



Clinical trial results:

A Multicentre Randomized Phase II Study to Assess the Safety and Resectability in Patients With Initially Unresectable Liver Metastases Secondary to Colorectal Cancer Receiving First-Line Treatment Either With mFOLFOX-6 Plus Bevacizumab or FOLFOXIRI Plus Bevacizumab (OLIVIA)

Summary

EudraCT number	2007-007863-26
Trial protocol	AT GB FR ES
Global end of trial date	21 October 2013

Results information

Result version number	v1 (current)
This version publication date	20 April 2016
First version publication date	07 August 2015

Trial information

Trial identification

Sponsor protocol code	MO18725
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00778102
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	F. Hoffmann-La Roche
Sponsor organisation address	Grenzacherstrasse 124, Basel, Switzerland, CH-4070
Public contact	Roche Trial Information Hotline, F. Hoffmann-La Roche Ltd, 41 616878333, global.trial_information@roche.com
Scientific contact	Roche Trial Information Hotline, F. Hoffmann-La Roche Ltd, 41 616878333, 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	28 April 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	21 October 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This multicenter, randomized, Phase II study was designed to assess the safety and resectability in participants with initially unresectable liver metastases secondary to colorectal cancer receiving first-line treatment with bevacizumab plus 1 of 2 fluoropyrimidine/oxaliplatin-based chemotherapy regimens.

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 fully adhere to the principles outlined in Guideline for Good Clinical Practice International Conference on Harmonisation (ICH) Tripartite Guideline (January 1997) or with local law if it affords greater protection to the participant.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	23 October 2008
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	United Kingdom: 17
Country: Number of subjects enrolled	Spain: 24
Country: Number of subjects enrolled	Austria: 15
Country: Number of subjects enrolled	France: 24
Worldwide total number of subjects	80
EEA total number of subjects	80

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)	51
From 65 to 84 years	29
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

After informed consent was obtained, a 2-part Screening/Baseline investigation was carried out. During the first part (Day -28 to Day 1), investigations largely involved demography, physical examination, and other noninvasive measurements. The second part (Day -7 to Day 1) involved collection of clinical laboratory data.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
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Arm title	Bevacizumab + mFOLFOX-6
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Arm description:

Participants received a chemotherapy regimen of bevacizumab plus oxaliplatin, leucovorin, and 5-fluorouracil (5-FU) (mFOLFOX-6). Each drug was administered on Day 1 of each 2-week cycle. Dosing was as follows: bevacizumab 5 milligrams per kilogram (mg/kg) via intravenous (IV) infusion; oxaliplatin 85 milligrams per meter-squared (mg/m²) via IV infusion; leucovorin 400 mg/m² via IV infusion; 5-FU 400 mg/m² via IV bolus; and 5-FU 2400 mg/m² via continuous 46-hour IV infusion. Following completion of 12 cycles, participants could discontinue oxaliplatin and continue with bevacizumab, leucovorin, and 5-FU. Treatment was continued until resectability, progressive disease (PD), unacceptable toxicity, or participant refusal.

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 administered on Day 1 of each cycle and repeated every 2 weeks: 5 mg/kg via IV infusion. Treatment was continued until resectability, PD, unacceptable toxicity, or participant refusal.

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 administered on Day 1 of each cycle and repeated every 2 weeks: 85 mg/m² via IV infusion. Treatment was continued until resectability, PD, unacceptable toxicity, or participant refusal. Following completion of 12 cycles, participants could discontinue oxaliplatin.

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

Dosage and administration details:

Leucovorin was administered on Day 1 of each cycle and repeated every 2 weeks: 200 or 400 mg/m² via IV infusion. Treatment was continued until resectability, PD, unacceptable toxicity, or participant refusal.

refusal.

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-FU was administered on Day 1 of each cycle and repeated every 2 weeks. Dosing was based upon treatment assignment. Participants could have received either: 400 mg/m² via IV bolus and 2400 mg/m² via continuous 46-hour IV infusion, or (without bolus) 3200 mg/m² via continuous 46-hour IV infusion. Treatment was continued until resectability, PD, unacceptable toxicity, or participant refusal.

Arm title	Bevacizumab + FOLFOXIRI
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Arm description:

Participants received a chemotherapy regimen of bevacizumab plus oxaliplatin, irinotecan, leucovorin, and 5-FU (FOLFOXIRI). Each drug was administered on Day 1 of each 2-week cycle. Dosing was as follows: bevacizumab 5 mg/kg via IV infusion; oxaliplatin 85 mg/m² via IV infusion; irinotecan 165 mg/m² via IV infusion; leucovorin 200 mg/m² via IV infusion; and 5-FU 3200 mg/m² via continuous 46-hour IV infusion. Following completion of 12 cycles, participants were to discontinue either irinotecan, oxaliplatin, or both. Treatment was continued until resectability, PD, unacceptable toxicity, or participant refusal.

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 administered on Day 1 of each cycle and repeated every 2 weeks: 5 mg/kg via IV infusion. Treatment was continued until resectability, PD, unacceptable toxicity, or participant refusal.

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 administered on Day 1 of each cycle and repeated every 2 weeks: 85 mg/m² via IV infusion. Treatment was continued until resectability, PD, unacceptable toxicity, or participant refusal. Following completion of 12 cycles, participants could discontinue oxaliplatin.

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

Dosage and administration details:

Leucovorin was administered on Day 1 of each cycle and repeated every 2 weeks: 200 or 400 mg/m² via IV infusion. Treatment was continued until resectability, PD, unacceptable toxicity, or participant refusal.

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-FU was administered on Day 1 of each cycle and repeated every 2 weeks. Dosing was based upon treatment assignment. Participants could have received either: 400 mg/m² via IV bolus and 2400 mg/m² via continuous 46-hour IV infusion, or (without bolus) 3200 mg/m² via continuous 46-hour

IV infusion. Treatment was continued until resectability, PD, unacceptable toxicity, or participant refusal.

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 administered on Day 1 of each cycle and repeated every 2 weeks: 165 mg/m² via IV infusion. Treatment was continued until resectability, PD, unacceptable toxicity, or participant refusal. Following completion of 12 cycles, participants could discontinue irinotecan.

Number of subjects in period 1	Bevacizumab + mFOLFOX-6	Bevacizumab + FOLFOXIRI
Started	39	41
Completed	18	19
Not completed	21	22
Consent withdrawn by subject	1	1
Death	1	1
Refused treatment	2	3
Violation of selection criteria	1	1
Adverse event	8	5
Lost to follow-up	1	-
Administrative reason	7	10
Protocol deviation	-	1

Baseline characteristics

Reporting groups

Reporting group title	Bevacizumab + mFOLFOX-6
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Reporting group description:

Participants received a chemotherapy regimen of bevacizumab plus oxaliplatin, leucovorin, and 5-fluorouracil (5-FU) (mFOLFOX-6). Each drug was administered on Day 1 of each 2-week cycle. Dosing was as follows: bevacizumab 5 milligrams per kilogram (mg/kg) via intravenous (IV) infusion; oxaliplatin 85 milligrams per meter-squared (mg/m²) via IV infusion; leucovorin 400 mg/m² via IV infusion; 5-FU 400 mg/m² via IV bolus; and 5-FU 2400 mg/m² via continuous 46-hour IV infusion. Following completion of 12 cycles, participants could discontinue oxaliplatin and continue with bevacizumab, leucovorin, and 5-FU. Treatment was continued until resectability, progressive disease (PD), unacceptable toxicity, or participant refusal.

Reporting group title	Bevacizumab + FOLFOXIRI
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Reporting group description:

Participants received a chemotherapy regimen of bevacizumab plus oxaliplatin, irinotecan, leucovorin, and 5-FU (FOLFOXIRI). Each drug was administered on Day 1 of each 2-week cycle. Dosing was as follows: bevacizumab 5 mg/kg via IV infusion; oxaliplatin 85 mg/m² via IV infusion; irinotecan 165 mg/m² via IV infusion; leucovorin 200 mg/m² via IV infusion; and 5-FU 3200 mg/m² via continuous 46-hour IV infusion. Following completion of 12 cycles, participants were to discontinue either irinotecan, oxaliplatin, or both. Treatment was continued until resectability, PD, unacceptable toxicity, or participant refusal.

Reporting group values	Bevacizumab + mFOLFOX-6	Bevacizumab + FOLFOXIRI	Total
Number of subjects	39	41	80
Age categorical			
Units: Subjects			

Age continuous			
Units: years			
arithmetic mean	57.1	61.8	
standard deviation	± 10.32	± 11.02	-
Gender categorical			
Units: Subjects			
Female	21	12	33
Male	18	29	47

End points

End points reporting groups

Reporting group title	Bevacizumab + mFOLFOX-6
Reporting group description: Participants received a chemotherapy regimen of bevacizumab plus oxaliplatin, leucovorin, and 5-fluorouracil (5-FU) (mFOLFOX-6). Each drug was administered on Day 1 of each 2-week cycle. Dosing was as follows: bevacizumab 5 milligrams per kilogram (mg/kg) via intravenous (IV) infusion; oxaliplatin 85 milligrams per meter-squared (mg/m ²) via IV infusion; leucovorin 400 mg/m ² via IV infusion; 5-FU 400 mg/m ² via IV bolus; and 5-FU 2400 mg/m ² via continuous 46-hour IV infusion. Following completion of 12 cycles, participants could discontinue oxaliplatin and continue with bevacizumab, leucovorin, and 5-FU. Treatment was continued until resectability, progressive disease (PD), unacceptable toxicity, or participant refusal.	
Reporting group title	Bevacizumab + FOLFOXIRI
Reporting group description: Participants received a chemotherapy regimen of bevacizumab plus oxaliplatin, irinotecan, leucovorin, and 5-FU (FOLFOXIRI). Each drug was administered on Day 1 of each 2-week cycle. Dosing was as follows: bevacizumab 5 mg/kg via IV infusion; oxaliplatin 85 mg/m ² via IV infusion; irinotecan 165 mg/m ² via IV infusion; leucovorin 200 mg/m ² via IV infusion; and 5-FU 3200 mg/m ² via continuous 46-hour IV infusion. Following completion of 12 cycles, participants were to discontinue either irinotecan, oxaliplatin, or both. Treatment was continued until resectability, PD, unacceptable toxicity, or participant refusal.	

Primary: Percentage of Participants With Complete Resection or Residual (Microscopic or Macroscopic) Tumor

End point title	Percentage of Participants With Complete Resection or Residual (Microscopic or Macroscopic) Tumor
End point description: Following resective surgery, participants were evaluated for complete resection (R0) or the presence of microscopic (R1) or macroscopic (R2) residual tumor. The percentage of participants within each residual tumor classification was calculated as [number of participants with R0, R1, and/or R2 divided by the total number of participants] multiplied by 100. Associated 95% confidence intervals were calculated for one-sample binomial using the Clopper-Pearson method. Intent-to-Treat (ITT) Population: All randomized participants. Participants were analyzed according to which treatment group they were randomized, regardless of the treatment actually received.	
End point type	Primary
End point timeframe: Up to 5 years (at Screening; every 6 weeks, and within 4 weeks prior to surgery; and at time of/after surgery)	

End point values	Bevacizumab + mFOLFOX-6	Bevacizumab + FOLFOXIRI		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	41		
Units: percentage of participants				
number (confidence interval 95%)				
R0, R1, or R2	48.7 (32.4 to 65.2)	61 (44.5 to 75.8)		
R0 or R1	33.3 (19.1 to 50.2)	51.2 (35.1 to 67.1)		
R0	23.1 (11.1 to 39.3)	48.8 (32.9 to 64.9)		

Statistical analyses

Statistical analysis title	Difference in resection rate (R0, R1, R2)
Statistical analysis description: Difference between groups in the collective percentage of participants with R0, R1, or R2.	
Comparison groups	Bevacizumab + mFOLFOX-6 v Bevacizumab + FOLFOXIRI
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.2707
Method	Chi-squared
Parameter estimate	Difference in resection rate
Point estimate	12.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11
upper limit	35.5

Secondary: Time to Resection

End point title	Time to Resection
End point description: Time to resection was defined as the time from randomization to the date of first resective surgery. For participants who did not undergo resective surgery, time to resection was censored at Day 1. Time to resection was estimated by Kaplan-Meier analysis. ITT Population.	
End point type	Secondary
End point timeframe: Up to 5 years (at Screening; prior to each cycle, and within 7 days prior to surgery; and at time of surgery)	

End point values	Bevacizumab + mFOLFOX-6	Bevacizumab + FOLFOXIRI		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	41		
Units: months				
median (confidence interval 95%)	4.4 (4.1 to 5.8)	4.3 (3.9 to 5.5)		

Statistical analyses

Secondary: Percentage of Participants With Histopathological Response

End point title	Percentage of Participants With Histopathological Response
End point description:	
At the time of resective surgery, participants were evaluated for histopathological response as defined through pathologist review of the resected metastatic lesions, including assessment of margin status and tumor cell viability. Histopathological response classification was based upon the percentage of viable tumor cells, where 'Complete response' was considered for those with 0 percent (%) viable tumor cells, 'Major response' for those with 1% to 49% viable tumor cells, 'Minor response' for 50% to 99% viable tumor cells, and 'No response' for 100% viable tumor cells. The response could not be determined in some cases and was documented as 'Unknown.' The percentage of participants within each response category was calculated as [number of participants with a given response divided by the number of participants who completed the assessment] multiplied by 100. ITT Population.	
End point type	Secondary
End point timeframe:	
Up to 5 years (at Screening; every 6 weeks, and within 4 weeks prior to surgery; and at time of/after surgery)	

End point values	Bevacizumab + mFOLFOX-6	Bevacizumab + FOLFOXIRI		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14 ^[1]	21 ^[2]		
Units: percentage of participants				
number (not applicable)				
Complete response	0	4.8		
Major response	57.1	47.6		
Minor response	28.6	33.3		
No response	0	0		
Unknown	14.3	14.3		

Notes:

[1] - Only participants with histopathological assessment after first resective surgery were considered.

[2] - Only participants with histopathological assessment after first resective surgery were considered.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Complete or Major Histopathological Response

End point title	Percentage of Participants With Complete or Major Histopathological Response
End point description:	
At the time of resective surgery, participants were evaluated for histopathological response as defined through pathologist review of the resected metastatic lesions, including assessment of margin status and tumor cell viability. Histopathological response classification was based upon the percentage of viable tumor cells, as described previously. The collective percentage of participants assessed as having a complete or major response was calculated as [number of participants with complete or major response divided by the number of participants who completed the assessment] multiplied by 100. Associated 95% confidence intervals were calculated for one-sample binomial using the Clopper-Pearson method. ITT Population.	
End point type	Secondary
End point timeframe:	
Up to 5 years (at Screening; every 6 weeks, and within 4 weeks prior to surgery; and at time of/after surgery)	

End point values	Bevacizumab + mFOLFOX-6	Bevacizumab + FOLFOXIRI		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14 ^[3]	21 ^[4]		
Units: percentage of participants				
number (confidence interval 95%)	57.1 (28.9 to 82.3)	52.4 (29.8 to 74.3)		

Notes:

[3] - Only participants with histopathological assessment after first resective surgery were included.

[4] - Only participants with histopathological assessment after first resective surgery were included.

Statistical analyses

Statistical analysis title	Difference in response rate
Statistical analysis description:	
Difference between groups in the collective percentage of participants with complete or major histopathological response.	
Comparison groups	Bevacizumab + mFOLFOX-6 v Bevacizumab + FOLFOXIRI
Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.7817
Method	Chi-squared
Parameter estimate	Difference in response rate
Point estimate	-4.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-43
upper limit	33.5

Secondary: Percentage of Participants Experiencing Relapse Following Curative Resection

End point title	Percentage of Participants Experiencing Relapse Following Curative Resection
End point description:	
Among participants with curative resection (complete resection [R0] or microscopic residual tumor [R1]), relapse was defined as the first new occurrence of cancer or death. The percentage of participants who experienced relapse was calculated as [number of participants with a relapse event divided by the number of participants initially classified as R0 or R1 following resective surgery] multiplied by 100. ITT Population.	
End point type	Secondary
End point timeframe:	
Up to 5 years (at time of surgery; 48 hours and 4 and 12 weeks after surgery; within 4 weeks after completion of treatment; every 3 to 6 months for 1 year; then annually)	

End point values	Bevacizumab + mFOLFOX-6	Bevacizumab + FOLFOXIRI		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13 ^[5]	21 ^[6]		
Units: percentage of participants				
number (not applicable)	76.9	57.1		

Notes:

[5] - Only those with residual tumor classification of R0 or R1 were considered in the analysis.

[6] - Only those with residual tumor classification of R0 or R1 were considered in the analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Relapse-Free Survival (RFS)

End point title	Relapse-Free Survival (RFS)
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End point description:

RFS was defined as the time from curative resection (complete resection [R0] or microscopic residual tumor [R1]) to the date of first diagnosis of relapse. For participants with curative resection and without relapse, RFS was censored at the last known relapse-free assessment. RFS was estimated by Kaplan-Meier analysis. ITT Population. (99999 = not estimable due to insufficient follow-up.)

End point type	Secondary
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End point timeframe:

Up to 5 years (at time of surgery; 48 hours and 4 and 12 weeks after surgery; within 4 weeks after completion of treatment; every 3 to 6 months for 1 year; then annually)

End point values	Bevacizumab + mFOLFOX-6	Bevacizumab + FOLFOXIRI		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13 ^[7]	21 ^[8]		
Units: months				
median (confidence interval 95%)	8.1 (3.8 to 11.7)	17.1 (12.3 to 99999)		

Notes:

[7] - Only those with residual tumor classification of R0 or R1 were considered in the analysis.

[8] - Only those with residual tumor classification of R0 or R1 were considered in the analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Experiencing Death or Disease Progression

End point title	Percentage of Participants Experiencing Death or Disease Progression
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End point description:

PD was defined, using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0, as at least a 20% increase in the sum of the longest diameter of target lesions, or the appearance of one or more new lesions. The percentage of participants experiencing PD or death was calculated as [number of participants with event divided by the number of participants analyzed] multiplied by 100. ITT

Population.

End point type	Secondary
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End point timeframe:

Up to 5 years (at Screening; every 6 weeks, and within 4 weeks prior to surgery; 4 and 12 weeks after surgery; and at the end of Cycles 4 and 8 if assessed as R0 or R1, or every 6 weeks until progression or resectability if assessed as R2)

End point values	Bevacizumab + mFOLFOX-6	Bevacizumab + FOLFOXIRI		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	41		
Units: percentage of participants				
number (not applicable)	89.7	68.3		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-Free Survival (PFS)

End point title	Progression-Free Survival (PFS)
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End point description:

PFS was defined, using RECIST version 1.0, as the time from randomization to the date of first documented PD or death from any cause. PD was defined as at least a 20% increase in the sum of the longest diameter of target lesions, or the appearance of one or more new lesions. For participants without documented PD or death, PFS was censored at the time of last tumor assessment. PFS was estimated by Kaplan-Meier analysis. ITT Population.

End point type	Secondary
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End point timeframe:

Up to 5 years (at Screening; every 6 weeks, and within 4 weeks prior to surgery; 4 and 12 weeks after surgery; and at the end of Cycles 4 and 8 if assessed as R0 or R1, or every 6 weeks until progression or resectability if assessed as R2)

End point values	Bevacizumab + mFOLFOX-6	Bevacizumab + FOLFOXIRI		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	41		
Units: months				
median (confidence interval 95%)	11.5 (9.6 to 13.6)	18.6 (12.9 to 22.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Who Died

End point title	Percentage of Participants Who Died
End point description:	
ITT Population.	
End point type	Secondary
End point timeframe:	
Up to 5 years (prior to each cycle, and within 7 days prior to surgery; at time of surgery; 48 hours and 4 and 12 weeks after surgery; within 4 weeks after completion of treatment; every 3 to 6 months for 1 year; then annually)	

End point values	Bevacizumab + mFOLFOX-6	Bevacizumab + FOLFOXIRI		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	41		
Units: percentage of participants				
number (not applicable)	48.7	19.5		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)
End point description:	
OS was defined as the time from randomization to death from any cause. For participants without an event of death, OS was censored at the last-known alive date. OS was estimated by Kaplan-Meier analysis. ITT Population. (99999 = not estimable due to insufficient follow-up.)	
End point type	Secondary
End point timeframe:	
Up to 5 years (prior to each cycle, and within 7 days prior to surgery; at time of surgery; 48 hours and 4 and 12 weeks after surgery; within 4 weeks after completion of treatment; every 3 to 6 months for 1 year; then annually)	

End point values	Bevacizumab + mFOLFOX-6	Bevacizumab + FOLFOXIRI		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	41		
Units: months				
median (confidence interval 95%)	32.2 (21.5 to 99999)	99999 (99999 to 99999)		

Statistical analyses

Secondary: Percentage of Participants With a Confirmed Best Overall Response of Complete Response (CR) or Partial Response (PR) According to RECIST Version 1.0

End point title	Percentage of Participants With a Confirmed Best Overall Response of Complete Response (CR) or Partial Response (PR) According to RECIST Version 1.0
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End point description:

Using RECIST version 1.0, participants were considered to have achieved CR upon the disappearance of all target and non-target lesions. Participants who achieved PR demonstrated at least a 30% decrease in the sum of the largest diameter of target lesions, taking as reference the Screening sum largest diameter. Responses were confirmed by repeat assessments no less than 4 weeks after criteria for response were first met. The collective percentage of participants with confirmed best overall response of CR or PR was calculated as [number of participants meeting RECIST criteria for CR or PR divided by the number of participants analyzed] multiplied by 100. Associated 95% confidence intervals were calculated for one-sample binomial using the Clopper-Pearson method. ITT Population.

End point type	Secondary
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End point timeframe:

Up to 5 years (at Screening; every 6 weeks, and within 4 weeks prior to surgery; 4 and 12 weeks after surgery; and at the end of Cycles 4 and 8 if assessed as R0 or R1, or every 6 weeks until progression or resectability if assessed as R2)

End point values	Bevacizumab + mFOLFOX-6	Bevacizumab + FOLFOXIRI		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	41		
Units: percentage of participants				
number (confidence interval 95%)	61.5 (44.6 to 76.6)	80.5 (65.1 to 91.2)		

Statistical analyses

Statistical analysis title	Difference in response rate (CR or PR)
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Statistical analysis description:

Difference between groups in the collective percentage of participants with confirmed best overall response of CR or PR.

Comparison groups	Bevacizumab + mFOLFOX-6 v Bevacizumab + FOLFOXIRI
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0612
Method	Chi-squared
Parameter estimate	Difference in response rate
Point estimate	18.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.1
upper limit	40

Secondary: Time to Response

End point title	Time to Response
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End point description:

Time to response according to RECIST version 1.0 was defined as the time from randomization to the date of first documented CR or PR. Participants were considered to have achieved CR upon the disappearance of all target and non-target lesions. Participants who achieved PR demonstrated at least a 30% decrease in the sum of the largest diameter of target lesions, taking as reference the Screening sum largest diameter. Responses were confirmed by repeat assessments no less than 4 weeks after criteria for response were first met. For participants who did not complete a confirmatory tumor assessment, time to response was censored at the date of last tumor assessment, or if unavailable, at the date of first dose. Time to response was estimated by Kaplan-Meier analysis. ITT Population.

End point type	Secondary
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End point timeframe:

Up to 5 years (at Screening; every 6 weeks, and within 4 weeks prior to surgery; 4 and 12 weeks after surgery; and at the end of Cycles 4 and 8 if assessed as R0 or R1, or every 6 weeks until progression or resectability if assessed as R2)

End point values	Bevacizumab + mFOLFOX-6	Bevacizumab + FOLFOXIRI		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	41		
Units: months				
median (confidence interval 95%)	3.1 (2.7 to 8.6)	3.1 (1.9 to 3.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Complications Related to First Resective Surgery

End point title	Percentage of Participants With Complications Related to First Resective Surgery
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End point description:

Complications related to the first resective surgery were evaluated using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 3.0, and classified according to severity. The NCI-CTCAE severity classification criteria are as follows: Grade 5 equals (=) resulting in death; Grade 4 = life-threatening; Grade 3 = severe; Grade 2 = moderate; and Grade 1 = mild. The percentage of participants experiencing a given adverse event (AE) by severity grade was calculated as [number of participants with an AE divided by the number of participants who underwent first resective surgery] multiplied by 100. Safety Population (First Surgery Subpopulation): All participants who underwent a first resective surgery and who received at least one dose of trial medication, whether prematurely withdrawn or not. Participants were analyzed according to the actual treatment they received.

End point type	Secondary
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End point timeframe:

Up to 5 years (at time of surgery; 48 hours and 4 and 12 weeks after surgery; within 4 weeks after completion of treatment; every 3 to 6 months for 1 year; then annually)

End point values	Bevacizumab + mFOLFOX-6	Bevacizumab + FOLFOXIRI		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	25		
Units: percentage of participants				
number (not applicable)				
Any complication, Total	73.7	52		
Any complication, Grade 1	15.8	4		
Any complication, Grade 2	36.8	12		
Any complication, Grade 3	10.5	24		
Any complication, Grade 4	0	12		
Any complication, Grade 5	10.5	0		
Bleeding, Total	15.8	8		
Bleeding, Grade 1	5.3	0		
Bleeding, Grade 2	5.3	4		
Bleeding, Grade 3	5.3	4		
Cardiovascular, Total	10.5	4		
Cardiovascular, Grade 2	0	4		
Cardiovascular, Grade 3	5.3	0		
Cardiovascular, Grade 4	5.3	0		
Infections, Total	26.3	32		
Infections, Grade 1	10.5	12		
Infections, Grade 2	5.3	0		
Infections, Grade 3	5.3	16		
Infections, Grade 4	5.3	4		
Liver insufficiency, Total	10.5	0		
Liver insufficiency, Grade 5	10.5	0		
Neural disorder, Total	5.3	0		
Neural disorder, Grade 2	5.3	0		
Noninfected perihepatic fluid collections, Total	0	4		
Noninfected perihepatic fluid collections, Grade 2	0	4		
Other complication, Total	52.6	28		
Other complication, Grade 1	26.3	8		
Other complication, Grade 2	21.1	8		
Other complication, Grade 3	0	12		
Other complication, Grade 4	5.3	0		
Pulmonary, Total	5.3	4		
Pulmonary, Grade 3	5.3	4		
Renal impairment, Total	10.5	4		
Renal impairment, Grade 2	5.3	4		
Renal impairment, Grade 4	5.3	0		
Wound healing, Total	5.3	12		
Wound healing, Grade 1	5.3	0		
Wound healing, Grade 3	0	4		
Wound healing, Grade 4	0	8		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Complications Related to Second Resective Surgery

End point title	Percentage of Participants With Complications Related to Second Resective Surgery
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End point description:

Complications related to the second resective surgery were evaluated using the NCI-CTCAE version 3.0, and classified according to severity. The NCI-CTCAE severity classification criteria are as follows: Grade 5 = resulting in death; Grade 4 = life-threatening; Grade 3 = severe; Grade 2 = moderate; and Grade 1 = mild. The percentage of participants experiencing a given AE by severity grade was calculated as [number of participants with an AE divided by the number of participants who underwent second resective surgery] multiplied by 100. Safety Population (Second Surgery Subpopulation): All participants who underwent a second resective surgery and who received at least one dose of trial medication, whether prematurely withdrawn or not. Participants were analyzed according to the actual treatment they received.

End point type	Secondary
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End point timeframe:

Up to 5 years (at time of surgery; 48 hours and 4 and 12 weeks after surgery; within 4 weeks after completion of treatment; every 3 to 6 months for 1 year; then annually)

End point values	Bevacizumab + mFOLFOX-6	Bevacizumab + FOLFOXIRI		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	3		
Units: percentage of participants				
number (not applicable)				
Any complication, Total	100	66.7		
Any complication, Grade 1	0	33.3		
Any complication, Grade 2	66.7	0		
Any complication, Grade 3	0	33.3		
Any complication, Grade 3a	33.3	0		
Bleeding, Total	33.3	33.3		
Bleeding, Grade 1	0	33.3		
Bleeding, Grade 2	33.3	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 5 years (at Screening; prior to each cycle, and within 7 days prior to surgery; at time of surgery; 48 hours and 4 and 12 weeks after surgery; within 4 weeks after completion of treatment; every 3 to 6 months for 1 year; then annually)

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	15.0

Reporting groups

Reporting group title	Bevacizumab + mFOLFOX-6
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Reporting group description:

Participants received a chemotherapy regimen of bevacizumab plus mFOLFOX-6. Each drug was administered on Day 1 of each 2-week cycle. Dosing was as follows: bevacizumab 5 mg/kg via IV infusion; oxaliplatin 85 mg/m² via IV infusion; leucovorin 400 mg/m² via IV infusion; 5-FU 400 mg/m² via IV bolus; and 5-FU 2400 mg/m² via continuous 46-hour IV infusion. Following completion of 12 cycles, participants could discontinue oxaliplatin and continue with bevacizumab, leucovorin, and 5-FU. Treatment was continued until resectability, PD, unacceptable toxicity, or participant refusal.

Reporting group title	Bevacizumab + FOLFOXIRI
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Reporting group description:

Participants received a chemotherapy regimen of bevacizumab plus FOLFOXIRI. Each drug was administered on Day 1 of each 2-week cycle. Dosing was as follows: bevacizumab 5 mg/kg via IV infusion; oxaliplatin 85 mg/m² via IV infusion; irinotecan 165 mg/m² via IV infusion; leucovorin 200 mg/m² via IV infusion; and 5-FU 3200 mg/m² via continuous 46-hour IV infusion. Following completion of 12 cycles, participants were to discontinue either irinotecan, oxaliplatin, or both. Treatment was continued until resectability, PD, unacceptable toxicity, or participant refusal.

Serious adverse events	Bevacizumab + mFOLFOX-6	Bevacizumab + FOLFOXIRI	
Total subjects affected by serious adverse events			
subjects affected / exposed	24 / 37 (64.86%)	24 / 40 (60.00%)	
number of deaths (all causes)	19	8	
number of deaths resulting from adverse events			
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	2 / 37 (5.41%)	2 / 40 (5.00%)	
occurrences causally related to treatment / all	1 / 2	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombosis			
subjects affected / exposed	1 / 37 (2.70%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			

Pyrexia			
subjects affected / exposed	0 / 37 (0.00%)	2 / 40 (5.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	1 / 37 (2.70%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Impaired healing			
subjects affected / exposed	0 / 37 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	1 / 37 (2.70%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Pelvic fluid collection			
subjects affected / exposed	0 / 37 (0.00%)	1 / 40 (2.50%)	
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	2 / 37 (5.41%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	1 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	0 / 37 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			

subjects affected / exposed	1 / 37 (2.70%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	1 / 37 (2.70%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Endoscopic retrograde cholangiopancreatography			
subjects affected / exposed	1 / 37 (2.70%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 37 (2.70%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Wound dehiscence			
subjects affected / exposed	0 / 37 (0.00%)	3 / 40 (7.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Failure to anastomose			
subjects affected / exposed	1 / 37 (2.70%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	1 / 37 (2.70%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			

subjects affected / exposed	1 / 37 (2.70%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Paraesthesia			
subjects affected / exposed	0 / 37 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	3 / 37 (8.11%)	6 / 40 (15.00%)	
occurrences causally related to treatment / all	3 / 3	6 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	3 / 37 (8.11%)	4 / 40 (10.00%)	
occurrences causally related to treatment / all	3 / 3	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disseminated intravascular coagulation			
subjects affected / exposed	0 / 37 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 37 (2.70%)	6 / 40 (15.00%)	
occurrences causally related to treatment / all	1 / 1	6 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	1 / 37 (2.70%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	1 / 37 (2.70%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Abdominal pain upper			
subjects affected / exposed	1 / 37 (2.70%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 37 (2.70%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal hypomotility			
subjects affected / exposed	0 / 37 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	0 / 37 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestinal obstruction			
subjects affected / exposed	1 / 37 (2.70%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine perforation			
subjects affected / exposed	0 / 37 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Localised intraabdominal fluid collection			
subjects affected / exposed	0 / 37 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	0 / 37 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritoneal haemorrhage			

subjects affected / exposed	0 / 37 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retroperitoneal haematoma			
subjects affected / exposed	1 / 37 (2.70%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	1 / 37 (2.70%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatic failure			
subjects affected / exposed	2 / 37 (5.41%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Cholangitis			
subjects affected / exposed	1 / 37 (2.70%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Portal vein thrombosis			
subjects affected / exposed	1 / 37 (2.70%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Muscle spasms			
subjects affected / exposed	0 / 37 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal disorder			
subjects affected / exposed	1 / 37 (2.70%)	0 / 40 (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 Peritonitis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 37 (0.00%) 0 / 0 0 / 0	2 / 40 (5.00%) 0 / 2 0 / 0	
Bacterial sepsis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 37 (2.70%) 1 / 1 0 / 0	0 / 40 (0.00%) 0 / 0 0 / 0	
Campylobacter infection subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 37 (0.00%) 0 / 0 0 / 0	1 / 40 (2.50%) 1 / 1 0 / 0	
Cholecystitis infective subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 37 (0.00%) 0 / 0 0 / 0	1 / 40 (2.50%) 0 / 1 0 / 0	
Device related infection subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 37 (2.70%) 1 / 1 0 / 0	0 / 40 (0.00%) 0 / 0 0 / 0	
Infection subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 37 (0.00%) 0 / 0 0 / 0	1 / 40 (2.50%) 0 / 1 0 / 0	
Liver abscess subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 37 (2.70%) 0 / 1 0 / 0	0 / 40 (0.00%) 0 / 0 0 / 0	
Lower respiratory tract infection subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 37 (0.00%) 0 / 0 0 / 0	1 / 40 (2.50%) 1 / 1 0 / 0	
Lung infection			

subjects affected / exposed	0 / 37 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic sepsis			
subjects affected / exposed	1 / 37 (2.70%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			
subjects affected / exposed	1 / 37 (2.70%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Bevacizumab + mFOLFOX-6	Bevacizumab + FOLFOXIRI	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	36 / 37 (97.30%)	40 / 40 (100.00%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	8 / 37 (21.62%)	5 / 40 (12.50%)	
occurrences (all)	12	5	
Hypotension			
subjects affected / exposed	2 / 37 (5.41%)	0 / 40 (0.00%)	
occurrences (all)	2	0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	14 / 37 (37.84%)	16 / 40 (40.00%)	
occurrences (all)	35	40	
Mucosal inflammation			
subjects affected / exposed	20 / 37 (54.05%)	17 / 40 (42.50%)	
occurrences (all)	37	31	
Fatigue			
subjects affected / exposed	10 / 37 (27.03%)	12 / 40 (30.00%)	
occurrences (all)	27	35	
Pyrexia			

subjects affected / exposed	7 / 37 (18.92%)	12 / 40 (30.00%)	
occurrences (all)	15	15	
Catheter site pain			
subjects affected / exposed	2 / 37 (5.41%)	1 / 40 (2.50%)	
occurrences (all)	2	1	
Pain			
subjects affected / exposed	1 / 37 (2.70%)	2 / 40 (5.00%)	
occurrences (all)	1	2	
Chest pain			
subjects affected / exposed	2 / 37 (5.41%)	0 / 40 (0.00%)	
occurrences (all)	2	0	
Oedema peripheral			
subjects affected / exposed	0 / 37 (0.00%)	2 / 40 (5.00%)	
occurrences (all)	0	2	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	3 / 37 (8.11%)	3 / 40 (7.50%)	
occurrences (all)	4	4	
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	13 / 37 (35.14%)	16 / 40 (40.00%)	
occurrences (all)	17	26	
Cough			
subjects affected / exposed	3 / 37 (8.11%)	5 / 40 (12.50%)	
occurrences (all)	5	6	
Rhinorrhoea			
subjects affected / exposed	3 / 37 (8.11%)	3 / 40 (7.50%)	
occurrences (all)	6	4	
Dyspnoea			
subjects affected / exposed	3 / 37 (8.11%)	2 / 40 (5.00%)	
occurrences (all)	4	2	
Dysphonia			
subjects affected / exposed	2 / 37 (5.41%)	2 / 40 (5.00%)	
occurrences (all)	2	3	
Dyspnoea exertional			

subjects affected / exposed occurrences (all)	2 / 37 (5.41%) 3	2 / 40 (5.00%) 2	
Oropharyngeal pain subjects affected / exposed occurrences (all)	1 / 37 (2.70%) 1	4 / 40 (10.00%) 4	
Nasal congestion subjects affected / exposed occurrences (all)	1 / 37 (2.70%) 1	2 / 40 (5.00%) 2	
Psychiatric disorders			
Insomnia subjects affected / exposed occurrences (all)	7 / 37 (18.92%) 8	2 / 40 (5.00%) 2	
Anxiety subjects affected / exposed occurrences (all)	2 / 37 (5.41%) 3	1 / 40 (2.50%) 1	
Investigations			
Platelet count decreased subjects affected / exposed occurrences (all)	5 / 37 (13.51%) 12	3 / 40 (7.50%) 5	
Haemoglobin decreased subjects affected / exposed occurrences (all)	2 / 37 (5.41%) 10	2 / 40 (5.00%) 3	
White blood cell count decreased subjects affected / exposed occurrences (all)	2 / 37 (5.41%) 2	1 / 40 (2.50%) 6	
Gamma-glutamyltransferase increased subjects affected / exposed occurrences (all)	3 / 37 (8.11%) 6	1 / 40 (2.50%) 1	
Blood lactate dehydrogenase increased subjects affected / exposed occurrences (all)	2 / 37 (5.41%) 5	0 / 40 (0.00%) 0	
Alanine aminotransferase increased subjects affected / exposed occurrences (all)	2 / 37 (5.41%) 2	1 / 40 (2.50%) 2	
Aspartate aminotransferase increased			

subjects affected / exposed occurrences (all)	2 / 37 (5.41%) 3	1 / 40 (2.50%) 1	
Weight decreased subjects affected / exposed occurrences (all)	2 / 37 (5.41%) 2	1 / 40 (2.50%) 2	
Blood alkaline phosphatase increased subjects affected / exposed occurrences (all)	2 / 37 (5.41%) 3	0 / 40 (0.00%) 0	
Injury, poisoning and procedural complications Procedural pain subjects affected / exposed occurrences (all)	1 / 37 (2.70%) 2	3 / 40 (7.50%) 3	
Nervous system disorders Neuropathy peripheral subjects affected / exposed occurrences (all)	22 / 37 (59.46%) 63	19 / 40 (47.50%) 56	
Paraesthesia subjects affected / exposed occurrences (all)	12 / 37 (32.43%) 26	7 / 40 (17.50%) 12	
Peripheral sensory neuropathy subjects affected / exposed occurrences (all)	4 / 37 (10.81%) 22	4 / 40 (10.00%) 10	
Headache subjects affected / exposed occurrences (all)	9 / 37 (24.32%) 15	7 / 40 (17.50%) 8	
Dysgeusia subjects affected / exposed occurrences (all)	5 / 37 (13.51%) 8	10 / 40 (25.00%) 13	
Lethargy subjects affected / exposed occurrences (all)	3 / 37 (8.11%) 8	2 / 40 (5.00%) 12	
Dysaesthesia subjects affected / exposed occurrences (all)	3 / 37 (8.11%) 5	2 / 40 (5.00%) 3	
Dizziness			

subjects affected / exposed occurrences (all)	3 / 37 (8.11%) 3	1 / 40 (2.50%) 1	
Polyneuropathy subjects affected / exposed occurrences (all)	3 / 37 (8.11%) 3	1 / 40 (2.50%) 1	
Blood and lymphatic system disorders Neutropenia subjects affected / exposed occurrences (all)	20 / 37 (54.05%) 33	26 / 40 (65.00%) 75	
Thrombocytopenia subjects affected / exposed occurrences (all)	4 / 37 (10.81%) 8	8 / 40 (20.00%) 16	
Anaemia subjects affected / exposed occurrences (all)	4 / 37 (10.81%) 4	6 / 40 (15.00%) 8	
Leukopenia subjects affected / exposed occurrences (all)	1 / 37 (2.70%) 1	4 / 40 (10.00%) 6	
Lymphopenia subjects affected / exposed occurrences (all)	2 / 37 (5.41%) 4	0 / 40 (0.00%) 0	
Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences (all)	2 / 37 (5.41%) 2	2 / 40 (5.00%) 5	
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all)	20 / 37 (54.05%) 39	33 / 40 (82.50%) 103	
Nausea subjects affected / exposed occurrences (all)	23 / 37 (62.16%) 64	21 / 40 (52.50%) 66	
Vomiting subjects affected / exposed occurrences (all)	14 / 37 (37.84%) 19	25 / 40 (62.50%) 56	
Constipation			

subjects affected / exposed	18 / 37 (48.65%)	15 / 40 (37.50%)	
occurrences (all)	31	25	
Abdominal pain			
subjects affected / exposed	15 / 37 (40.54%)	15 / 40 (37.50%)	
occurrences (all)	20	28	
Dry mouth			
subjects affected / exposed	7 / 37 (18.92%)	8 / 40 (20.00%)	
occurrences (all)	13	11	
Abdominal pain upper			
subjects affected / exposed	8 / 37 (21.62%)	5 / 40 (12.50%)	
occurrences (all)	11	8	
Stomatitis			
subjects affected / exposed	5 / 37 (13.51%)	3 / 40 (7.50%)	
occurrences (all)	5	6	
Toothache			
subjects affected / exposed	4 / 37 (10.81%)	2 / 40 (5.00%)	
occurrences (all)	6	3	
Dyspepsia			
subjects affected / exposed	2 / 37 (5.41%)	2 / 40 (5.00%)	
occurrences (all)	2	2	
Proctalgia			
subjects affected / exposed	1 / 37 (2.70%)	2 / 40 (5.00%)	
occurrences (all)	2	2	
Haemorrhoids			
subjects affected / exposed	1 / 37 (2.70%)	2 / 40 (5.00%)	
occurrences (all)	1	2	
Flatulence			
subjects affected / exposed	2 / 37 (5.41%)	0 / 40 (0.00%)	
occurrences (all)	2	0	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	2 / 37 (5.41%)	12 / 40 (30.00%)	
occurrences (all)	2	13	
Pruritus			
subjects affected / exposed	2 / 37 (5.41%)	3 / 40 (7.50%)	
occurrences (all)	5	3	

Rash			
subjects affected / exposed	5 / 37 (13.51%)	2 / 40 (5.00%)	
occurrences (all)	6	2	
Palmar-plantar erythrodysesthesia syndrome			
subjects affected / exposed	2 / 37 (5.41%)	3 / 40 (7.50%)	
occurrences (all)	2	5	
Skin hyperpigmentation			
subjects affected / exposed	2 / 37 (5.41%)	2 / 40 (5.00%)	
occurrences (all)	2	2	
Skin lesion			
subjects affected / exposed	2 / 37 (5.41%)	0 / 40 (0.00%)	
occurrences (all)	2	0	
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	2 / 37 (5.41%)	4 / 40 (10.00%)	
occurrences (all)	2	4	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	8 / 37 (21.62%)	7 / 40 (17.50%)	
occurrences (all)	8	7	
Musculoskeletal pain			
subjects affected / exposed	3 / 37 (8.11%)	4 / 40 (10.00%)	
occurrences (all)	4	9	
Pain in extremity			
subjects affected / exposed	2 / 37 (5.41%)	6 / 40 (15.00%)	
occurrences (all)	6	6	
Neck pain			
subjects affected / exposed	4 / 37 (10.81%)	1 / 40 (2.50%)	
occurrences (all)	5	1	
Arthralgia			
subjects affected / exposed	0 / 37 (0.00%)	4 / 40 (10.00%)	
occurrences (all)	0	4	
Muscle spasms			
subjects affected / exposed	1 / 37 (2.70%)	2 / 40 (5.00%)	
occurrences (all)	1	3	
Myalgia			

subjects affected / exposed	2 / 37 (5.41%)	1 / 40 (2.50%)	
occurrences (all)	2	1	
Musculoskeletal chest pain			
subjects affected / exposed	2 / 37 (5.41%)	0 / 40 (0.00%)	
occurrences (all)	2	0	
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	4 / 37 (10.81%)	4 / 40 (10.00%)	
occurrences (all)	5	4	
Nasopharyngitis			
subjects affected / exposed	4 / 37 (10.81%)	1 / 40 (2.50%)	
occurrences (all)	5	1	
Oral herpes			
subjects affected / exposed	3 / 37 (8.11%)	3 / 40 (7.50%)	
occurrences (all)	3	3	
Rhinitis			
subjects affected / exposed	1 / 37 (2.70%)	2 / 40 (5.00%)	
occurrences (all)	1	3	
Device related infection			
subjects affected / exposed	2 / 37 (5.41%)	1 / 40 (2.50%)	
occurrences (all)	2	1	
Lower respiratory tract infection			
subjects affected / exposed	0 / 37 (0.00%)	3 / 40 (7.50%)	
occurrences (all)	0	3	
Candida infection			
subjects affected / exposed	2 / 37 (5.41%)	0 / 40 (0.00%)	
occurrences (all)	2	0	
Tracheitis			
subjects affected / exposed	0 / 37 (0.00%)	2 / 40 (5.00%)	
occurrences (all)	0	2	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	8 / 37 (21.62%)	13 / 40 (32.50%)	
occurrences (all)	16	19	
Hypokalaemia			

subjects affected / exposed	2 / 37 (5.41%)	6 / 40 (15.00%)	
occurrences (all)	2	7	
Hypocalcaemia			
subjects affected / exposed	0 / 37 (0.00%)	3 / 40 (7.50%)	
occurrences (all)	0	3	
Hypophosphataemia			
subjects affected / exposed	0 / 37 (0.00%)	2 / 40 (5.00%)	
occurrences (all)	0	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 February 2009	The protocol was amended to remove an eligible age upper limit and to allow all participants at least 18 years of age. Select prior intervention-related exclusion criteria were omitted based upon new safety findings. Additional guidance was provided for the maximum duration (12 cycles) of the full regimen of FOLFOXIRI, and dosing criteria were updated to reflect the most current bevacizumab safety and dose modification guidance. Tumor tissue collection methods were modified, and the schedule of objective tumor assessments was changed from a 6-month to a 3-month frequency to ensure timely capturing of relapse data. A new action plan for the management of several specific AEs was added, and guidance for the assessment of causality for clinical AEs was updated. Further, AEs caused by underlying disease were not to be reported as AEs in accordance with common oncology practice.
30 August 2011	The protocol was amended to exclude participants with a diagnosis of metastatic disease for more than 3 months prior to study entry and to allow participants who received prior therapy for a primary tumor in the case of synchronous metastatic rectal cancer, as well as to clarify additional eligibility criteria. Participants with R1 residual tumor classification were considered as having achieved complete resection. The analysis of AEs was also expanded and clarified, and the Schedule of Assessments was updated to include several missing assessments previously specified elsewhere in the protocol. Study treatment was updated, so that participants with complete resection (R0 or R1) could continue to receive the original randomized treatment post-surgery. Discontinuation of oxaliplatin was allowed in the Bevacizumab + mFOLFOX-6 arm, and the protocol-required discontinuation of at least one cytotoxic agent in the Bevacizumab + FOLFOXIRI arm was clarified. Resumption of treatment and second resective surgery was permitted, at the discretion of the investigator, among participants who relapsed after a previous complete resection. Further, participants with PD were to discontinue treatment and enter a follow-up period.
30 April 2013	The protocol was amended to shorten the treatment period to 2 years, resulting in an expected length of study approximately 5 years. The procedure for reporting and managing serious AEs was updated and clarified.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported