

Reporting group values	Bevacizumab + mFOLFOX6	Bevacizumab + FOLFIRI	Bevacizumab + mFOLFOX/FOLFIRI
Number of subjects	188	188	376
Age categorical			
Units: Subjects			

Age continuous			
Units: years			
arithmetic mean	59.2	60.7	59.9
standard deviation	± 10.88	± 10.66	± 10.78
Gender categorical			
Units: Subjects			
Female	66	71	137
Male	122	117	239

Reporting group values	Total		
Number of subjects	376		
Age categorical			
Units: Subjects			



Age continuous Units: years arithmetic mean standard deviation	-		
Gender categorical Units: Subjects			
Female	137		
Male	239		

## End points

### End points reporting groups

Reporting group title	Bevacizumab + mFOLFOX6
Reporting group description: Participants with untreated mCRC who were candidates for first-line therapy received bevacizumab plus mFOLFOX6 until disease progression or unacceptable toxicity. Bevacizumab was given as 5 milligrams per kilogram (mg/kg), leucovorin as 400 milligrams per meter-squared (mg/m <sup>2</sup> ), oxaliplatin as 85 mg/m <sup>2</sup> , and 5-fluorouracil as 400 mg/m <sup>2</sup> bolus followed by 2400 mg/m <sup>2</sup> continuous 46-hour infusion. All treatments were administered via intravenous (IV) infusion and started on Day 1 of each 2-week cycle. Participants could be transitioned to oral capecitabine in the event of unacceptable toxicity to oxaliplatin and given as 850 or 1000 mg/m <sup>2</sup> twice a day on Days 1 to 14, with bevacizumab continued in 3-week cycles.	
Reporting group title	Bevacizumab + FOLFIRI
Reporting group description: Participants with untreated mCRC who were candidates for first-line therapy received bevacizumab plus FOLFIRI until disease progression or unacceptable toxicity. Bevacizumab was given as 5 mg/kg, leucovorin as 400 mg/m <sup>2</sup> , irinotecan as 180 mg/m <sup>2</sup> , and 5-fluorouracil as 400 mg/m <sup>2</sup> bolus followed by 2400 mg/m <sup>2</sup> continuous 46-hour infusion. All treatments were administered via IV infusion and started on Day 1 of each 2-week cycle. Participants could be transitioned to oral capecitabine in the event of unacceptable toxicity to irinotecan and given as 850 or 1000 mg/m <sup>2</sup> twice a day on Days 1 to 14, with bevacizumab continued in 3-week cycles.	
Reporting group title	Bevacizumab + mFOLFOX/FOLFIRI
Reporting group description: Participants with untreated mCRC who were candidates for first-line therapy received bevacizumab plus mFOLFOX6 or bevacizumab plus FOLFIRI until disease progression or unacceptable toxicity. Depending on the regimen to which the participant was randomized, bevacizumab was given as 5 mg/kg, leucovorin as 400 mg/m <sup>2</sup> , oxaliplatin as 85 mg/m <sup>2</sup> , irinotecan as 180 mg/m <sup>2</sup> , and 5-fluorouracil as 400 mg/m <sup>2</sup> bolus followed by 2400 mg/m <sup>2</sup> continuous 46-hour infusion. All treatments were administered via IV infusion and started on Day 1 of each 2-week cycle. Participants could be transitioned to oral capecitabine in the event of unacceptable toxicity to oxaliplatin or irinotecan and given as 850 or 1000 mg/m <sup>2</sup> twice a day on Days 1 to 14, with bevacizumab continued in 3-week cycles.	
Subject analysis set title	Bevacizumab + mFOLFOX6 (ERCC-1 High)
Subject analysis set type	Sub-group analysis
Subject analysis set description: Participants with untreated mCRC who were candidates for first-line therapy received bevacizumab plus mFOLFOX6 until disease progression or unacceptable toxicity. Bevacizumab was given as 5 mg/kg, leucovorin as 400 mg/m <sup>2</sup> , oxaliplatin as 85 mg/m <sup>2</sup> , and 5-fluorouracil as 400 mg/m <sup>2</sup> bolus followed by 2400 mg/m <sup>2</sup> continuous 46-hour infusion. All treatments were administered via IV infusion and started on Day 1 of each 2-week cycle. Participants could be transitioned to oral capecitabine in the event of unacceptable toxicity to oxaliplatin and given as 850 or 1000 mg/m <sup>2</sup> twice a day on Days 1 to 14, with bevacizumab continued in 3-week cycles. Participants with excision repair cross-complementing (ERCC)-1 level greater than (>) $1.7 \times 10^{-3}$ ERCC-1/B-actin messenger ribonucleic acid (mRNA) at Baseline were included in separate analyses.	
Subject analysis set title	Bevacizumab + FOLFIRI (ERCC-1 High)
Subject analysis set type	Sub-group analysis
Subject analysis set description: Participants with untreated mCRC who were candidates for first-line therapy received bevacizumab plus FOLFIRI until disease progression or unacceptable toxicity. Bevacizumab was given as 5 mg/kg, leucovorin as 400 mg/m <sup>2</sup> , irinotecan as 180 mg/m <sup>2</sup> , and 5-fluorouracil as 400 mg/m <sup>2</sup> bolus followed by 2400 mg/m <sup>2</sup> continuous 46-hour infusion. All treatments were administered via IV infusion and started on Day 1 of each 2-week cycle. Participants could be transitioned to oral capecitabine in the event of unacceptable toxicity to irinotecan and given as 850 or 1000 mg/m <sup>2</sup> twice a day on Days 1 to 14, with bevacizumab continued in 3-week cycles. Participants with ERCC-1 level $>1.7 \times 10^{-3}$ ERCC-1/B-actin mRNA at Baseline were included in separate analyses.	
Subject analysis set title	Bevacizumab + mFOLFOX6 (ERCC-1 Low)
Subject analysis set type	Sub-group analysis
Subject analysis set description: Participants with untreated mCRC who were candidates for first-line therapy received bevacizumab plus mFOLFOX6 until disease progression or unacceptable toxicity. Bevacizumab was given as 5 mg/kg,	

leucovorin as 400 mg/m<sup>2</sup>, oxaliplatin as 85 mg/m<sup>2</sup>, and 5-fluorouracil as 400 mg/m<sup>2</sup> bolus followed by 2400 mg/m<sup>2</sup> continuous 46-hour infusion. All treatments were administered via IV infusion and started on Day 1 of each 2-week cycle. Participants could be transitioned to oral capecitabine in the event of unacceptable toxicity to oxaliplatin and given as 850 or 1000 mg/m<sup>2</sup> twice a day on Days 1 to 14, with bevacizumab continued in 3-week cycles. Participants with ERCC-1 level less than or equal to ( $\leq$ )  $1.7 \times 10^{-3}$  ERCC-1/B-actin mRNA at Baseline were included in separate analyses.

Subject analysis set title	Bevacizumab + FOLFIRI (ERCC-1 Low)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants with untreated mCRC who were candidates for first-line therapy received bevacizumab plus FOLFIRI until disease progression or unacceptable toxicity. Bevacizumab was given as 5 mg/kg, leucovorin as 400 mg/m<sup>2</sup>, irinotecan as 180 mg/m<sup>2</sup>, and 5-fluorouracil as 400 mg/m<sup>2</sup> bolus followed by 2400 mg/m<sup>2</sup> continuous 46-hour infusion. All treatments were administered via IV infusion and started on Day 1 of each 2-week cycle. Participants could be transitioned to oral capecitabine in the event of unacceptable toxicity to irinotecan and given as 850 or 1000 mg/m<sup>2</sup> twice a day on Days 1 to 14, with bevacizumab continued in 3-week cycles. Participants with ERCC-1 level  $\leq 1.7 \times 10^{-3}$  ERCC-1/B-actin mRNA at Baseline were included in separate analyses.

Subject analysis set title	Bevacizumab + mFOLFOX/FOLFIRI (ERCC-1 High)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants with untreated mCRC who were candidates for first-line therapy received bevacizumab plus mFOLFOX6 or bevacizumab plus FOLFIRI until disease progression or unacceptable toxicity. Depending on the regimen to which the participant was randomized, bevacizumab was given as 5 mg/kg, leucovorin as 400 mg/m<sup>2</sup>, oxaliplatin as 85 mg/m<sup>2</sup>, irinotecan as 180 mg/m<sup>2</sup>, and 5-fluorouracil as 400 mg/m<sup>2</sup> bolus followed by 2400 mg/m<sup>2</sup> continuous 46-hour infusion. All treatments were administered via IV infusion and started on Day 1 of each 2-week cycle. Participants could be transitioned to oral capecitabine in the event of unacceptable toxicity to oxaliplatin or irinotecan and given as 850 or 1000 mg/m<sup>2</sup> twice a day on Days 1 to 14, with bevacizumab continued in 3-week cycles. Participants with ERCC-1 level  $> 1.7 \times 10^{-3}$  ERCC-1/B-actin mRNA at Baseline were included in separate analyses.

Subject analysis set title	Bevacizumab + mFOLFOX/FOLFIRI (ERCC-1 Low)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants with untreated mCRC who were candidates for first-line therapy received bevacizumab plus mFOLFOX6 or bevacizumab plus FOLFIRI until disease progression or unacceptable toxicity. Depending on the regimen to which the participant was randomized, bevacizumab was given as 5 mg/kg, leucovorin as 400 mg/m<sup>2</sup>, oxaliplatin as 85 mg/m<sup>2</sup>, irinotecan as 180 mg/m<sup>2</sup>, and 5-fluorouracil as 400 mg/m<sup>2</sup> bolus followed by 2400 mg/m<sup>2</sup> continuous 46-hour infusion. All treatments were administered via IV infusion and started on Day 1 of each 2-week cycle. Participants could be transitioned to oral capecitabine in the event of unacceptable toxicity to oxaliplatin or irinotecan and given as 850 or 1000 mg/m<sup>2</sup> twice a day on Days 1 to 14, with bevacizumab continued in 3-week cycles. Participants with ERCC-1 level  $\leq 1.7 \times 10^{-3}$  ERCC-1/B-actin mRNA at Baseline were included in separate analyses.

Subject analysis set title	Bevacizumab + mFOLFOX/FOLFIRI (VEGF-A High)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants with untreated mCRC who were candidates for first-line therapy received bevacizumab plus mFOLFOX6 or bevacizumab plus FOLFIRI until disease progression or unacceptable toxicity. Depending on the regimen to which the participant was randomized, bevacizumab was given as 5 mg/kg, leucovorin as 400 mg/m<sup>2</sup>, oxaliplatin as 85 mg/m<sup>2</sup>, irinotecan as 180 mg/m<sup>2</sup>, and 5-fluorouracil as 400 mg/m<sup>2</sup> bolus followed by 2400 mg/m<sup>2</sup> continuous 46-hour infusion. All treatments were administered via IV infusion and started on Day 1 of each 2-week cycle. Participants could be transitioned to oral capecitabine in the event of unacceptable toxicity to oxaliplatin or irinotecan and given as 850 or 1000 mg/m<sup>2</sup> twice a day on Days 1 to 14, with bevacizumab continued in 3-week cycles. Participants with vascular endothelial growth factor (VEGF)-A level  $> 5$  picograms per milliliter (pg/mL) at Baseline were included in separate analyses.

Subject analysis set title	Bevacizumab + mFOLFOX/FOLFIRI (VEGF-A Low)
Subject analysis set type	Sub-group analysis

#### Subject analysis set description:

Participants with untreated mCRC who were candidates for first-line therapy received bevacizumab plus mFOLFOX6 or bevacizumab plus FOLFIRI until disease progression or unacceptable toxicity. Depending on the regimen to which the participant was randomized, bevacizumab was given as 5 mg/kg, leucovorin as 400 mg/m<sup>2</sup>, oxaliplatin as 85 mg/m<sup>2</sup>, irinotecan as 180 mg/m<sup>2</sup>, and 5-fluorouracil as 400 mg/m<sup>2</sup> bolus followed by 2400 mg/m<sup>2</sup> continuous 46-hour infusion. All treatments were administered via IV infusion and started on Day 1 of each 2-week cycle. Participants could be transitioned to oral capecitabine in the event of unacceptable toxicity to oxaliplatin or irinotecan and given as 850 or 1000 mg/m<sup>2</sup> twice a day on Days 1 to 14, with bevacizumab continued in 3-week cycles. Participants with VEGF-A level ≤5 pg/mL at Baseline were included in separate analyses.

Subject analysis set title	Bevacizumab + mFOLFOX6 (ERCC-1 High, VEGF-A Low)
Subject analysis set type	Sub-group analysis

#### Subject analysis set description:

Participants with untreated mCRC who were candidates for first-line therapy received bevacizumab plus mFOLFOX6 until disease progression or unacceptable toxicity. Bevacizumab was given as 5 mg/kg, leucovorin as 400 mg/m<sup>2</sup>, oxaliplatin as 85 mg/m<sup>2</sup>, and 5-fluorouracil as 400 mg/m<sup>2</sup> bolus followed by 2400 mg/m<sup>2</sup> continuous 46-hour infusion. All treatments were administered via IV infusion and started on Day 1 of each 2-week cycle. Participants could be transitioned to oral capecitabine in the event of unacceptable toxicity to oxaliplatin and given as 850 or 1000 mg/m<sup>2</sup> twice a day on Days 1 to 14, with bevacizumab continued in 3-week cycles. Participants with ERCC-1 level >1.7 × 10<sup>-3</sup> ERCC-1/B-actin mRNA and VEGF-A level ≤5 pg/mL at Baseline were included in separate analyses.

Subject analysis set title	Bevacizumab + FOLFIRI (ERCC-1 High, VEGF-A Low)
Subject analysis set type	Sub-group analysis

#### Subject analysis set description:

Participants with untreated mCRC who were candidates for first-line therapy received bevacizumab plus FOLFIRI until disease progression or unacceptable toxicity. Bevacizumab was given as 5 mg/kg, leucovorin as 400 mg/m<sup>2</sup>, irinotecan as 180 mg/m<sup>2</sup>, and 5-fluorouracil as 400 mg/m<sup>2</sup> bolus followed by 2400 mg/m<sup>2</sup> continuous 46-hour infusion. All treatments were administered via IV infusion and started on Day 1 of each 2-week cycle. Participants could be transitioned to oral capecitabine in the event of unacceptable toxicity to irinotecan and given as 850 or 1000 mg/m<sup>2</sup> twice a day on Days 1 to 14, with bevacizumab continued in 3-week cycles. Participants with ERCC-1 level >1.7 × 10<sup>-3</sup> ERCC-1/B-actin mRNA and VEGF-A level ≤5 pg/mL at Baseline were included in separate analyses.

Subject analysis set title	Bevacizumab + mFOLFOX6 (ERCC-1 High, VEGF-A High)
Subject analysis set type	Sub-group analysis

#### Subject analysis set description:

Participants with untreated mCRC who were candidates for first-line therapy received bevacizumab plus mFOLFOX6 until disease progression or unacceptable toxicity. Bevacizumab was given as 5 mg/kg, leucovorin as 400 mg/m<sup>2</sup>, oxaliplatin as 85 mg/m<sup>2</sup>, and 5-fluorouracil as 400 mg/m<sup>2</sup> bolus followed by 2400 mg/m<sup>2</sup> continuous 46-hour infusion. All treatments were administered via IV infusion and started on Day 1 of each 2-week cycle. Participants could be transitioned to oral capecitabine in the event of unacceptable toxicity to oxaliplatin and given as 850 or 1000 mg/m<sup>2</sup> twice a day on Days 1 to 14, with bevacizumab continued in 3-week cycles. Participants with ERCC-1 level >1.7 × 10<sup>-3</sup> ERCC-1/B-actin mRNA and VEGF-A level >5 pg/mL at Baseline were included in separate analyses.

Subject analysis set title	Bevacizumab + FOLFIRI (ERCC-1 High, VEGF-A High)
Subject analysis set type	Sub-group analysis

#### Subject analysis set description:

Participants with untreated mCRC who were candidates for first-line therapy received bevacizumab plus FOLFIRI until disease progression or unacceptable toxicity. Bevacizumab was given as 5 mg/kg, leucovorin as 400 mg/m<sup>2</sup>, irinotecan as 180 mg/m<sup>2</sup>, and 5-fluorouracil as 400 mg/m<sup>2</sup> bolus followed by 2400 mg/m<sup>2</sup> continuous 46-hour infusion. All treatments were administered via IV infusion and started on Day 1 of each 2-week cycle. Participants could be transitioned to oral capecitabine in the event of unacceptable toxicity to irinotecan and given as 850 or 1000 mg/m<sup>2</sup> twice a day on Days 1 to 14, with bevacizumab continued in 3-week cycles. Participants with ERCC-1 level >1.7 × 10<sup>-3</sup> ERCC-1/B-actin mRNA and VEGF-A level >5 pg/mL at Baseline were included in separate analyses.

Subject analysis set title	Bevacizumab + mFOLFOX6 (ERCC-1 Low, VEGF-A High)
Subject analysis set type	Sub-group analysis

#### Subject analysis set description:

Participants with untreated mCRC who were candidates for first-line therapy received bevacizumab plus mFOLFOX6 until disease progression or unacceptable toxicity. Bevacizumab was given as 5 mg/kg,

leucovorin as 400 mg/m<sup>2</sup>, oxaliplatin as 85 mg/m<sup>2</sup>, and 5-fluorouracil as 400 mg/m<sup>2</sup> bolus followed by 2400 mg/m<sup>2</sup> continuous 46-hour infusion. All treatments were administered via IV infusion and started on Day 1 of each 2-week cycle. Participants could be transitioned to oral capecitabine in the event of unacceptable toxicity to oxaliplatin and given as 850 or 1000 mg/m<sup>2</sup> twice a day on Days 1 to 14, with bevacizumab continued in 3-week cycles. Participants with ERCC-1 level  $\leq 1.7 \times 10^{-3}$  ERCC-1/B-actin mRNA and VEGF-A level >5 pg/mL at Baseline were included in separate analyses.

Subject analysis set title	Bevacizumab + FOLFIRI (ERCC-1 Low, VEGF-A High)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants with untreated mCRC who were candidates for first-line therapy received bevacizumab plus FOLFIRI until disease progression or unacceptable toxicity. Bevacizumab was given as 5 mg/kg, leucovorin as 400 mg/m<sup>2</sup>, irinotecan as 180 mg/m<sup>2</sup>, and 5-fluorouracil as 400 mg/m<sup>2</sup> bolus followed by 2400 mg/m<sup>2</sup> continuous 46-hour infusion. All treatments were administered via IV infusion and started on Day 1 of each 2-week cycle. Participants could be transitioned to oral capecitabine in the event of unacceptable toxicity to irinotecan and given as 850 or 1000 mg/m<sup>2</sup> twice a day on Days 1 to 14, with bevacizumab continued in 3-week cycles. Participants with ERCC-1 level  $\leq 1.7 \times 10^{-3}$  ERCC-1/B-actin mRNA and VEGF-A level >5 pg/mL at Baseline were included in separate analyses.

Subject analysis set title	Bevacizumab + mFOLFOX6 (ERCC-1 Low, VEGF-A Low)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants with untreated mCRC who were candidates for first-line therapy received bevacizumab plus mFOLFOX6 until disease progression or unacceptable toxicity. Bevacizumab was given as 5 mg/kg, leucovorin as 400 mg/m<sup>2</sup>, oxaliplatin as 85 mg/m<sup>2</sup>, and 5-fluorouracil as 400 mg/m<sup>2</sup> bolus followed by 2400 mg/m<sup>2</sup> continuous 46-hour infusion. All treatments were administered via IV infusion and started on Day 1 of each 2-week cycle. Participants could be transitioned to oral capecitabine in the event of unacceptable toxicity to oxaliplatin and given as 850 or 1000 mg/m<sup>2</sup> twice a day on Days 1 to 14, with bevacizumab continued in 3-week cycles. Participants with ERCC-1 level  $\leq 1.7 \times 10^{-3}$  ERCC-1/B-actin mRNA and VEGF-A level  $\leq 5$  pg/mL at Baseline were included in separate analyses.

Subject analysis set title	Bevacizumab + FOLFIRI (ERCC-1 Low, VEGF-A Low)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants with untreated mCRC who were candidates for first-line therapy received bevacizumab plus FOLFIRI until disease progression or unacceptable toxicity. Bevacizumab was given as 5 mg/kg, leucovorin as 400 mg/m<sup>2</sup>, irinotecan as 180 mg/m<sup>2</sup>, and 5-fluorouracil as 400 mg/m<sup>2</sup> bolus followed by 2400 mg/m<sup>2</sup> continuous 46-hour infusion. All treatments were administered via IV infusion and started on Day 1 of each 2-week cycle. Participants could be transitioned to oral capecitabine in the event of unacceptable toxicity to irinotecan and given as 850 or 1000 mg/m<sup>2</sup> twice a day on Days 1 to 14, with bevacizumab continued in 3-week cycles. Participants with ERCC-1 level  $\leq 1.7 \times 10^{-3}$  ERCC-1/B-actin mRNA and VEGF-A level  $\leq 5$  pg/mL at Baseline were included in separate analyses.

Subject analysis set title	Bevacizumab + mFOLFOX/FOLFIRI (KRAS Wild-Type)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants with untreated mCRC who were candidates for first-line therapy received bevacizumab plus mFOLFOX6 or bevacizumab plus FOLFIRI until disease progression or unacceptable toxicity. Depending on the regimen to which the participant was randomized, bevacizumab was given as 5 mg/kg, leucovorin as 400 mg/m<sup>2</sup>, oxaliplatin as 85 mg/m<sup>2</sup>, irinotecan as 180 mg/m<sup>2</sup>, and 5-fluorouracil as 400 mg/m<sup>2</sup> bolus followed by 2400 mg/m<sup>2</sup> continuous 46-hour infusion. All treatments were administered via IV infusion and started on Day 1 of each 2-week cycle. Participants could be transitioned to oral capecitabine in the event of unacceptable toxicity to oxaliplatin or irinotecan and given as 850 or 1000 mg/m<sup>2</sup> twice a day on Days 1 to 14, with bevacizumab continued in 3-week cycles. Participants with wild-type V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog (KRAS) at Baseline were included in separate analyses.

Subject analysis set title	Bevacizumab + mFOLFOX/FOLFIRI (KRAS Mutant)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants with untreated mCRC who were candidates for first-line therapy received bevacizumab plus mFOLFOX6 or bevacizumab plus FOLFIRI until disease progression or unacceptable toxicity. Depending on the regimen to which the participant was randomized, bevacizumab was given as 5 mg/kg, leucovorin as 400 mg/m<sup>2</sup>, oxaliplatin as 85 mg/m<sup>2</sup>, irinotecan as 180 mg/m<sup>2</sup>, and 5-fluorouracil as 400 mg/m<sup>2</sup> bolus followed by 2400 mg/m<sup>2</sup> continuous 46-hour infusion. All treatments were

administered via IV infusion and started on Day 1 of each 2-week cycle. Participants could be transitioned to oral capecitabine in the event of unacceptable toxicity to oxaliplatin or irinotecan and given as 850 or 1000 mg/m<sup>2</sup> twice a day on Days 1 to 14, with bevacizumab continued in 3-week cycles. Participants with mutant KRAS at Baseline were included in separate analyses.

## Primary: PFS According to Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1

End point title	PFS According to Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 <sup>[1]</sup>
-----------------	---------------------------------------------------------------------------------------------------

End point description:

Tumor assessments were performed according to RECIST Version 1.1. Disease progression was defined as greater than or equal to ( $\geq$ ) 20 percent (%) increase in sum of largest diameters (LD) of target lesions in reference to the smallest sum of LD on study, in addition to an absolute increase  $\geq$  5 millimeters (mm). Disease progression was further defined as the last documented progression determined by the Investigator no later than 1 day before initiation of second-line therapy. Death on study included death from any cause occurring no later than 3 months after the last component of study treatment. PFS was defined as the time from randomization to death or disease progression, whichever occurred first. The median duration of PFS was estimated by Kaplan-Meier analysis and expressed in months. The 95% confidence interval (CI) was computed using the method of Brookmeyer and Crowley. Intent-to-Treat (ITT) Population: All randomized participants regardless of receiving any study drug.

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

End point timeframe:

From Baseline until death or disease progression; assessed every 6 weeks (maximum up to 45 months overall)

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Analyses were planned and reported for the separate Bevacizumab + mFOLFOX6 and Bevacizumab + FOLFIRI arms, not for all participants combined.

End point values	Bevacizumab + mFOLFOX6	Bevacizumab + FOLFIRI		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	188	188		
Units: months				
median (confidence interval 95%)	10.09 (8.8 to 11.56)	12.55 (10.48 to 14.29)		

## Statistical analyses

Statistical analysis title	Hazard Ratio
----------------------------	--------------

Statistical analysis description:

Analysis stratified by high/low ERCC-1 level and region of enrollment. Hazard ratio (HR, relative to Bevacizumab + mFOLFOX6) was estimated by Cox regression.

Comparison groups	Bevacizumab + mFOLFOX6 v Bevacizumab + FOLFIRI
Number of subjects included in analysis	376
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0555 <sup>[2]</sup>
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.79

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.61
upper limit	1.01

Notes:

[2] - P-value (relative to Bevacizumab + mFOLFOX6) based on two-sided stratified log rank test and not adjusted for multiple comparisons.

### Primary: PFS According to RECIST Version 1.1 in Participants With High ERCC-1 Levels

End point title	PFS According to RECIST Version 1.1 in Participants With High ERCC-1 Levels
-----------------	-----------------------------------------------------------------------------

End point description:

Tumor assessments were performed according to RECIST Version 1.1. Disease progression was defined as  $\geq 20\%$  increase in sum of LD of target lesions in reference to the smallest sum of LD on study, in addition to an absolute increase  $\geq 5$  mm. Disease progression was further defined as the last documented progression determined by the Investigator no later than 1 day before initiation of second-line therapy. Death on study included death from any cause occurring no later than 3 months after the last component of study treatment. PFS was defined as the time from randomization to death or disease progression, whichever occurred first. The median duration of PFS was estimated by Kaplan-Meier analysis and expressed in months. The 95% CI was computed using the method of Brookmeyer and Crowley. ITT Population. "Number of subjects analysed" reflects the number of evaluable participants for the outcome measure.

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

End point timeframe:

From Baseline until death or disease progression; assessed every 6 weeks (maximum up to 45 months overall)

End point values	Bevacizumab + mFOLFOX6 (ERCC-1 High)	Bevacizumab + FOLFIRI (ERCC-1 High)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	64	67		
Units: months				
median (confidence interval 95%)	9.92 (8.51 to 12.48)	11.17 (9.1 to 17.84)		

### Statistical analyses

Statistical analysis title	Hazard Ratio
----------------------------	--------------

Statistical analysis description:

Analysis stratified by region of enrollment. HR (relative to Bevacizumab + mFOLFOX6) was estimated by Cox regression.

Comparison groups	Bevacizumab + mFOLFOX6 (ERCC-1 High) v Bevacizumab + FOLFIRI (ERCC-1 High)
-------------------	----------------------------------------------------------------------------

Number of subjects included in analysis	131
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.3944 <sup>[3]</sup>
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.84
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.56
upper limit	1.26

Notes:

[3] - P-value (relative to Bevacizumab + mFOLFOX6) based on two-sided stratified log rank test and not adjusted for multiple comparisons.

### Primary: PFS According to RECIST Version 1.1 in Participants With Low ERCC-1 Levels

End point title	PFS According to RECIST Version 1.1 in Participants With Low ERCC-1 Levels
-----------------	----------------------------------------------------------------------------

End point description:

Tumor assessments were performed according to RECIST Version 1.1. Disease progression was defined as ≥20% increase in sum of LD of target lesions in reference to the smallest sum of LD on study, in addition to an absolute increase ≥5 mm. Disease progression was further defined as the last documented progression determined by the Investigator no later than 1 day before initiation of second-line therapy. Death on study included death from any cause occurring no later than 3 months after the last component of study treatment. PFS was defined as the time from randomization to death or disease progression, whichever occurred first. The median duration of PFS was estimated by Kaplan-Meier analysis and expressed in months. The 95% CI was computed using the method of Brookmeyer and Crowley. ITT Population. "Number of subjects analysed" reflects the number of evaluable participants for the outcome measure.

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

End point timeframe:

From Baseline until death or disease progression; assessed every 6 weeks (maximum up to 45 months overall)

End point values	Bevacizumab + mFOLFOX6 (ERCC-1 Low)	Bevacizumab + FOLFIRI (ERCC-1 Low)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	124	120		
Units: months				
median (confidence interval 95%)	10.97 (8.54 to 12.29)	12.68 (10.48 to 14.49)		

### Statistical analyses

Statistical analysis title	Hazard Ratio
----------------------------	--------------

Statistical analysis description:

Analysis stratified by region of enrollment. HR (relative to Bevacizumab + mFOLFOX6) was estimated by Cox regression.



Comparison groups	Bevacizumab + mFOLFOX6 (ERCC-1 Low) v Bevacizumab + FOLFIRI (ERCC-1 Low)
Number of subjects included in analysis	244
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0786 <sup>[4]</sup>
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.76
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.55
upper limit	1.03

Notes:

[4] - P-value (relative to Bevacizumab + mFOLFOX6) based on two-sided stratified log rank test and not adjusted for multiple comparisons.

### Primary: PFS According to RECIST Version 1.1 in Participants With High ERCC-1 Levels Versus Participants With Low ERCC-1 Levels

End point title	PFS According to RECIST Version 1.1 in Participants With High ERCC-1 Levels Versus Participants With Low ERCC-1 Levels
-----------------	------------------------------------------------------------------------------------------------------------------------

End point description:

Tumor assessments were performed according to RECIST Version 1.1. Disease progression was defined as ≥20% increase in sum of LD of target lesions in reference to the smallest sum of LD on study, in addition to an absolute increase ≥5 mm. Disease progression was further defined as the last documented progression determined by the Investigator no later than 1 day before initiation of second-line therapy. Death on study included death from any cause occurring no later than 3 months after the last component of study treatment. PFS was defined as the time from randomization to death or disease progression, whichever occurred first. The median duration of PFS was estimated by Kaplan-Meier analysis and expressed in months. The 95% CI was computed using the method of Brookmeyer and Crowley. ITT Population. "Number of subjects analysed" reflects the number of evaluable participants for the outcome measure.

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

End point timeframe:

From Baseline until death or disease progression (maximum up to 45 months overall)

End point values	Bevacizumab + mFOLFOX/FOLFIRI (ERCC-1 High)	Bevacizumab + mFOLFOX/FOLFIRI (ERCC-1 Low)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	131	244		
Units: months				
median (confidence interval 95%)	10.87 (9.1 to 12.68)	11.56 (9.95 to 12.98)		

### Statistical analyses

Statistical analysis title	Hazard Ratio
----------------------------	--------------

# Statistical analysis description:

Analysis stratified by region of enrollment. HR (relative to ERCC-1 Low subgroup) was estimated by Cox regression.

Comparison groups	Bevacizumab + mFOLFOX/FOLFIRI (ERCC-1 High) v Bevacizumab + mFOLFOX/FOLFIRI (ERCC-1 Low)
Number of subjects included in analysis	375
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.9576 <sup>[5]</sup>
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.99
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.77
upper limit	1.28

## Notes:

[5] - P-value (relative to ERCC-1 Low subgroup) based on two-sided stratified log rank test and not adjusted for multiple comparisons.

## Primary: PFS According to RECIST Version 1.1 in Participants With High VEGF-A Levels Versus Participants With Low VEGF-A Levels

End point title	PFS According to RECIST Version 1.1 in Participants With High VEGF-A Levels Versus Participants With Low VEGF-A Levels
-----------------	------------------------------------------------------------------------------------------------------------------------

## End point description:

Tumor assessments were performed according to RECIST Version 1.1. Disease progression was defined as  $\geq 20\%$  increase in sum of LD of target lesions in reference to the smallest sum of LD on study, in addition to an absolute increase  $\geq 5$  mm. Disease progression was further defined as the last documented progression determined by the Investigator no later than 1 day before initiation of second-line therapy. Death on study included death from any cause occurring no later than 3 months after the last component of study treatment. PFS was defined as the time from randomization to death or disease progression, whichever occurred first. The median duration of PFS was estimated by Kaplan-Meier analysis and expressed in months. The 95% CI was computed using the method of Brookmeyer and Crowley. ITT Population. "Number of subjects analysed" reflects the number of evaluable participants for the outcome measure.

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

## End point timeframe:

From Baseline until death or disease progression; assessed every 6 weeks (maximum up to 45 months overall)

End point values	Bevacizumab + mFOLFOX/FOLFIRI (VEGF-A High)	Bevacizumab + mFOLFOX/FOLFIRI (VEGF-A Low)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	185	185		
Units: months				
median (confidence interval 95%)	10.02 (8.8 to 11.17)	12.68 (10.9 to 14.26)		

## Statistical analyses

Statistical analysis title	Hazard Ratio
Statistical analysis description:	
Analysis stratified by high/low ERCC-1 level and region of enrollment. HR (relative to VEGF-A Low subgroup) was estimated by Cox regression.	
Comparison groups	Bevacizumab + mFOLFOX/FOLFIRI (VEGF-A High) v Bevacizumab + mFOLFOX/FOLFIRI (VEGF-A Low)
Number of subjects included in analysis	370
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1658 <sup>[6]</sup>
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.93
upper limit	1.53

Notes:

[6] - P-value (relative to VEGF-A Low subgroup) based on two-sided stratified log rank test and not adjusted for multiple comparisons.

## Secondary: PFS According to RECIST Version 1.1 in Participants With High ERCC-1 and High VEGF-A Levels

End point title	PFS According to RECIST Version 1.1 in Participants With High ERCC-1 and High VEGF-A Levels
End point description:	
Tumor assessments were performed according to RECIST Version 1.1. Disease progression was defined as $\geq 20\%$ increase in sum of LD of target lesions in reference to the smallest sum of LD on study, in addition to an absolute increase $\geq 5$ mm. Disease progression was further defined as the last documented progression determined by the Investigator no later than 1 day before initiation of second-line therapy. Death on study included death from any cause occurring no later than 3 months after the last component of study treatment. PFS was defined as the time from randomization to death or disease progression, whichever occurred first. The median duration of PFS was estimated by Kaplan-Meier analysis and expressed in months. The 95% CI was computed using the method of Brookmeyer and Crowley. ITT Population. "Number of subjects analysed" reflects the number of evaluable participants for the outcome measure.	
End point type	Secondary
End point timeframe:	
From Baseline until death or disease progression; assessed every 6 weeks (maximum up to 45 months overall)	

End point values	Bevacizumab + mFOLFOX6 (ERCC-1 High, VEGF-A High)	Bevacizumab + FOLFIRI (ERCC-1 High, VEGF-A High)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	28	31		
Units: months				
median (confidence interval 95%)	8.8 (5.91 to 10.02)	11.17 (8.11 to 18.07)		

## Statistical analyses

<b>Statistical analysis title</b>	Hazard Ratio Stratified
Statistical analysis description: Analysis stratified by region of enrollment. HR (relative to Bevacizumab + mFOLFOX6) was estimated by Cox regression.	
Comparison groups	Bevacizumab + mFOLFOX6 (ERCC-1 High, VEGF-A High) v Bevacizumab + FOLFIRI (ERCC-1 High, VEGF-A High)
Number of subjects included in analysis	59
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.3019 <sup>[7]</sup>
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.73
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.41
upper limit	1.32

Notes:

[7] - P-value (relative to Bevacizumab + mFOLFOX6) based on two-sided stratified log rank test and not adjusted for multiple comparisons.

<b>Statistical analysis title</b>	Hazard Ratio Unstratified
Statistical analysis description: Unstratified analysis. HR (relative to Bevacizumab + mFOLFOX6) was estimated by Cox regression.	
Comparison groups	Bevacizumab + mFOLFOX6 (ERCC-1 High, VEGF-A High) v Bevacizumab + FOLFIRI (ERCC-1 High, VEGF-A High)
Number of subjects included in analysis	59
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.5308 <sup>[8]</sup>
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.47
upper limit	1.47

Notes:

[8] - P-value (relative to Bevacizumab + mFOLFOX6) based on two-sided unstratified log rank test and not adjusted for multiple comparisons.

## Secondary: PFS According to RECIST Version 1.1 in Participants With High ERCC-1 and Low VEGF-A Levels

End point title	PFS According to RECIST Version 1.1 in Participants With High ERCC-1 and Low VEGF-A Levels
End point description:	
Tumor assessments were performed according to RECIST Version 1.1. Disease progression was defined as $\geq 20\%$ increase in sum of LD of target lesions in reference to the smallest sum of LD on study, in addition to an absolute increase $\geq 5$ mm. Disease progression was further defined as the last documented progression determined by the Investigator no later than 1 day before initiation of second-line therapy. Death on study included death from any cause occurring no later than 3 months after the last component of study treatment. PFS was defined as the time from randomization to death or disease progression, whichever occurred first. The median duration of PFS was estimated by Kaplan-Meier analysis and expressed in months. The 95% CI was computed using the method of Brookmeyer and Crowley. ITT Population. "Number of subjects analysed" reflects the number of evaluable participants for the outcome measure.	
End point type	Secondary
End point timeframe:	
From Baseline until death or disease progression; assessed every 6 weeks (maximum up to 45 months overall)	

<b>End point values</b>	Bevacizumab + mFOLFOX6 (ERCC-1 High, VEGF-A Low)	Bevacizumab + FOLFIRI (ERCC-1 High, VEGF-A Low)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	35	35		
Units: months				
median (confidence interval 95%)	12.52 (9.43 to 15.64)	12.68 (8.18 to 20.83)		

## Statistical analyses

<b>Statistical analysis title</b>	Hazard Ratio Stratified
Statistical analysis description:	
Analysis stratified by region of enrollment. HR (relative to Bevacizumab + mFOLFOX6) was estimated by Cox regression.	
Comparison groups	Bevacizumab + mFOLFOX6 (ERCC-1 High, VEGF-A Low) v Bevacizumab + FOLFIRI (ERCC-1 High, VEGF-A Low)
Number of subjects included in analysis	70
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.6035 <sup>[9]</sup>
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.86
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.48
upper limit	1.53

Notes:

[9] - P-value (relative to Bevacizumab + mFOLFOX6) based on two-sided stratified log rank test and not adjusted for multiple comparisons.

<b>Statistical analysis title</b>	Hazard Ratio Unstratified
Statistical analysis description: Unstratified analysis. HR (relative to Bevacizumab + mFOLFOX6) was estimated by Cox regression.	
Comparison groups	Bevacizumab + mFOLFOX6 (ERCC-1 High, VEGF-A Low) v Bevacizumab + FOLFIRI (ERCC-1 High, VEGF-A Low)
Number of subjects included in analysis	70
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.5026 <sup>[10]</sup>
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.82
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.46
upper limit	1.46

Notes:

[10] - P-value (relative to Bevacizumab + mFOLFOX6) based on two-sided unstratified log rank test and not adjusted for multiple comparisons.

### Secondary: PFS According to RECIST Version 1.1 in Participants With Low ERCC-1 and High VEGF-A Levels

End point title	PFS According to RECIST Version 1.1 in Participants With Low ERCC-1 and High VEGF-A Levels
-----------------	--------------------------------------------------------------------------------------------

End point description:

Tumor assessments were performed according to RECIST Version 1.1. Disease progression was defined as ≥20% increase in sum of LD of target lesions in reference to the smallest sum of LD on study, in addition to an absolute increase ≥5 mm. Disease progression was further defined as the last documented progression determined by the Investigator no later than 1 day before initiation of second-line therapy. Death on study included death from any cause occurring no later than 3 months after the last component of study treatment. PFS was defined as the time from randomization to death or disease progression, whichever occurred first. The median duration of PFS was estimated by Kaplan-Meier analysis and expressed in months. The 95% CI was computed using the method of Brookmeyer and Crowley. ITT Population. "Number of subjects analysed" reflects the number of evaluable participants for the outcome measure.

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

End point timeframe:

From Baseline until death or disease progression; assessed every 6 weeks (maximum up to 45 months overall)

<b>End point values</b>	Bevacizumab + mFOLFOX6 (ERCC-1 Low, VEGF-A High)	Bevacizumab + FOLFIRI (ERCC-1 Low, VEGF-A High)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	66	59		
Units: months				
median (confidence interval 95%)	9.76 (8.18 to 12.45)	11.07 (8.18 to 14.29)		

## Statistical analyses

Statistical analysis title	Hazard Ratio Stratified
Statistical analysis description: Analysis stratified by region of enrollment. HR (relative to Bevacizumab + mFOLFOX6) was estimated by Cox regression.	
Comparison groups	Bevacizumab + mFOLFOX6 (ERCC-1 Low, VEGF-A High) v Bevacizumab + FOLFIRI (ERCC-1 Low, VEGF-A High)
Number of subjects included in analysis	125
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.4032 <sup>[11]</sup>
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.54
upper limit	1.28

Notes:

[11] - P-value (relative to Bevacizumab + mFOLFOX6) based on two-sided stratified log rank test and not adjusted for multiple comparisons.

Statistical analysis title	Hazard Ratio Unstratified
Statistical analysis description: Unstratified analysis. HR (relative to Bevacizumab + mFOLFOX6) was estimated by Cox regression.	
Comparison groups	Bevacizumab + mFOLFOX6 (ERCC-1 Low, VEGF-A High) v Bevacizumab + FOLFIRI (ERCC-1 Low, VEGF-A High)
Number of subjects included in analysis	125
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.235 <sup>[12]</sup>
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.77
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.51
upper limit	1.18

Notes:

[12] - P-value (relative to Bevacizumab + mFOLFOX6) based on two-sided unstratified log rank test and not adjusted for multiple comparisons.

## Secondary: PFS According to RECIST Version 1.1 in Participants With Low ERCC-1 and Low VEGF-A Levels

End point title	PFS According to RECIST Version 1.1 in Participants With Low ERCC-1 and Low VEGF-A Levels
-----------------	-------------------------------------------------------------------------------------------

End point description:

Tumor assessments were performed according to RECIST Version 1.1. Disease progression was defined as  $\geq 20\%$  increase in sum of LD of target lesions in reference to the smallest sum of LD on study, in addition to an absolute increase  $\geq 5$  mm. Disease progression was further defined as the last documented progression determined by the Investigator no later than 1 day before initiation of second-line therapy. Death on study included death from any cause occurring no later than 3 months after the last component of study treatment. PFS was defined as the time from randomization to death or disease

progression, whichever occurred first. The median duration of PFS was estimated by Kaplan-Meier analysis and expressed in months. The 95% CI was computed using the method of Brookmeyer and Crowley. ITT Population. "Number of subjects analysed" reflects the number of evaluable participants for the outcome measure.

End point type	Secondary
End point timeframe:	
From Baseline until death or disease progression; assessed every 6 weeks (maximum up to 45 months overall)	

End point values	Bevacizumab + mFOLFOX6 (ERCC-1 Low, VEGF-A Low)	Bevacizumab + FOLFIRI (ERCC-1 Low, VEGF-A Low)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	55	60		
Units: months				
median (confidence interval 95%)	11.1 (8.54 to 13.08)	14.32 (11.56 to 14.98)		

## Statistical analyses

<b>Statistical analysis title</b>	Hazard Ratio Stratified
-----------------------------------	-------------------------

Statistical analysis description:

Analysis stratified by region of enrollment. HR (relative to Bevacizumab + mFOLFOX6) was estimated by Cox regression.

Comparison groups	Bevacizumab + mFOLFOX6 (ERCC-1 Low, VEGF-A Low) v Bevacizumab + FOLFIRI (ERCC-1 Low, VEGF-A Low)
Number of subjects included in analysis	115
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0647 <sup>[13]</sup>
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.65
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.41
upper limit	1.03

Notes:

[13] - P-value (relative to Bevacizumab + mFOLFOX6) based on two-sided stratified log rank test and not adjusted for multiple comparisons.

<b>Statistical analysis title</b>	Hazard Ratio Unstratified
-----------------------------------	---------------------------

Statistical analysis description:

Unstratified analysis. HR (relative to Bevacizumab + mFOLFOX6) was estimated by Cox regression.

Comparison groups	Bevacizumab + mFOLFOX6 (ERCC-1 Low, VEGF-A Low) v Bevacizumab + FOLFIRI (ERCC-1 Low, VEGF-A Low)
-------------------	--------------------------------------------------------------------------------------------------



Number of subjects included in analysis	115
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0856 <sup>[14]</sup>
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.67
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.43
upper limit	1.06

Notes:

[14] - P-value (relative to Bevacizumab + mFOLFOX6) based on two-sided unstratified log rank test and not adjusted for multiple comparisons.

## Secondary: Overall Survival (OS)

End point title	Overall Survival (OS) <sup>[15]</sup>
End point description:	Death on study included death from any cause occurring no later than 3 months after the last component of study treatment. OS was defined as the time from randomization to death. The median duration of OS was estimated by Kaplan-Meier analysis and expressed in months. The 95% CI was computed using the method of Brookmeyer and Crowley. ITT Population.
End point type	Secondary
End point timeframe:	From Baseline until death (maximum up to 45 months overall)

Notes:

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

Justification: Analyses were planned and reported for the separate Bevacizumab + mFOLFOX6 and Bevacizumab + FOLFIRI arms, not for all participants combined.

End point values	Bevacizumab + mFOLFOX6	Bevacizumab + FOLFIRI		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	188	188		
Units: months				
median (confidence interval 95%)	23.85 (20.4 to 26.05)	27.47 (24.64 to 36.73)		

## Statistical analyses

Statistical analysis title	Hazard Ratio
Statistical analysis description:	Analysis stratified by high/low ERCC-1 level and region of enrollment. HR (relative to Bevacizumab + mFOLFOX6) was estimated by Cox regression.
Comparison groups	Bevacizumab + mFOLFOX6 v Bevacizumab + FOLFIRI

Number of subjects included in analysis	376
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0861 <sup>[16]</sup>
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.76
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.56
upper limit	1.04

Notes:

[16] - P-value (relative to Bevacizumab + mFOLFOX6) based on two-sided stratified log rank test and not adjusted for multiple comparisons.

## Secondary: OS in Participants With High ERCC-1 Levels

End point title	OS in Participants With High ERCC-1 Levels
End point description:	
Death on study included death from any cause occurring no later than 3 months after the last component of study treatment. OS was defined as the time from randomization to death. The median duration of OS was estimated by Kaplan-Meier analysis and expressed in months. The 95% CI was computed using the method of Brookmeyer and Crowley. ITT Population. "Number of subjects analysed" reflects the number of evaluable participants for the outcome measure.	
End point type	Secondary
End point timeframe:	
From Baseline until death (maximum up to 45 months overall)	

End point values	Bevacizumab + mFOLFOX6 (ERCC-1 High)	Bevacizumab + FOLFIRI (ERCC-1 High)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	64	67		
Units: months				
median (confidence interval 95%)	22.54 (17.02 to 26.05)	26.51 (19.09 to 36.73)		

## Statistical analyses

Statistical analysis title	Hazard Ratio
Statistical analysis description:	
Analysis stratified by region of enrollment. HR (relative to Bevacizumab + mFOLFOX6) was estimated by Cox regression.	
Comparison groups	Bevacizumab + FOLFIRI (ERCC-1 High) v Bevacizumab + mFOLFOX6 (ERCC-1 High)

Number of subjects included in analysis	131
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.3295 <sup>[17]</sup>
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.51
upper limit	1.26

Notes:

[17] - P-value (relative to Bevacizumab + mFOLFOX6) based on two-sided stratified log rank test and not adjusted for multiple comparisons.

## Secondary: OS in Participants With Low ERCC-1 Levels

End point title	OS in Participants With Low ERCC-1 Levels
End point description:	
Death on study included death from any cause occurring no later than 3 months after the last component of study treatment. OS was defined as the time from randomization to death. The median duration of OS was estimated by Kaplan-Meier analysis and expressed in months. The 95% CI was computed using the method of Brookmeyer and Crowley. ITT Population. "Number of subjects analysed" reflects the number of evaluable participants for the outcome measure.	
End point type	Secondary
End point timeframe:	
From Baseline until death (maximum up to 45 months overall)	

End point values	Bevacizumab + mFOLFOX6 (ERCC-1 Low)	Bevacizumab + FOLFIRI (ERCC-1 Low)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	124	120		
Units: months				
median (confidence interval 95%)	25.53 (20.4 to 28.75)	27.93 (24.97 to 38.44)		

## Statistical analyses

Statistical analysis title	Hazard Ratio
Statistical analysis description:	
Analysis stratified by region of enrollment. HR (relative to Bevacizumab + mFOLFOX6) was estimated by Cox regression.	
Comparison groups	Bevacizumab + mFOLFOX6 (ERCC-1 Low) v Bevacizumab + FOLFIRI (ERCC-1 Low)

Number of subjects included in analysis	244
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1519 <sup>[18]</sup>
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.74
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.49
upper limit	1.12

Notes:

[18] - P-value (relative to Bevacizumab + mFOLFOX6) based on two-sided stratified log rank test and not adjusted for multiple comparisons.

### Secondary: OS in Participants With High ERCC-1 Levels Versus Participants With Low ERCC-1 Levels

End point title	OS in Participants With High ERCC-1 Levels Versus Participants With Low ERCC-1 Levels
-----------------	---------------------------------------------------------------------------------------

End point description:

Death on study included death from any cause occurring no later than 3 months after the last component of study treatment. OS was defined as the time from randomization to death. The median duration of OS was estimated by Kaplan-Meier analysis and expressed in months. The 95% CI was computed using the method of Brookmeyer and Crowley. ITT Population. "Number of subjects analysed" reflects the number of evaluable participants for the outcome measure.

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

End point timeframe:

From Baseline until death (maximum up to 45 months overall)

End point values	Bevacizumab + mFOLFOX/FOLFIRI (ERCC-1 High)	Bevacizumab + mFOLFOX/FOLFIRI (ERCC-1 Low)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	131	244		
Units: months				
median (confidence interval 95%)	23.23 (19.09 to 26.94)	27.27 (24.34 to 31.28)		

### Statistical analyses

Statistical analysis title	Hazard Ratio
----------------------------	--------------

Statistical analysis description:

Analysis stratified by region of enrollment. HR (relative to ERCC-1 Low subgroup) was estimated by Cox regression.

Comparison groups	Bevacizumab + mFOLFOX/FOLFIRI (ERCC-1 High) v Bevacizumab + mFOLFOX/FOLFIRI (ERCC-1 Low)
-------------------	------------------------------------------------------------------------------------------

Number of subjects included in analysis	375
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.2774 <sup>[19]</sup>
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.87
upper limit	1.62

Notes:

[19] - P-value (relative to ERCC-1 Low subgroup) based on two-sided stratified log rank test and not adjusted for multiple comparisons.

## Secondary: Percentage of Participants With Objective Response According to RECIST Version 1.1

End point title	Percentage of Participants With Objective Response According to RECIST Version 1.1 <sup>[20]</sup>
-----------------	----------------------------------------------------------------------------------------------------

End point description:

Objective response was defined as complete response (CR) or partial response (PR) according to RECIST Version 1.1. CR was defined as disappearance of all target lesions and short-axis reduction to less than (<) 10 mm of any pathological lymph nodes. PR was defined as ≥30% decrease in sum of LD of target lesions in reference to sum of LD at Baseline. Confirmation of response at a consecutive assessment was not required. The percentage of participants with CR or PR was reported. The 95% CI was computed using normal approximation to the binomial distribution. ITT Population.

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

End point timeframe:

From Baseline until disease progression; assessed every 6 weeks (maximum up to 45 months overall)

Notes:

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

Justification: Analyses were planned and reported for the separate Bevacizumab + mFOLFOX6 and Bevacizumab + FOLFIRI arms, not for all participants combined.

End point values	Bevacizumab + mFOLFOX6	Bevacizumab + FOLFIRI		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	188	188		
Units: percentage of participants				
number (confidence interval 95%)	61.2 (54.2 to 68.1)	65.4 (58.6 to 72.2)		

## Statistical analyses

Statistical analysis title	Difference in Objective Response Rates
----------------------------	----------------------------------------

Statistical analysis description:

The difference was calculated as the percentage of participants with objective response in the Bevacizumab + FOLFIRI arm minus the Bevacizumab + mFOLFOX6 arm. The 95% CI was computed using normal approximation to the binomial distribution.

Comparison groups	Bevacizumab + mFOLFOX6 v Bevacizumab + FOLFIRI
-------------------	------------------------------------------------

Number of subjects included in analysis	376
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference in objective response rates
Point estimate	4.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.5
upper limit	14

### Secondary: Percentage of Participants With Objective Response According to RECIST Version 1.1 in Participants With High ERCC-1 Levels

End point title	Percentage of Participants With Objective Response According to RECIST Version 1.1 in Participants With High ERCC-1 Levels
-----------------	----------------------------------------------------------------------------------------------------------------------------

End point description:

Objective response was defined as CR or PR according to RECIST Version 1.1. CR was defined as disappearance of all target lesions and short-axis reduction to <10 mm of any pathological lymph nodes. PR was defined as  $\geq 30\%$  decrease in sum of LD of target lesions in reference to sum of LD at Baseline. Confirmation of response at a consecutive assessment was not required. The percentage of participants with CR or PR was reported. The 95% CI was computed using normal approximation to the binomial distribution. ITT Population. "Number of subjects analysed" reflects the number of evaluable participants for the outcome measure.

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

End point timeframe:

From Baseline until disease progression; assessed every 6 weeks (maximum up to 45 months overall)

End point values	Bevacizumab + mFOLFOX6 (ERCC-1 High)	Bevacizumab + FOLFIRI (ERCC-1 High)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	64	67		
Units: percentage of participants				
number (confidence interval 95%)	56.3 (44.1 to 68.4)	65.7 (54.3 to 77)		

### Statistical analyses

Statistical analysis title	Difference in Objective Response Rates
----------------------------	----------------------------------------

Statistical analysis description:

The difference was calculated as the percentage of participants with objective response in the Bevacizumab + FOLFIRI arm minus the Bevacizumab + mFOLFOX6 arm. The 95% CI was computed using normal approximation to the binomial distribution.

Comparison groups	Bevacizumab + mFOLFOX6 (ERCC-1 High) v Bevacizumab + FOLFIRI (ERCC-1 High)
-------------------	----------------------------------------------------------------------------

Number of subjects included in analysis	131
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference in objective response rates
Point estimate	9.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	7.2
upper limit	26.1

### Secondary: Percentage of Participants With Objective Response According to RECIST Version 1.1 in Participants With Low ERCC-1 Levels

End point title	Percentage of Participants With Objective Response According to RECIST Version 1.1 in Participants With Low ERCC-1 Levels
-----------------	---------------------------------------------------------------------------------------------------------------------------

End point description:

Objective response was defined as CR or PR according to RECIST Version 1.1. CR was defined as disappearance of all target lesions and short-axis reduction to <10 mm of any pathological lymph nodes. PR was defined as  $\geq 30\%$  decrease in sum of LD of target lesions in reference to sum of LD at Baseline. Confirmation of response at a consecutive assessment was not required. The percentage of participants with CR or PR was reported. The 95% CI was computed using normal approximation to the binomial distribution. ITT Population. "Number of subjects analysed" reflects the number of evaluable participants for the outcome measure.

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

End point timeframe:

From Baseline until disease progression; assessed every 6 weeks (maximum up to 45 months overall)

End point values	Bevacizumab + mFOLFOX6 (ERCC-1 Low)	Bevacizumab + FOLFIRI (ERCC-1 Low)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	124	120		
Units: percentage of participants				
number (confidence interval 95%)	63.7 (55.2 to 72.2)	65.8 (57.3 to 74.3)		

### Statistical analyses

Statistical analysis title	Difference in Objective Response Rates
----------------------------	----------------------------------------

Statistical analysis description:

The difference was calculated as the percentage of participants with objective response in the Bevacizumab + FOLFIRI arm minus the Bevacizumab + mFOLFOX6 arm. The 95% CI was computed using normal approximation to the binomial distribution.

Comparison groups	Bevacizumab + mFOLFOX6 (ERCC-1 Low) v Bevacizumab + FOLFIRI (ERCC-1 Low)
-------------------	--------------------------------------------------------------------------

Number of subjects included in analysis	244
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference in objective response rates
Point estimate	2.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.9
upper limit	14.1

### Secondary: Percentage of Participants With Objective Response According to RECIST Version 1.1 in Participants With High ERCC-1 Levels Versus Participants With Low ERCC-1 Levels

End point title	Percentage of Participants With Objective Response According to RECIST Version 1.1 in Participants With High ERCC-1 Levels Versus Participants With Low ERCC-1 Levels
-----------------	-----------------------------------------------------------------------------------------------------------------------------------------------------------------------

#### End point description:

Objective response was defined as CR or PR according to RECIST Version 1.1. CR was defined as disappearance of all target lesions and short-axis reduction to <10 mm of any pathological lymph nodes. PR was defined as ≥30% decrease in sum of LD of target lesions in reference to sum of LD at Baseline. Confirmation of response at a consecutive assessment was not required. The percentage of participants with CR or PR was reported. The 95% CI was computed using normal approximation to the binomial distribution. ITT Population. "Number of subjects analysed" reflects the number of evaluable participants for the outcome measure.

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

#### End point timeframe:

From Baseline until disease progression; assessed every 6 weeks (maximum up to 45 months overall)

End point values	Bevacizumab + mFOLFOX/FOLFIRI (ERCC-1 High)	Bevacizumab + mFOLFOX/FOLFIRI (ERCC-1 Low)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	131	244		
Units: percentage of participants				
number (confidence interval 95%)	61.1 (52.7 to 69.4)	64.8 (58.8 to 70.7)		

### Statistical analyses

Statistical analysis title	Difference in Objective Response Rates
----------------------------	----------------------------------------

#### Statistical analysis description:

The difference was calculated as the percentage of participants with objective response in the ERCC-1 High subgroup minus the ERCC-1 Low subgroup. The 95% CI was computed using normal approximation to the binomial distribution.

Comparison groups	Bevacizumab + mFOLFOX/FOLFIRI (ERCC-1 High) v Bevacizumab + mFOLFOX/FOLFIRI (ERCC-1 Low)
-------------------	---------------------------------------------------------------------------------------------



Number of subjects included in analysis	375
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference in objective response rates
Point estimate	-3.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-14
upper limit	6.6

## Secondary: Percentage of Participants With Disease Control According to RECIST Version 1.1

End point title	Percentage of Participants With Disease Control According to RECIST Version 1.1 <sup>[21]</sup>
-----------------	-------------------------------------------------------------------------------------------------

### End point description:

Disease control was defined as CR, PR, or stable disease (SD) according to RECIST Version 1.1. CR was defined as disappearance of all target lesions and short-axis reduction to <10 mm of any pathological lymph nodes. PR was defined as  $\geq 30\%$  decrease in sum of LD of target lesions in reference to sum of LD at Baseline. Confirmation of response at a consecutive assessment was not required. SD was defined as neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for disease progression ( $\geq 20\%$  increase in sum of LD of target lesions plus absolute increase  $\geq 5$  mm) in reference to the smallest sum of LD on study. The percentage of participants with CR, PR, or SD was reported. The 95% CI was computed using normal approximation to the binomial distribution. ITT Population.

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

### End point timeframe:

From Baseline until disease progression; assessed every 6 weeks (maximum up to 45 months overall)

### Notes:

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

Justification: Analyses were planned and reported for the separate Bevacizumab + mFOLFOX6 and Bevacizumab + FOLFIRI arms, not for all participants combined.

End point values	Bevacizumab + mFOLFOX6	Bevacizumab + FOLFIRI		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	188	188		
Units: percentage of participants				
number (confidence interval 95%)	93.1 (89.5 to 96.7)	91 (86.9 to 95.1)		

## Statistical analyses

Statistical analysis title	Difference in Disease Control Rates
----------------------------	-------------------------------------

### Statistical analysis description:

The difference was calculated as the percentage of participants with disease control in the Bevacizumab + FOLFIRI arm minus the Bevacizumab + mFOLFOX6 arm. The 95% CI was computed using normal approximation to the binomial distribution.

Comparison groups	Bevacizumab + mFOLFOX6 v Bevacizumab + FOLFIRI
-------------------	------------------------------------------------

Number of subjects included in analysis	376
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference in response rates
Point estimate	2.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.6
upper limit	3.3

### Secondary: Percentage of Participants With Disease Control According to RECIST Version 1.1 in Participants With High ERCC-1 Levels

End point title	Percentage of Participants With Disease Control According to RECIST Version 1.1 in Participants With High ERCC-1 Levels
End point description:	Disease control was defined as CR, PR, or SD according to RECIST Version 1.1. CR was defined as disappearance of all target lesions and short-axis reduction to <10 mm of any pathological lymph nodes. PR was defined as ≥30% decrease in sum of LD of target lesions in reference to sum of LD at Baseline. Confirmation of response at a consecutive assessment was not required. SD was defined as neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for disease progression (≥20% increase in sum of LD of target lesions plus absolute increase ≥5 mm) in reference to the smallest sum of LD on study. The percentage of participants with CR, PR, or SD was reported. The 95% CI was computed using normal approximation to the binomial distribution. ITT Population. "Number of subjects analysed" reflects the number of evaluable participants for the outcome measure.
End point type	Secondary
End point timeframe:	From Baseline until disease progression; assessed every 6 weeks (maximum up to 45 months overall)

End point values	Bevacizumab + mFOLFOX6 (ERCC-1 High)	Bevacizumab + FOLFIRI (ERCC-1 High)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	64	67		
Units: percentage of participants				
number (confidence interval 95%)	93.8 (87.8 to 99.7)	85.1 (76.5 to 93.6)		

### Statistical analyses

Statistical analysis title	Difference in Disease Control Rates
Statistical analysis description:	The difference was calculated as the percentage of participants with disease control in the Bevacizumab + FOLFIRI arm minus the Bevacizumab + mFOLFOX6 arm. The 95% CI was computed using normal approximation to the binomial distribution.
Comparison groups	Bevacizumab + mFOLFOX6 (ERCC-1 High) v Bevacizumab + FOLFIRI (ERCC-1 High)

Number of subjects included in analysis	131
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference in disease control rates
Point estimate	-8.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-19.1
upper limit	1.7

### Secondary: Percentage of Participants With Disease Control According to RECIST Version 1.1 in Participants With Low ERCC-1 Levels

End point title	Percentage of Participants With Disease Control According to RECIST Version 1.1 in Participants With Low ERCC-1 Levels
End point description:	
Disease control was defined as CR, PR, or SD according to RECIST Version 1.1. CR was defined as disappearance of all target lesions and short-axis reduction to <10 mm of any pathological lymph nodes. PR was defined as ≥30% decrease in sum of LD of target lesions in reference to sum of LD at Baseline. Confirmation of response at a consecutive assessment was not required. SD was defined as neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for disease progression (≥20% increase in sum of LD of target lesions plus absolute increase ≥5 mm) in reference to the smallest sum of LD on study. The percentage of participants with CR, PR, or SD was reported. The 95% CI was computed using normal approximation to the binomial distribution. ITT Population. "Number of subjects analysed" reflects the number of evaluable participants for the outcome measure.	
End point type	Secondary
End point timeframe:	
From Baseline until disease progression; assessed every 6 weeks (maximum up to 45 months overall)	

End point values	Bevacizumab + mFOLFOX6 (ERCC-1 Low)	Bevacizumab + FOLFIRI (ERCC-1 Low)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	124	120		
Units: percentage of participants				
number (confidence interval 95%)	92.7 (88.2 to 97.3)	95 (91.1 to 98.9)		

### Statistical analyses

Statistical analysis title	Difference in Disease Control Rates
Statistical analysis description:	
The difference was calculated as the percentage of participants with disease control in the Bevacizumab + FOLFIRI arm minus the Bevacizumab + mFOLFOX6 arm. The 95% CI was computed using normal approximation to the binomial distribution.	
Comparison groups	Bevacizumab + mFOLFOX6 (ERCC-1 Low) v Bevacizumab + FOLFIRI (ERCC-1 Low)

Number of subjects included in analysis	244
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference in disease control rates
Point estimate	2.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.7
upper limit	8.3

### Secondary: Percentage of Participants With Disease Control According to RECIST Version 1.1 in Participants With High ERCC-1 Levels Versus Participants With Low ERCC-1 Levels

End point title	Percentage of Participants With Disease Control According to RECIST Version 1.1 in Participants With High ERCC-1 Levels Versus Participants With Low ERCC-1 Levels
-----------------	--------------------------------------------------------------------------------------------------------------------------------------------------------------------

#### End point description:

Disease control was defined as CR, PR, or SD according to RECIST Version 1.1. CR was defined as disappearance of all target lesions and short-axis reduction to <10 mm of any pathological lymph nodes. PR was defined as ≥30% decrease in sum of LD of target lesions in reference to sum of LD at Baseline. Confirmation of response at a consecutive assessment was not required. SD was defined as neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for disease progression (≥20% increase in sum of LD of target lesions plus absolute increase ≥5 mm) in reference to the smallest sum of LD on study. The percentage of participants with CR, PR, or SD was reported. The 95% CI was computed using normal approximation to the binomial distribution. ITT Population. "Number of subjects analysed" reflects the number of evaluable participants for the outcome measure.

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

#### End point timeframe:

From Baseline until disease progression; assessed every 6 weeks (maximum up to 45 months overall)

End point values	Bevacizumab + mFOLFOX/FOLFIRI (ERCC-1 High)	Bevacizumab + mFOLFOX/FOLFIRI (ERCC-1 Low)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	131	244		
Units: percentage of participants				
number (confidence interval 95%)	89.3 (84 to 94.6)	93.9 (90.8 to 96.9)		

### Statistical analyses

Statistical analysis title	Difference in Disease Control Rates
----------------------------	-------------------------------------

#### Statistical analysis description:

The difference was calculated as the percentage of participants with disease control in the ERCC-1 High subgroup minus the ERCC-1 Low subgroup. The 95% CI was computed using normal approximation to the binomial distribution.

Comparison groups	Bevacizumab + mFOLFOX/FOLFIRI (ERCC-1 High) v
-------------------	-----------------------------------------------

	Bevacizumab + mFOLFOX/FOLFIRI (ERCC-1 Low)
Number of subjects included in analysis	375
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference in disease control rates
Point estimate	-4.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.6
upper limit	1.5

## Secondary: Percentage of Participants With Liver Metastasis Resection

End point title	Percentage of Participants With Liver Metastasis Resection <sup>[22]</sup>
-----------------	----------------------------------------------------------------------------

End point description:

The timing of resective surgery was not defined in the protocol and was left at the discretion of the Investigator. Resection was classified as R0, R1, or R2 following surgery. R0 was defined as complete resection with clear margins  $\geq 1$  mm. R1 was defined as the presence of exposed tumor or histologically detected tumor cells at the line of transection, or  $<1$  mm microscopic margins. In the case of use of radiofrequency ablation or cryotherapy, the resection was considered as R1. R2 was defined as macroscopic positive margins or incomplete resection at time of surgery. The percentage of participants with resection of liver or liver plus lymph node metastases was reported. The 95% CI was computed using normal approximation to the binomial distribution. ITT Population; only those participants with liver or liver plus lymph node metastases were included in the analysis.

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

End point timeframe:

At time of resective surgery during study (maximum up to 45 months overall)

Notes:

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

Justification: Analyses were planned and reported for the separate Bevacizumab + mFOLFOX6 and Bevacizumab + FOLFIRI arms, not for all participants combined.

End point values	Bevacizumab + mFOLFOX6	Bevacizumab + FOLFIRI		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	67	55		
Units: percentage of participants				
number (confidence interval 95%)	14.9 (6.4 to 23.5)	10.9 (2.7 to 19.1)		

## Statistical analyses

Statistical analysis title	Difference in Resection Rates
----------------------------	-------------------------------

Statistical analysis description:

The difference was calculated as the percentage of participants with resection in the Bevacizumab + FOLFIRI arm minus the Bevacizumab + mFOLFOX6 arm. The 95% CI was computed using normal approximation to the binomial distribution.

Comparison groups	Bevacizumab + FOLFIRI v Bevacizumab + mFOLFOX6
-------------------	------------------------------------------------

Number of subjects included in analysis	122
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference in resection rates
Point estimate	-4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-15.9
upper limit	7.8

## Secondary: Percentage of Participants With Complete Liver Metastasis Resection

End point title	Percentage of Participants With Complete Liver Metastasis Resection <sup>[23]</sup>
-----------------	-------------------------------------------------------------------------------------

End point description:

The timing of resective surgery was not defined in the protocol and was left at the discretion of the Investigator. Resection was classified as R0, R1, or R2 following surgery. R0 was defined as complete resection with clear margins  $\geq 1$  mm. The percentage of participants with R0 resection of liver or liver plus lymph node metastases was reported. The 95% CI was computed using normal approximation to the binomial distribution. ITT Population; only those participants with liver or liver plus lymph node metastases were included in the analysis.

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

End point timeframe:

At time of resective surgery during study (maximum up to 45 months overall)

Notes:

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

Justification: Analyses were planned and reported for the separate Bevacizumab + mFOLFOX6 and Bevacizumab + FOLFIRI arms, not for all participants combined.

End point values	Bevacizumab + mFOLFOX6	Bevacizumab + FOLFIRI		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	67	55		
Units: percentage of participants				
number (confidence interval 95%)	11.9 (4.2 to 19.7)	5.5 (0 to 11.5)		

## Statistical analyses

Statistical analysis title	Difference in Complete Resection Rates
----------------------------	----------------------------------------

Statistical analysis description:

The difference was calculated as the percentage of participants with complete resection in the Bevacizumab + FOLFIRI arm minus the Bevacizumab + mFOLFOX6 arm. The 95% CI was computed using normal approximation to the binomial distribution.

Comparison groups	Bevacizumab + mFOLFOX6 v Bevacizumab + FOLFIRI
-------------------	------------------------------------------------

Number of subjects included in analysis	122
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference in complete resection rates
Point estimate	-6.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-16.3
upper limit	3.3

## Secondary: Percentage of Participants With Liver Metastasis Resection in Participants With High ERCC-1 Levels

End point title	Percentage of Participants With Liver Metastasis Resection in Participants With High ERCC-1 Levels
-----------------	----------------------------------------------------------------------------------------------------

### End point description:

The timing of resective surgery was not defined in the protocol and was left at the discretion of the Investigator. Resection was classified as R0, R1, or R2 following surgery. R0 was defined as complete resection with clear margins  $\geq 1$  mm. R1 was defined as the presence of exposed tumor or histologically detected tumor cells at the line of transection, or  $<1$  mm microscopic margins. In the case of use of radiofrequency ablation or cryotherapy, the resection was considered as R1. R2 was defined as macroscopic positive margins or incomplete resection at time of surgery. The percentage of participants with resection of liver or liver plus lymph node metastases was reported. The 95% CI was computed using normal approximation to the binomial distribution. ITT Population; only those participants with liver or liver plus lymph node metastases were included in the analysis. "Number of subjects analysed" reflects the number of evaluable participants for the outcome measure.

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

### End point timeframe:

At time of resective surgery during study (maximum up to 45 months overall)

End point values	Bevacizumab + mFOLFOX6 (ERCC-1 High)	Bevacizumab + FOLFIRI (ERCC-1 High)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	17	15		
Units: percentage of participants				
number (confidence interval 95%)	17.6 (0 to 35.8)	6.7 (0 to 19.3)		

## Statistical analyses

Statistical analysis title	Difference in Resection Rates
----------------------------	-------------------------------

### Statistical analysis description:

The difference was calculated as the percentage of participants with resection in the Bevacizumab + FOLFIRI arm minus the Bevacizumab + mFOLFOX6 arm. The 95% CI was computed using normal approximation to the binomial distribution.

Comparison groups	Bevacizumab + mFOLFOX6 (ERCC-1 High) v Bevacizumab + FOLFIRI (ERCC-1 High)
-------------------	----------------------------------------------------------------------------

Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference in resection rates
Point estimate	-11
Confidence interval	
level	95 %
sides	2-sided
lower limit	-33.1
upper limit	11.1

### Secondary: Percentage of Participants With Complete Liver Metastasis Resection in Participants With High ERCC-1 Levels

End point title	Percentage of Participants With Complete Liver Metastasis Resection in Participants With High ERCC-1 Levels
End point description:	
The timing of resective surgery was not defined in the protocol and was left at the discretion of the Investigator. Resection was classified as R0, R1, or R2 following surgery. R0 was defined as complete resection with clear margins $\geq 1$ mm. The percentage of participants with R0 resection of liver or liver plus lymph node metastases was reported. The 95% CI was computed using normal approximation to the binomial distribution. ITT Population; only those participants with liver or liver plus lymph node metastases were included in the analysis. "Number of subjects analysed" reflects the number of evaluable participants for the outcome measure.	
End point type	Secondary
End point timeframe:	
At time of resective surgery during study (maximum up to 45 months overall)	

End point values	Bevacizumab + mFOLFOX6 (ERCC-1 High)	Bevacizumab + FOLFIRI (ERCC-1 High)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	17	15		
Units: percentage of participants				
number (confidence interval 95%)	17.6 (0 to 35.8)	6.7 (0 to 19.3)		

### Statistical analyses

Statistical analysis title	Difference in Complete Resection Rates
Statistical analysis description:	
The difference was calculated as the percentage of participants with complete resection in the Bevacizumab + FOLFIRI arm minus the Bevacizumab + mFOLFOX6 arm. The 95% CI was computed using normal approximation to the binomial distribution.	
Comparison groups	Bevacizumab + mFOLFOX6 (ERCC-1 High) v Bevacizumab + FOLFIRI (ERCC-1 High)



Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference in complete resection rates
Point estimate	-11
Confidence interval	
level	95 %
sides	2-sided
lower limit	-33.1
upper limit	11.1

## Secondary: Percentage of Participants With Liver Metastasis Resection in Participants With Low ERCC-1 Levels

End point title	Percentage of Participants With Liver Metastasis Resection in Participants With Low ERCC-1 Levels
End point description:	
<p>The timing of resective surgery was not defined in the protocol and was left at the discretion of the Investigator. Resection was classified as R0, R1, or R2 following surgery. R0 was defined as complete resection with clear margins <math>\geq 1</math> mm. R1 was defined as the presence of exposed tumor or histologically detected tumor cells at the line of transection, or <math>&lt;1</math> mm microscopic margins. In the case of use of radiofrequency ablation or cryotherapy, the resection was considered as R1. R2 was defined as macroscopic positive margins or incomplete resection at time of surgery. The percentage of participants with resection of liver or liver plus lymph node metastases was reported. The 95% CI was computed using normal approximation to the binomial distribution. ITT Population; only those participants with liver or liver plus lymph node metastases were included in the analysis. "Number of subjects analysed" reflects the number of evaluable participants for the outcome measure.</p>	
End point type	Secondary
End point timeframe:	
At time of resective surgery during study (maximum up to 45 months overall)	

End point values	Bevacizumab + mFOLFOX6 (ERCC-1 Low)	Bevacizumab + FOLFIRI (ERCC-1 Low)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	124	120		
Units: percentage of participants				
number (confidence interval 95%)	10.5 (5.1 to 15.9)	7.5 (2.8 to 12.2)		

## Statistical analyses

Statistical analysis title	Difference in Resection Rates
Statistical analysis description:	
<p>The difference was calculated as the percentage of participants with resection in the Bevacizumab + FOLFIRI arm minus the Bevacizumab + mFOLFOX6 arm. The 95% CI was computed using normal approximation to the binomial distribution.</p>	
Comparison groups	Bevacizumab + mFOLFOX6 (ERCC-1 Low) v Bevacizumab + FOLFIRI (ERCC-1 Low)

Number of subjects included in analysis	244
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference in resection rates
Point estimate	-3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.1
upper limit	4.2

## Secondary: Percentage of Participants With Complete Liver Metastasis Resection in Participants With Low ERCC-1 Levels

End point title	Percentage of Participants With Complete Liver Metastasis Resection in Participants With Low ERCC-1 Levels
End point description:	
The timing of resective surgery was not defined in the protocol and was left at the discretion of the Investigator. Resection was classified as R0, R1, or R2 following surgery. R0 was defined as complete resection with clear margins $\geq 1$ mm. The percentage of participants with R0 resection of liver or liver plus lymph node metastases was reported. The 95% CI was computed using normal approximation to the binomial distribution. ITT Population; only those participants with liver or liver plus lymph node metastases were included in the analysis. "Number of subjects analysed" reflects the number of evaluable participants for the outcome measure.	
End point type	Secondary
End point timeframe:	
At time of resective surgery during study (maximum up to 45 months overall)	

End point values	Bevacizumab + mFOLFOX6 (ERCC-1 Low)	Bevacizumab + FOLFIRI (ERCC-1 Low)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	124	120		
Units: percentage of participants				
number (confidence interval 95%)	8.9 (3.9 to 13.9)	3.3 (0.1 to 6.5)		

## Statistical analyses

Statistical analysis title	Difference in Complete Resection Rates
Statistical analysis description:	
The difference was calculated as the percentage of participants with complete resection in the Bevacizumab + FOLFIRI arm minus the Bevacizumab + mFOLFOX6 arm. The 95% CI was computed using normal approximation to the binomial distribution.	
Comparison groups	Bevacizumab + mFOLFOX6 (ERCC-1 Low) v Bevacizumab + FOLFIRI (ERCC-1 Low)

Number of subjects included in analysis	244
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference in complete resection rates
Point estimate	-5.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.5
upper limit	0.4

### Secondary: Percentage of Participants With Liver Metastasis Resection in Participants With High ERCC-1 Levels Versus Participants With Low ERCC-1 Levels

End point title	Percentage of Participants With Liver Metastasis Resection in Participants With High ERCC-1 Levels Versus Participants With Low ERCC-1 Levels
-----------------	-----------------------------------------------------------------------------------------------------------------------------------------------

#### End point description:

The timing of resective surgery was not defined in the protocol and was left at the discretion of the Investigator. Resection was classified as R0, R1, or R2 following surgery. R0 was defined as complete resection with clear margins  $\geq 1$  mm. R1 was defined as the presence of exposed tumor or histologically detected tumor cells at the line of transection, or  $<1$  mm microscopic margins. In the case of use of radiofrequency ablation or cryotherapy, the resection was considered as R1. R2 was defined as macroscopic positive margins or incomplete resection at time of surgery. The percentage of participants with resection of liver or liver plus lymph node metastases was reported. The 95% CI was computed using normal approximation to the binomial distribution. ITT Population; only those participants with liver or liver plus lymph node metastases were included in the analysis. "Number of subjects analysed" reflects the number of evaluable participants for the outcome measure.

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

#### End point timeframe:

At time of resective surgery during study (maximum up to 45 months overall)

End point values	Bevacizumab + mFOLFOX/FOLFIRI (ERCC-1 High)	Bevacizumab + mFOLFOX/FOLFIRI (ERCC-1 Low)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	131	244		
Units: percentage of participants				
number (confidence interval 95%)	4.6 (1 to 8.2)	9 (5.4 to 12.6)		

### Statistical analyses

Statistical analysis title	Difference in Resection Rates
----------------------------	-------------------------------

#### Statistical analysis description:

The difference was calculated as the percentage of participants with resection in the ERCC-1 High subgroup minus the ERCC-1 Low subgroup. The 95% CI was computed using normal approximation to the binomial distribution.

Comparison groups	Bevacizumab + mFOLFOX/FOLFIRI (ERCC-1 High) v Bevacizumab + mFOLFOX/FOLFIRI (ERCC-1 Low)
-------------------	------------------------------------------------------------------------------------------

Number of subjects included in analysis	375
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference in resection rates
Point estimate	-4.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.5
upper limit	0.6

### Secondary: Percentage of Participants With Complete Liver Metastasis Resection in Participants With High ERCC-1 Levels Versus Participants With Low ERCC-1 Levels

End point title	Percentage of Participants With Complete Liver Metastasis Resection in Participants With High ERCC-1 Levels Versus Participants With Low ERCC-1 Levels
-----------------	--------------------------------------------------------------------------------------------------------------------------------------------------------

#### End point description:

The timing of resective surgery was not defined in the protocol and was left at the discretion of the Investigator. Resection was classified as R0, R1, or R2 following surgery. R0 was defined as complete resection with clear margins  $\geq 1$  mm. The percentage of participants with R0 resection of liver or liver plus lymph node metastases was reported. The 95% CI was computed using normal approximation to the binomial distribution. ITT Population; only those participants with liver or liver plus lymph node metastases were included in the analysis. "Number of subjects analysed" reflects the number of evaluable participants for the outcome measure.

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

#### End point timeframe:

At time of resective surgery during study (maximum up to 45 months overall)

End point values	Bevacizumab + mFOLFOX/FOLFIRI (ERCC-1 High)	Bevacizumab + mFOLFOX/FOLFIRI (ERCC-1 Low)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	131	244		
Units: percentage of participants				
number (confidence interval 95%)	4.6 (1 to 8.2)	6.1 (3.1 to 9.2)		

### Statistical analyses

Statistical analysis title	Difference in Complete Resection Rates
----------------------------	----------------------------------------

#### Statistical analysis description:

The difference was calculated as the percentage of participants with complete resection in the ERCC-1 High subgroup minus the ERCC-1 Low subgroup. The 95% CI was computed using normal approximation to the binomial distribution.

Comparison groups	Bevacizumab + mFOLFOX/FOLFIRI (ERCC-1 High) v Bevacizumab + mFOLFOX/FOLFIRI (ERCC-1 Low)
-------------------	---------------------------------------------------------------------------------------------

Number of subjects included in analysis	375
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference in complete resection rates
Point estimate	-1.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.2
upper limit	3.1

### Secondary: PFS According to RECIST Version 1.1 in Participants With Wild-Type KRAS Versus Participants With Mutant KRAS

End point title	PFS According to RECIST Version 1.1 in Participants With Wild-Type KRAS Versus Participants With Mutant KRAS
-----------------	--------------------------------------------------------------------------------------------------------------

#### End point description:

Tumor assessments were performed according to RECIST Version 1.1. Disease progression was defined as  $\geq 20\%$  increase in sum of LD of target lesions in reference to the smallest sum of LD on study, in addition to an absolute increase  $\geq 5$  mm. Disease progression was further defined as the last documented progression determined by the Investigator no later than 1 day before initiation of second-line therapy. Death on study included death from any cause occurring no later than 3 months after the last component of study treatment. PFS was defined as the time from randomization to death or disease progression, whichever occurred first. The median duration of PFS was estimated by Kaplan-Meier analysis and expressed in months. The 95% CI was computed using the method of Brookmeyer and Crowley. ITT Population. "Number of subjects analysed" reflects the number of evaluable participants for the outcome measure.

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

#### End point timeframe:

From Baseline until death or disease progression; assessed every 6 weeks (maximum up to 45 months overall)

End point values	Bevacizumab + mFOLFOX/FOLFIRI (KRAS Wild-Type)	Bevacizumab + mFOLFOX/FOLFIRI (KRAS Mutant)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	208	128		
Units: months				
median (confidence interval 95%)	12.45 (10.48 to 14.06)	10.94 (8.77 to 12.35)		

### Statistical analyses

Statistical analysis title	Hazard Ratio
Comparison groups	Bevacizumab + mFOLFOX/FOLFIRI (KRAS Mutant) v Bevacizumab + mFOLFOX/FOLFIRI (KRAS Wild-Type)

Number of subjects included in analysis	336
Analysis specification	Pre-specified
Analysis type	other <sup>[24]</sup>
P-value	= 0.0593 <sup>[25]</sup>
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.29
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.99
upper limit	1.69

Notes:

[24] - Analysis stratified by high/low ERCC-1 level and region of enrollment. HR (relative to KRAS Wild-Type subgroup) was estimated by Cox regression.

[25] - P-value (relative to KRAS Wild-Type subgroup) based on two-sided stratified log rank test and not adjusted for multiple comparisons.

## Secondary: OS in Participants With High VEGF-A Levels Versus Participants With Low VEGF-A Levels

End point title	OS in Participants With High VEGF-A Levels Versus Participants With Low VEGF-A Levels
-----------------	---------------------------------------------------------------------------------------

End point description:

Death on study included death from any cause occurring no later than 3 months after the last component of study treatment. OS was defined as the time from randomization to death. The median duration of OS was estimated by Kaplan-Meier analysis and expressed in months. The 95% CI was computed using the method of Brookmeyer and Crowley. ITT Population. "Number of subjects analysed" reflects the number of evaluable participants for the outcome measure.

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

End point timeframe:

From Baseline until death (maximum up to 45 months overall)

End point values	Bevacizumab + mFOLFOX/FOLFIRI (VEGF-A High)	Bevacizumab + mFOLFOX/FOLFIRI (VEGF-A Low)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	185	185		
Units: months				
median (confidence interval 95%)	22.83 (18.76 to 27.27)	27.93 (24.97 to 36.01)		

## Statistical analyses

Statistical analysis title	Hazard Ratio
----------------------------	--------------

Statistical analysis description:

Analysis stratified by high/low ERCC-1 level and region of enrollment. HR (relative to VEGF-A Low subgroup) was estimated by Cox regression.

Comparison groups	Bevacizumab + mFOLFOX/FOLFIRI (VEGF-A High) v Bevacizumab + mFOLFOX/FOLFIRI (VEGF-A Low)
-------------------	---------------------------------------------------------------------------------------------

Number of subjects included in analysis	370
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.002 <sup>[26]</sup>
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.64
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.2
upper limit	2.24

Notes:

[26] - P-value (relative to VEGF-A Low subgroup) based on two-sided stratified log rank test and not adjusted for multiple comparisons.

## Secondary: OS in Participants With Wild-Type KRAS Versus Participants With Mutant KRAS

End point title	OS in Participants With Wild-Type KRAS Versus Participants With Mutant KRAS
-----------------	-----------------------------------------------------------------------------

End point description:

Death on study included death from any cause occurring no later than 3 months after the last component of study treatment. OS was defined as the time from randomization to death. The median duration of OS was estimated by Kaplan-Meier analysis and expressed in months. The 95% CI was computed using the method of Brookmeyer and Crowley. ITT Population. "Number of subjects analysed" reflects the number of evaluable participants for the outcome measure.

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

End point timeframe:

From Baseline until death (maximum up to 45 months overall)

End point values	Bevacizumab + mFOLFOX/FOLFIRI (KRAS Wild-Type)	Bevacizumab + mFOLFOX/FOLFIRI (KRAS Mutant)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	208	128		
Units: months				
median (confidence interval 95%)	28.75 (24.77 to 36.73)	24.64 (19.98 to 26.94)		

## Statistical analyses

Statistical analysis title	Hazard Ratio
----------------------------	--------------

Statistical analysis description:

Analysis stratified by high/low ERCC-1 level and region of enrollment. HR (relative to KRAS Wild-Type subgroup) was estimated by Cox regression.

Comparison groups	Bevacizumab + mFOLFOX/FOLFIRI (KRAS Wild-Type) v Bevacizumab + mFOLFOX/FOLFIRI (KRAS Mutant)
-------------------	-------------------------------------------------------------------------------------------------

Number of subjects included in analysis	336
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0955 <sup>[27]</sup>
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.34
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.95
upper limit	1.88

Notes:

[27] - P-value (relative to KRAS Wild-Type subgroup) based on two-sided stratified log rank test and not adjusted for multiple comparisons.

### Secondary: Percentage of Participants With Objective Response According to RECIST Version 1.1 in Participants With High VEGF-A Levels Versus Participants With Low VEGF-A Levels

End point title	Percentage of Participants With Objective Response According to RECIST Version 1.1 in Participants With High VEGF-A Levels Versus Participants With Low VEGF-A Levels
-----------------	-----------------------------------------------------------------------------------------------------------------------------------------------------------------------

End point description:

Objective response was defined as CR or PR according to RECIST Version 1.1. CR was defined as disappearance of all target lesions and short-axis reduction to <10 mm of any pathological lymph nodes. PR was defined as ≥30% decrease in sum of LD of target lesions in reference to sum of LD at Baseline. Confirmation of response at a consecutive assessment was not required. The percentage of participants with CR or PR was reported. The 95% CI was computed using normal approximation to the binomial distribution. ITT Population. "Number of subjects analysed" reflects the number of evaluable participants for the outcome measure.

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

End point timeframe:

From Baseline until disease progression; assessed every 6 weeks (maximum up to 45 months overall)

End point values	Bevacizumab + mFOLFOX/FOLFIRI (VEGF-A High)	Bevacizumab + mFOLFOX/FOLFIRI (VEGF-A Low)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	185	185		
Units: percentage of participants				
number (confidence interval 95%)	60.5 (53.5 to 67.6)	66.5 (59.7 to 73.3)		

### Statistical analyses

Statistical analysis title	Difference in Objective Response Rates
----------------------------	----------------------------------------

Statistical analysis description:

The difference was calculated as the percentage of participants with objective response in the VEGF-A High subgroup minus the VEGF-A Low subgroup. The 95% CI was computed using normal approximation to the binomial distribution.



Comparison groups	Bevacizumab + mFOLFOX/FOLFIRI (VEGF-A High) v Bevacizumab + mFOLFOX/FOLFIRI (VEGF-A Low)
Number of subjects included in analysis	370
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference in objective response rates
Point estimate	-5.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-15.7
upper limit	3.8

### Secondary: Percentage of Participants With Objective Response According to RECIST Version 1.1 in Participants With Wild-Type KRAS Versus Participants With Mutant KRAS

End point title	Percentage of Participants With Objective Response According to RECIST Version 1.1 in Participants With Wild-Type KRAS Versus Participants With Mutant KRAS
-----------------	-------------------------------------------------------------------------------------------------------------------------------------------------------------

End point description:

Objective response was defined as CR or PR according to RECIST Version 1.1. CR was defined as disappearance of all target lesions and short-axis reduction to <10 mm of any pathological lymph nodes. PR was defined as ≥30% decrease in sum of LD of target lesions in reference to sum of LD at Baseline. Confirmation of response at a consecutive assessment was not required. The percentage of participants with CR or PR was reported. The 95% CI was computed using normal approximation to the binomial distribution. ITT Population. "Number of subjects analysed" reflects the number of evaluable participants for the outcome measure.

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

End point timeframe:

From Baseline until disease progression; assessed every 6 weeks (maximum up to 45 months overall)

End point values	Bevacizumab + mFOLFOX/FOLFIRI (KRAS Wild-Type)	Bevacizumab + mFOLFOX/FOLFIRI (KRAS Mutant)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	208	128		
Units: percentage of participants				
number (confidence interval 95%)	66.3 (59.9 to 72.8)	60.9 (52.5 to 69.4)		

### Statistical analyses

Statistical analysis title	Difference in Objective Response Rates
----------------------------	----------------------------------------

Statistical analysis description:

The difference was calculated as the percentage of participants with objective response in the KRAS Mutant subgroup minus the KRAS Wild-Type subgroup. The 95% CI was computed using normal approximation to the binomial distribution.

Comparison groups	Bevacizumab + mFOLFOX/FOLFIRI (KRAS Wild-Type) v
-------------------	--------------------------------------------------

	Bevacizumab + mFOLFOX/FOLFIRI (KRAS Mutant)
Number of subjects included in analysis	336
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference in objective response rates
Point estimate	-5.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-16
upper limit	5.2

### Secondary: Percentage of Participants With Disease Control According to RECIST Version 1.1 in Participants With High VEGF-A Levels Versus Participants With Low VEGF-A Levels

End point title	Percentage of Participants With Disease Control According to RECIST Version 1.1 in Participants With High VEGF-A Levels Versus Participants With Low VEGF-A Levels
End point description:	Disease control was defined as CR, PR, or SD according to RECIST Version 1.1. CR was defined as disappearance of all target lesions and short-axis reduction to <10 mm of any pathological lymph nodes. PR was defined as ≥30% decrease in sum of LD of target lesions in reference to sum of LD at Baseline. Confirmation of response at a consecutive assessment was not required. SD was defined as neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for disease progression (≥20% increase in sum of LD of target lesions plus absolute increase ≥5 mm) in reference to the smallest sum of LD on study. The percentage of participants with CR, PR, or SD was reported. The 95% CI was computed using normal approximation to the binomial distribution. ITT Population. "Number of subjects analysed" reflects the number of evaluable participants for the outcome measure.
End point type	Secondary
End point timeframe:	From Baseline until disease progression; assessed every 6 weeks (maximum up to 45 months overall)

End point values	Bevacizumab + mFOLFOX/FOLFIRI (VEGF-A High)	Bevacizumab + mFOLFOX/FOLFIRI (VEGF-A Low)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	185	185		
Units: percentage of participants				
number (confidence interval 95%)	91.9 (88 to 95.8)	93 (89.3 to 96.7)		

### Statistical analyses

Statistical analysis title	Difference in Disease Control Rates
Statistical analysis description:	The difference was calculated as the percentage of participants with disease control in the VEGF-A High subgroup minus the VEGF-A Low subgroup. The 95% CI was computed using normal approximation to the binomial distribution.

Comparison groups	Bevacizumab + mFOLFOX/FOLFIRI (VEGF-A High) v Bevacizumab + mFOLFOX/FOLFIRI (VEGF-A Low)
Number of subjects included in analysis	370
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference in disease control rates
Point estimate	-1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.5
upper limit	4.3

### Secondary: Percentage of Participants With Liver Metastasis Resection in Participants With High VEGF-A Levels Versus Participants With Low VEGF-A Levels

End point title	Percentage of Participants With Liver Metastasis Resection in Participants With High VEGF-A Levels Versus Participants With Low VEGF-A Levels
End point description:	<p>The timing of resective surgery was not defined in the protocol and was left at the discretion of the Investigator. Resection was classified as R0, R1, or R2 following surgery. R0 was defined as complete resection with clear margins <math>\geq 1</math> mm. R1 was defined as the presence of exposed tumor or histologically detected tumor cells at the line of transection, or <math>&lt;1</math> mm microscopic margins. In the case of use of radiofrequency ablation or cryotherapy, the resection was considered as R1. R2 was defined as macroscopic positive margins or incomplete resection at time of surgery. The percentage of participants with resection of liver or liver plus lymph node metastases was reported. The 95% CI was computed using normal approximation to the binomial distribution. ITT Population; only those participants with liver or liver plus lymph node metastases were included in the analysis. "Number of subjects analysed" reflects the number of evaluable participants for the outcome measure.</p>
End point type	Secondary
End point timeframe:	At time of resective surgery during study (maximum up to 45 months overall)

End point values	Bevacizumab + mFOLFOX/FOLFIRI (VEGF-A High)	Bevacizumab + mFOLFOX/FOLFIRI (VEGF-A Low)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	185	185		
Units: percentage of participants				
number (confidence interval 95%)	5.9 (2.5 to 9.4)	9.2 (5 to 13.4)		

### Statistical analyses

Statistical analysis title	Difference in Resection Rates
Statistical analysis description:	<p>The difference was calculated as the percentage of participants with resection in the VEGF-A High subgroup minus the VEGF-A Low subgroup. The 95% CI was computed using normal approximation to the binomial distribution.</p>

Comparison groups	Bevacizumab + mFOLFOX/FOLFIRI (VEGF-A High) v Bevacizumab + mFOLFOX/FOLFIRI (VEGF-A Low)
Number of subjects included in analysis	370
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference in resection rates
Point estimate	-3.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.6
upper limit	2.1

### Secondary: Percentage of Participants With Complete Liver Metastasis Resection in Participants With High VEGF-A Levels Versus Participants With Low VEGF-A Levels

End point title	Percentage of Participants With Complete Liver Metastasis Resection in Participants With High VEGF-A Levels Versus Participants With Low VEGF-A Levels
End point description:	The timing of resective surgery was not defined in the protocol and was left at the discretion of the Investigator. Resection was classified as R0, R1, or R2 following surgery. R0 was defined as complete resection with clear margins $\geq 1$ mm. The percentage of participants with R0 resection of liver or liver plus lymph node metastases was reported. The 95% CI was computed using normal approximation to the binomial distribution. ITT Population; only those participants with liver or liver plus lymph node metastases were included in the analysis. "Number of subjects analysed" reflects the number of evaluable participants for the outcome measure.
End point type	Secondary
End point timeframe:	At time of resective surgery during study (maximum up to 45 months overall)

End point values	Bevacizumab + mFOLFOX/FOLFIRI (VEGF-A High)	Bevacizumab + mFOLFOX/FOLFIRI (VEGF-A Low)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	185	185		
Units: percentage of participants				
number (confidence interval 95%)	3.2 (0.7 to 5.8)	8.1 (4.2 to 12)		

### Statistical analyses

Statistical analysis title	Difference in Complete Resection Rates
Statistical analysis description:	The difference was calculated as the percentage of participants with complete resection in the VEGF-A High subgroup minus the VEGF-A Low subgroup. The 95% CI was computed using normal approximation to the binomial distribution.
Comparison groups	Bevacizumab + mFOLFOX/FOLFIRI (VEGF-A High) v Bevacizumab + mFOLFOX/FOLFIRI (VEGF-A Low)

Number of subjects included in analysis	370
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference in complete resection rates
Point estimate	-4.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.6
upper limit	-0.2

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Serious Adverse Events (AEs): Baseline until 3 months after last dose or study discontinuation/termination (up to 45 months overall); Non-Serious AEs: Baseline until 28 days after last dose or study discontinuation/termination (up to 45 months overall).

Adverse event reporting additional description:

Safety Population: All randomized participants who received at least one partial or complete dose of study drug.

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

### Dictionary used

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

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

### Reporting groups

Reporting group title	Bevacizumab + mFOLFOX6
-----------------------	------------------------

Reporting group description:

Participants with untreated mCRC who were candidates for first-line therapy received bevacizumab plus mFOLFOX6 until disease progression or unacceptable toxicity. Bevacizumab was given as 5 mg/kg, leucovorin as 400 mg/m<sup>2</sup>, oxaliplatin as 85 mg/m<sup>2</sup>, and 5-fluorouracil as 400 mg/m<sup>2</sup> bolus followed by 2400 mg/m<sup>2</sup> continuous 46-hour infusion. All treatments were administered via IV infusion and started on Day 1 of each 2-week cycle. Participants could be transitioned to oral capecitabine in the event of unacceptable toxicity to oxaliplatin and given as 850 or 1000 mg/m<sup>2</sup> twice a day on Days 1 to 14, with bevacizumab continued in 3-week cycles.

Reporting group title	Bevacizumab + FOLFIRI
-----------------------	-----------------------

Reporting group description:

Participants with untreated mCRC who were candidates for first-line therapy received bevacizumab plus FOLFIRI until disease progression or unacceptable toxicity. Bevacizumab was given as 5 mg/kg, leucovorin as 400 mg/m<sup>2</sup>, irinotecan as 180 mg/m<sup>2</sup>, and 5-fluorouracil as 400 mg/m<sup>2</sup> bolus followed by 2400 mg/m<sup>2</sup> continuous 46-hour infusion. All treatments were administered via IV infusion and started on Day 1 of each 2-week cycle. Participants could be transitioned to oral capecitabine in the event of unacceptable toxicity to irinotecan and given as 850 or 1000 mg/m<sup>2</sup> twice a day on Days 1 to 14, with bevacizumab continued in 3-week cycles.

Serious adverse events	Bevacizumab + mFOLFOX6	Bevacizumab + FOLFIRI	
Total subjects affected by serious adverse events			
subjects affected / exposed	79 / 185 (42.70%)	87 / 183 (47.54%)	
number of deaths (all causes)	96	73	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Meningioma			
subjects affected / exposed	0 / 185 (0.00%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypotension			

subjects affected / exposed	5 / 185 (2.70%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	1 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	3 / 185 (1.62%)	6 / 183 (3.28%)	
occurrences causally related to treatment / all	3 / 3	9 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arterial thrombosis			
subjects affected / exposed	1 / 185 (0.54%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	1 / 185 (0.54%)	4 / 183 (2.19%)	
occurrences causally related to treatment / all	1 / 1	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolism venous			
subjects affected / exposed	1 / 185 (0.54%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous thrombosis			
subjects affected / exposed	1 / 185 (0.54%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jugular vein thrombosis			
subjects affected / exposed	0 / 185 (0.00%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombosis			
subjects affected / exposed	0 / 185 (0.00%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Colostomy			

subjects affected / exposed	0 / 185 (0.00%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	3 / 185 (1.62%)	4 / 183 (2.19%)	
occurrences causally related to treatment / all	1 / 3	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	3 / 185 (1.62%)	4 / 183 (2.19%)	
occurrences causally related to treatment / all	2 / 3	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device dislocation			
subjects affected / exposed	2 / 185 (1.08%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthenia			
subjects affected / exposed	1 / 185 (0.54%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chills			
subjects affected / exposed	1 / 185 (0.54%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucosal inflammation			
subjects affected / exposed	1 / 185 (0.54%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multi-organ failure			
subjects affected / exposed	1 / 185 (0.54%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Peripheral swelling			



subjects affected / exposed	1 / 185 (0.54%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Systemic inflammatory response syndrome			
subjects affected / exposed	1 / 185 (0.54%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device malfunction			
subjects affected / exposed	0 / 185 (0.00%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	0 / 185 (0.00%)	3 / 183 (1.64%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gait disturbance			
subjects affected / exposed	0 / 185 (0.00%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Localised oedema			
subjects affected / exposed	0 / 185 (0.00%)	1 / 183 (0.55%)	
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			
Pulmonary embolism			
subjects affected / exposed	9 / 185 (4.86%)	9 / 183 (4.92%)	
occurrences causally related to treatment / all	8 / 10	7 / 9	
deaths causally related to treatment / all	1 / 1	0 / 0	
Acute respiratory failure			
subjects affected / exposed	2 / 185 (1.08%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory distress			

subjects affected / exposed	2 / 185 (1.08%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 185 (0.54%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	1 / 185 (0.54%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	1 / 185 (0.54%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hiccups			
subjects affected / exposed	1 / 185 (0.54%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary thrombosis			
subjects affected / exposed	1 / 185 (0.54%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthma			
subjects affected / exposed	0 / 185 (0.00%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cough			
subjects affected / exposed	0 / 185 (0.00%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial lung disease			

subjects affected / exposed	0 / 185 (0.00%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary artery thrombosis			
subjects affected / exposed	0 / 185 (0.00%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Confusional state			
subjects affected / exposed	1 / 185 (0.54%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental status changes			
subjects affected / exposed	0 / 185 (0.00%)	2 / 183 (1.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Platelet count decreased			
subjects affected / exposed	2 / 185 (1.08%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Weight decreased			
subjects affected / exposed	1 / 185 (0.54%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood bilirubin increased			
subjects affected / exposed	0 / 185 (0.00%)	2 / 183 (1.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	1 / 185 (0.54%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Laceration			
subjects affected / exposed	1 / 185 (0.54%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stoma site haemorrhage			
subjects affected / exposed	1 / 185 (0.54%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxicity to various agents			
subjects affected / exposed	1 / 185 (0.54%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound dehiscence			
subjects affected / exposed	1 / 185 (0.54%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal wound dehiscence			
subjects affected / exposed	0 / 185 (0.00%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal anastomosis complication			
subjects affected / exposed	0 / 185 (0.00%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal compression fracture			
subjects affected / exposed	0 / 185 (0.00%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial flutter			
subjects affected / exposed	1 / 185 (0.54%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardio-respiratory arrest			

subjects affected / exposed	1 / 185 (0.54%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Left ventricular dysfunction			
subjects affected / exposed	1 / 185 (0.54%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	1 / 185 (0.54%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	1 / 185 (0.54%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	0 / 185 (0.00%)	3 / 183 (1.64%)	
occurrences causally related to treatment / all	0 / 0	1 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial thrombosis			
subjects affected / exposed	0 / 185 (0.00%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Aphonia			
subjects affected / exposed	1 / 185 (0.54%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ataxia			
subjects affected / exposed	1 / 185 (0.54%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			

subjects affected / exposed	1 / 185 (0.54%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	1 / 185 (0.54%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	1 / 185 (0.54%)	2 / 183 (1.09%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage intracranial			
subjects affected / exposed	0 / 185 (0.00%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	0 / 185 (0.00%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombotic stroke			
subjects affected / exposed	0 / 185 (0.00%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	3 / 185 (1.62%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	2 / 185 (1.08%)	4 / 183 (2.19%)	
occurrences causally related to treatment / all	1 / 2	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			

subjects affected / exposed	1 / 185 (0.54%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune thrombocytopenic purpura			
subjects affected / exposed	1 / 185 (0.54%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	1 / 185 (0.54%)	2 / 183 (1.09%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	1 / 185 (0.54%)	1 / 183 (0.55%)	
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	6 / 185 (3.24%)	2 / 183 (1.09%)	
occurrences causally related to treatment / all	4 / 6	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	5 / 185 (2.70%)	6 / 183 (3.28%)	
occurrences causally related to treatment / all	2 / 5	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			
subjects affected / exposed	4 / 185 (2.16%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	2 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	3 / 185 (1.62%)	7 / 183 (3.83%)	
occurrences causally related to treatment / all	0 / 3	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			

subjects affected / exposed	3 / 185 (1.62%)	3 / 183 (1.64%)	
occurrences causally related to treatment / all	1 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	3 / 185 (1.62%)	4 / 183 (2.19%)	
occurrences causally related to treatment / all	0 / 6	2 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	2 / 185 (1.08%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	2 / 185 (1.08%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine perforation			
subjects affected / exposed	2 / 185 (1.08%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	2 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	2 / 185 (1.08%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 4	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophagitis			
subjects affected / exposed	2 / 185 (1.08%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	2 / 185 (1.08%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain lower			



subjects affected / exposed	1 / 185 (0.54%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	1 / 185 (0.54%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer haemorrhage			
subjects affected / exposed	1 / 185 (0.54%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteritis			
subjects affected / exposed	1 / 185 (0.54%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 185 (0.54%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileal perforation			
subjects affected / exposed	1 / 185 (0.54%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Large intestinal haemorrhage			
subjects affected / exposed	1 / 185 (0.54%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic colitis			
subjects affected / exposed	1 / 185 (0.54%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal motility disorder			

subjects affected / exposed	1 / 185 (0.54%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal varices haemorrhage			
subjects affected / exposed	1 / 185 (0.54%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumoperitoneum			
subjects affected / exposed	1 / 185 (0.54%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Small intestinal perforation			
subjects affected / exposed	1 / 185 (0.54%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal distension			
subjects affected / exposed	0 / 185 (0.00%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	0 / 185 (0.00%)	2 / 183 (1.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal fistula			
subjects affected / exposed	0 / 185 (0.00%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	0 / 185 (0.00%)	2 / 183 (1.09%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenitis			

subjects affected / exposed	0 / 185 (0.00%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterovesical fistula			
subjects affected / exposed	0 / 185 (0.00%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric haemorrhage			
subjects affected / exposed	0 / 185 (0.00%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 185 (0.00%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoidal haemorrhage			
subjects affected / exposed	0 / 185 (0.00%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	0 / 185 (0.00%)	2 / 183 (1.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestinal obstruction			
subjects affected / exposed	0 / 185 (0.00%)	2 / 183 (1.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pancreatitis			
subjects affected / exposed	0 / 185 (0.00%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reflux gastritis			

subjects affected / exposed	0 / 185 (0.00%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 185 (0.54%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			
subjects affected / exposed	1 / 185 (0.54%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperbilirubinaemia			
subjects affected / exposed	1 / 185 (0.54%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic hepatitis			
subjects affected / exposed	1 / 185 (0.54%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Biloma			
subjects affected / exposed	0 / 185 (0.00%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangitis			
subjects affected / exposed	0 / 185 (0.00%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis chronic			
subjects affected / exposed	0 / 185 (0.00%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			

subjects affected / exposed	0 / 185 (0.00%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic steatosis			
subjects affected / exposed	0 / 185 (0.00%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis			
subjects affected / exposed	0 / 185 (0.00%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaundice			
subjects affected / exposed	0 / 185 (0.00%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 185 (0.54%)	2 / 183 (1.09%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Proteinuria			
subjects affected / exposed	1 / 185 (0.54%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	0 / 185 (0.00%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Muscular weakness			
subjects affected / exposed	1 / 185 (0.54%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Polyarthritis			
subjects affected / exposed	1 / 185 (0.54%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhabdomyolysis			
subjects affected / exposed	1 / 185 (0.54%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Sepsis			
subjects affected / exposed	4 / 185 (2.16%)	3 / 183 (1.64%)	
occurrences causally related to treatment / all	1 / 6	1 / 3	
deaths causally related to treatment / all	0 / 0	1 / 2	
Pneumonia			
subjects affected / exposed	3 / 185 (1.62%)	7 / 183 (3.83%)	
occurrences causally related to treatment / all	0 / 3	1 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	2 / 185 (1.08%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	2 / 185 (1.08%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	2 / 185 (1.08%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal abscess			
subjects affected / exposed	1 / 185 (0.54%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal infection			

subjects affected / exposed	1 / 185 (0.54%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	1 / 185 (0.54%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	1 / 185 (0.54%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Candida sepsis			
subjects affected / exposed	1 / 185 (0.54%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Diverticulitis			
subjects affected / exposed	1 / 185 (0.54%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocarditis			
subjects affected / exposed	1 / 185 (0.54%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Infection			
subjects affected / exposed	1 / 185 (0.54%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	1 / 185 (0.54%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			

subjects affected / exposed	1 / 185 (0.54%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subcutaneous abscess			
subjects affected / exposed	1 / 185 (0.54%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 185 (0.54%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	1 / 185 (0.54%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	0 / 185 (0.00%)	2 / 183 (1.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	0 / 185 (0.00%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis viral			
subjects affected / exposed	0 / 185 (0.00%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Kidney infection			
subjects affected / exposed	0 / 185 (0.00%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			



subjects affected / exposed	0 / 185 (0.00%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic sepsis			
subjects affected / exposed	0 / 185 (0.00%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Perineal abscess			
subjects affected / exposed	0 / 185 (0.00%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia bacterial			
subjects affected / exposed	0 / 185 (0.00%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia parainfluenzae viral			
subjects affected / exposed	0 / 185 (0.00%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	8 / 185 (4.32%)	5 / 183 (2.73%)	
occurrences causally related to treatment / all	2 / 10	3 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Decreased appetite			
subjects affected / exposed	1 / 185 (0.54%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus			
subjects affected / exposed	1 / 185 (0.54%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Failure to thrive			

subjects affected / exposed	1 / 185 (0.54%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	1 / 185 (0.54%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	1 / 185 (0.54%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	1 / 185 (0.54%)	2 / 183 (1.09%)	
occurrences causally related to treatment / all	0 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malnutrition			
subjects affected / exposed	1 / 185 (0.54%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoalbuminaemia			
subjects affected / exposed	0 / 185 (0.00%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypophosphataemia			
subjects affected / exposed	0 / 185 (0.00%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolic alkalosis			
subjects affected / exposed	0 / 185 (0.00%)	1 / 183 (0.55%)	
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: 5 %

<b>Non-serious adverse events</b>	<b>Bevacizumab + mFOLFOX6</b>	<b>Bevacizumab + FOLFIRI</b>	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	185 / 185 (100.00%)	181 / 183 (98.91%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	61 / 185 (32.97%)	54 / 183 (29.51%)	
occurrences (all)	110	96	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	105 / 185 (56.76%)	104 / 183 (56.83%)	
occurrences (all)	145	177	
Mucosal inflammation			
subjects affected / exposed	37 / 185 (20.00%)	51 / 183 (27.87%)	
occurrences (all)	50	82	
Pyrexia			
subjects affected / exposed	18 / 185 (9.73%)	29 / 183 (15.85%)	
occurrences (all)	23	38	
Asthenia			
subjects affected / exposed	21 / 185 (11.35%)	18 / 183 (9.84%)	
occurrences (all)	24	28	
Oedema peripheral			
subjects affected / exposed	18 / 185 (9.73%)	18 / 183 (9.84%)	
occurrences (all)	22	20	
Temperature intolerance			
subjects affected / exposed	34 / 185 (18.38%)	1 / 183 (0.55%)	
occurrences (all)	39	1	
Chest pain			
subjects affected / exposed	15 / 185 (8.11%)	10 / 183 (5.46%)	
occurrences (all)	19	12	
Chills			
subjects affected / exposed	10 / 185 (5.41%)	10 / 183 (5.46%)	
occurrences (all)	12	13	
Influenza like illness			

subjects affected / exposed occurrences (all)	10 / 185 (5.41%) 13	6 / 183 (3.28%) 6	
Immune system disorders Hypersensitivity subjects affected / exposed occurrences (all)	10 / 185 (5.41%) 11	0 / 183 (0.00%) 0	
Respiratory, thoracic and mediastinal disorders Epistaxis subjects affected / exposed occurrences (all)	41 / 185 (22.16%) 51	59 / 183 (32.24%) 82	
Cough subjects affected / exposed occurrences (all)	31 / 185 (16.76%) 37	29 / 183 (15.85%) 43	
Dyspnoea subjects affected / exposed occurrences (all)	28 / 185 (15.14%) 39	26 / 183 (14.21%) 38	
Rhinorrhoea subjects affected / exposed occurrences (all)	12 / 185 (6.49%) 16	21 / 183 (11.48%) 23	
Dysphonia subjects affected / exposed occurrences (all)	14 / 185 (7.57%) 17	18 / 183 (9.84%) 39	
Hiccups subjects affected / exposed occurrences (all)	8 / 185 (4.32%) 11	14 / 183 (7.65%) 16	
Oropharyngeal pain subjects affected / exposed occurrences (all)	11 / 185 (5.95%) 11	8 / 183 (4.37%) 12	
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	29 / 185 (15.68%) 31	35 / 183 (19.13%) 44	
Depression subjects affected / exposed occurrences (all)	24 / 185 (12.97%) 26	18 / 183 (9.84%) 24	
Anxiety			

subjects affected / exposed occurrences (all)	19 / 185 (10.27%) 20	20 / 183 (10.93%) 23	
Investigations			
Weight decreased subjects affected / exposed occurrences (all)	33 / 185 (17.84%) 40	29 / 183 (15.85%) 32	
Neutrophil count decreased subjects affected / exposed occurrences (all)	33 / 185 (17.84%) 55	23 / 183 (12.57%) 33	
Platelet count decreased subjects affected / exposed occurrences (all)	24 / 185 (12.97%) 64	3 / 183 (1.64%) 6	
White blood cell count decreased subjects affected / exposed occurrences (all)	15 / 185 (8.11%) 25	9 / 183 (4.92%) 25	
Injury, poisoning and procedural complications			
Infusion related reaction subjects affected / exposed occurrences (all)	15 / 185 (8.11%) 27	8 / 183 (4.37%) 13	
Nervous system disorders			
Neuropathy peripheral subjects affected / exposed occurrences (all)	85 / 185 (45.95%) 134	23 / 183 (12.57%) 30	
Headache subjects affected / exposed occurrences (all)	31 / 185 (16.76%) 40	38 / 183 (20.77%) 51	
Dysgeusia subjects affected / exposed occurrences (all)	33 / 185 (17.84%) 38	31 / 183 (16.94%) 38	
Paraesthesia subjects affected / exposed occurrences (all)	35 / 185 (18.92%) 66	15 / 183 (8.20%) 18	
Peripheral sensory neuropathy subjects affected / exposed occurrences (all)	35 / 185 (18.92%) 50	12 / 183 (6.56%) 12	
Dizziness			

subjects affected / exposed occurrences (all)	15 / 185 (8.11%) 15	28 / 183 (15.30%) 36	
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	65 / 185 (35.14%)	86 / 183 (46.99%)	
occurrences (all)	103	158	
Anaemia			
subjects affected / exposed	25 / 185 (13.51%)	34 / 183 (18.58%)	
occurrences (all)	31	45	
Thrombocytopenia			
subjects affected / exposed	44 / 185 (23.78%)	13 / 183 (7.10%)	
occurrences (all)	134	22	
Eye disorders			
Vision blurred			
subjects affected / exposed	13 / 185 (7.03%)	12 / 183 (6.56%)	
occurrences (all)	16	13	
Lacrimation increased			
subjects affected / exposed	4 / 185 (2.16%)	10 / 183 (5.46%)	
occurrences (all)	4	13	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	99 / 185 (53.51%)	123 / 183 (67.21%)	
occurrences (all)	189	242	
Nausea			
subjects affected / exposed	106 / 185 (57.30%)	109 / 183 (59.56%)	
occurrences (all)	201	203	
Constipation			
subjects affected / exposed	63 / 185 (34.05%)	65 / 183 (35.52%)	
occurrences (all)	86	115	
Vomiting			
subjects affected / exposed	58 / 185 (31.35%)	57 / 183 (31.15%)	
occurrences (all)	80	89	
Abdominal pain			
subjects affected / exposed	39 / 185 (21.08%)	54 / 183 (29.51%)	
occurrences (all)	47	82	
Stomatitis			

subjects affected / exposed	35 / 185 (18.92%)	38 / 183 (20.77%)	
occurrences (all)	50	56	
Gastrooesophageal reflux disease			
subjects affected / exposed	17 / 185 (9.19%)	18 / 183 (9.84%)	
occurrences (all)	19	20	
Dyspepsia			
subjects affected / exposed	19 / 185 (10.27%)	14 / 183 (7.65%)	
occurrences (all)	22	15	
Rectal haemorrhage			
subjects affected / exposed	11 / 185 (5.95%)	18 / 183 (9.84%)	
occurrences (all)	16	31	
Abdominal pain upper			
subjects affected / exposed	8 / 185 (4.32%)	15 / 183 (8.20%)	
occurrences (all)	8	22	
Oral pain			
subjects affected / exposed	8 / 185 (4.32%)	14 / 183 (7.65%)	
occurrences (all)	9	14	
Haemorrhoids			
subjects affected / exposed	6 / 185 (3.24%)	16 / 183 (8.74%)	
occurrences (all)	6	17	
Proctalgia			
subjects affected / exposed	7 / 185 (3.78%)	13 / 183 (7.10%)	
occurrences (all)	7	13	
Dry mouth			
subjects affected / exposed	7 / 185 (3.78%)	11 / 183 (6.01%)	
occurrences (all)	8	12	
Abdominal distension			
subjects affected / exposed	5 / 185 (2.70%)	12 / 183 (6.56%)	
occurrences (all)	5	14	
Dysphagia			
subjects affected / exposed	10 / 185 (5.41%)	2 / 183 (1.09%)	
occurrences (all)	10	2	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	26 / 185 (14.05%)	61 / 183 (33.33%)	
occurrences (all)	30	69	

Dry skin			
subjects affected / exposed	27 / 185 (14.59%)	26 / 183 (14.21%)	
occurrences (all)	36	38	
Rash			
subjects affected / exposed	19 / 185 (10.27%)	26 / 183 (14.21%)	
occurrences (all)	25	31	
Palmar-plantar erythrodysesthesia syndrome			
subjects affected / exposed	24 / 185 (12.97%)	18 / 183 (9.84%)	
occurrences (all)	37	22	
Skin hyperpigmentation			
subjects affected / exposed	18 / 185 (9.73%)	13 / 183 (7.10%)	
occurrences (all)	19	17	
Pruritus			
subjects affected / exposed	11 / 185 (5.95%)	9 / 183 (4.92%)	
occurrences (all)	17	14	
Hyperhidrosis			
subjects affected / exposed	2 / 185 (1.08%)	10 / 183 (5.46%)	
occurrences (all)	2	14	
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	38 / 185 (20.54%)	39 / 183 (21.31%)	
occurrences (all)	58	52	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	22 / 185 (11.89%)	25 / 183 (13.66%)	
occurrences (all)	24	36	
Back pain			
subjects affected / exposed	21 / 185 (11.35%)	23 / 183 (12.57%)	
occurrences (all)	25	31	
Pain in extremity			
subjects affected / exposed	22 / 185 (11.89%)	19 / 183 (10.38%)	
occurrences (all)	23	25	
Musculoskeletal pain			
subjects affected / exposed	17 / 185 (9.19%)	11 / 183 (6.01%)	
occurrences (all)	17	12	
Muscle spasms			



subjects affected / exposed occurrences (all)	7 / 185 (3.78%) 8	11 / 183 (6.01%) 14	
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	18 / 185 (9.73%)	20 / 183 (10.93%)	
occurrences (all)	19	21	
Upper respiratory tract infection			
subjects affected / exposed	15 / 185 (8.11%)	18 / 183 (9.84%)	
occurrences (all)	18	18	
Sinusitis			
subjects affected / exposed	9 / 185 (4.86%)	13 / 183 (7.10%)	
occurrences (all)	10	13	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	56 / 185 (30.27%)	55 / 183 (30.05%)	
occurrences (all)	93	76	
Hypokalaemia			
subjects affected / exposed	36 / 185 (19.46%)	33 / 183 (18.03%)	
occurrences (all)	44	39	
Dehydration			
subjects affected / exposed	28 / 185 (15.14%)	27 / 183 (14.75%)	
occurrences (all)	51	36	
Hyperglycaemia			
subjects affected / exposed	9 / 185 (4.86%)	23 / 183 (12.57%)	
occurrences (all)	15	26	
Hyponatraemia			
subjects affected / exposed	8 / 185 (4.32%)	15 / 183 (8.20%)	
occurrences (all)	10	18	

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 July 2012	The protocol was modified to include geographic region (United States or non-United States) as a stratification factor for enrollment. The start of Screening was also changed to the date that biopsy tissue became available, and biomarker samplings were updated.
26 October 2012	The protocol was amended primarily to modify the requirement for follow-up after study discontinuation. Participants who discontinued bevacizumab or other study drug were to continue with the rest of the treatment regimen until progression or unacceptable toxicity, and the end of treatment was re-defined as the time at which all study drugs were discontinued or the participant progressed. Thereafter, participants could enter the survival follow-up phase.

Notes:

---

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported