



Clinical trial results:

A multi-center, open-label clinical trial to evaluate the objective response rate of bevacizumab in combination with modified FOLFOX-6 followed by one year of maintenance with bevacizumab alone in patients with initially not or borderline resectable colorectal liver metastases (The CLMO-001 Trial)

Summary

EudraCT number	2011-001364-22
Trial protocol	IT
Global end of trial date	18 May 2016

Results information

Result version number	v2
This version publication date	16 November 2016
First version publication date	07 August 2016
Version creation reason	<ul style="list-style-type: none">• Correction of full data setUpdate of data in line with other public registries.

Trial information

Trial identification

Sponsor protocol code	ML25625
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01383707
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	F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.com
Scientific contact	F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, +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	Interim
Date of interim/final analysis	02 March 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	28 May 2014
Global end of trial reached?	Yes
Global end of trial date	18 May 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the activity and efficacy of modified FOLFOX-6 (Levofolinic acid, 5-Fluorouracil [5-FU] and oxaliplatin) + bevacizumab regimen in terms of objective response rate (ORR) in subjects with colorectal liver metastases.

Protection of trial subjects:

All study subjects were required to read and sign an Informed Consent Form.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	10 August 2011
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	1 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects**Subjects enrolled per country**

Country: Number of subjects enrolled	Italy: 77
Worldwide total number of subjects	77
EEA total number of subjects	77

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)	34
From 65 to 84 years	43
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Subjects with histologically confirmed adenocarcinoma of the colon or rectum with measurable metastatic disease confined to the liver were enrolled. In case of primitive rectal tumour, those with metachronous metastases or with synchronous metastases could be enrolled (if primitive lesion was > 12 cm from anal margin).

Period 1

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

Arms

Arm title	Bevacizumab + mFOLFOX-6
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Arm description:

Subjects received combination therapy of bevacizumab 5 milligram/kilogram (mg/kg) intravenously (IV) and mFOLFOX-6 (Levofolonic acid, 5-FU and oxaliplatin) on Day 1 of every 2 weeks' cycle for 5 cycles (Cycle 1-5), followed by 1 cycle (Cycle 6) of mFOLFOX6 alone (preoperative treatment phase). After 3 weeks of preoperative treatment phase, participants satisfying the surgical criteria for hepatic resectability underwent a liver metastasectomy. Thereafter participants received combination therapy of mFOLFOX-6 + bevacizumab for another 6 cycles (Cycle 7-12); (post-operative treatment phase) followed by bevacizumab alone for 52 weeks (26 cycles) (maintenance therapy).

Arm type	Experimental
Investigational medicinal product name	5-Fluorouracil (5-FU)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received 5-FU 400 mg per metre-squared (mg/m²) IV dose on Day 1 of each 2 weeks' cycle followed by 2400 mg/m², continuous infusion over 46 hours up to 12 cycles.

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

Dosage and administration details:

Subjects received 5 mg/kg bevacizumab IV on Day 1 every 2 weeks.

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

Dosage and administration details:

Subjects received levofolonic acid 200 mg per metre-squared (mg/m²) IV infusion over 2 hours on Day 1 of each 2 weeks' cycle up to 12 cycles.

Investigational medicinal product name	Oxaliplatin
Investigational medicinal product code	
Other name	

Pharmaceutical forms	Powder and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received oxaliplatin 85 mg per metre-squared (mg/m²) IV infusion over 2 hours on Day 1 of each 2 weeks' cycle up to 12 cycles.

Number of subjects in period 1	Bevacizumab + mFOLFOX-6
Started	77
Completed	60
Not completed	17
Consent withdrawn by subject	1
Death	15
Not specified	1

Baseline characteristics

Reporting groups

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

Subjects received combination therapy of bevacizumab 5 milligram/kilogram (mg/kg) intravenously (IV) and mFOLFOX-6 (Levofolonic acid, 5-FU and oxaliplatin) on Day 1 of every 2 weeks' cycle for 5 cycles (Cycle 1-5), followed by 1 cycle (Cycle 6) of mFOLFOX6 alone (preoperative treatment phase). After 3 weeks of preoperative treatment phase, participants satisfying the surgical criteria for hepatic resectability underwent a liver metastasectomy. Thereafter participants received combination therapy of mFOLFOX-6 + bevacizumab for another 6 cycles (Cycle 7-12); (post-operative treatment phase) followed by bevacizumab alone for 52 weeks (26 cycles) (maintenance therapy).

Reporting group values	Bevacizumab + mFOLFOX-6	Total	
Number of subjects	77	77	
Age categorical Units: Subjects			
Adults (18-64 years)	34	34	
From 65-84 years	43	43	
Age continuous Units: years arithmetic mean standard deviation	63.7 ± 10.6	-	
Gender categorical Units: Subjects			
Female	31	31	
Male	46	46	

End points

End points reporting groups

Reporting group title	Bevacizumab + mFOLFOX-6
Reporting group description:	
Subjects received combination therapy of bevacizumab 5 milligram/kilogram (mg/kg) intravenously (IV) and mFOLFOX-6 (Levofolinic acid, 5-FU and oxaliplatin) on Day 1 of every 2 weeks' cycle for 5 cycles (Cycle 1-5), followed by 1 cycle (Cycle 6) of mFOLFOX6 alone (preoperative treatment phase). After 3 weeks of preoperative treatment phase, participants satisfying the surgical criteria for hepatic resectability underwent a liver metastasectomy. Thereafter participants received combination therapy of mFOLFOX-6 + bevacizumab for another 6 cycles (Cycle 7-12); (post-operative treatment phase) followed by bevacizumab alone for 52 weeks (26 cycles) (maintenance therapy).	

Primary: Objective Response Rate (ORR) in the Intent-to-treat (ITT) Analysis Set

End point title	Objective Response Rate (ORR) in the Intent-to-treat (ITT) Analysis Set ^[1]
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End point description:

ORR was defined as the percentage of subjects with shrinkage (partial response [PR]) or disappearance of cancer (complete response [CR]). Tumour response was evaluated according to the Response Evaluation Criteria In Solid Tumors (RECIST v1.1). The same method of tumour measurement and assessment had to be used to characterize each lesion throughout the study. Tumour assessment consisted of computerized tomography (CT) scan (abdomen + pelvis + chest) or contrast-enhanced magnetic resonance imaging (CE-MRI) (abdomen + pelvis) + non CE-CT (chest) according to the choice of the center. CR, Disappearance of all target lesions; PR, $\geq 30\%$ decrease in the sum of the longest diameter of target lesions; Overall Response (OR) = CR + PR.

Analysis Population: The ITT set, which included all enrolled subjects, who received at least one dose of any study medication.

End point type	Primary
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End point timeframe:

Up to 11 cycles of treatment (up to Week 22)

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analyses were performed as this study had one arm.

End point values	Bevacizumab + mFOLFOX-6			
Subject group type	Reporting group			
Number of subjects analysed	77			
Units: Percentage of subjects				
number (confidence interval 95%)	53.2 (41.5 to 64.7)			

Statistical analyses

No statistical analyses for this end point

Primary: Objective Response Rate (ORR) in the Per-protocol Analysis Set (PPAS)

End point title	Objective Response Rate (ORR) in the Per-protocol Analysis Set (PPAS) ^[2]
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End point description:

ORR was defined as the percentage of subjects with shrinkage (PR) or disappearance of cancer (CR). Tumour response was evaluated according to the RECIST v1.1. The same method of tumour measurement and assessment had to be used to characterize each lesion throughout the study. Tumour assessment consisted of CT scan (abdomen + pelvis + chest) or CE-MRI (abdomen + pelvis) + non CE-CT (chest) according to the choice of the center. CR, Disappearance of all target lesions; PR, $\geq 30\%$ decrease in the sum of the longest diameter of target lesions; OR = CR + PR.

Analysis Population: The PPAS included all subjects in the ITT set, who did not experience any major protocol violations.

End point type	Primary
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End point timeframe:

Up to 11 cycles of treatment (up to Week 22)

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analyses were performed as this study had one arm.

End point values	Bevacizumab + mFOLFOX-6			
Subject group type	Reporting group			
Number of subjects analysed	64			
Units: Percentage of subjects				
number (confidence interval 95%)	62.5 (49.5 to 74.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Achieving No Residual Tumor (R0)/Surgical Margin With Microscopic Residual Tumor (R1) Liver Resection

End point title	Percentage of Subjects Achieving No Residual Tumor (R0)/Surgical Margin With Microscopic Residual Tumor (R1) Liver Resection
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End point description:

The percentage of subjects achieving R0/R1 liver resection was defined as the percentage of subjects achieving R0 surgery (no residual tumour) plus percentage of subjects achieving R1 surgery (surgical margin with microscopic residual tumour).

Analysis Population: The ITT set, which included all enrolled subjects, who received at least one dose of any study medication.

End point type	Secondary
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End point timeframe:

End of study up to approximately 3 years

End point values	Bevacizumab + mFOLFOX-6			
Subject group type	Reporting group			
Number of subjects analysed	77			
Units: Percentage of subjects				
number (confidence interval 95%)	29.9 (20 to 41.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Disease-free Interval (DFI)

End point title	Disease-free Interval (DFI)
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End point description:

DFI was defined as the time from the date of R0/R1 surgery to the date of disease relapse or death due to any cause. Subjects who did not progress were considered censored at the date of the last assessment performed. For subjects receiving two-stage resection, the date of R0/R1 surgery was the date of the second surgery. Subjects, who did not receive surgery and subjects without R0/R1 surgery were censored at Day 1.

DFI was calculated as follows: $DFI \text{ (months)} = ([\text{Date of R0/R1 surgery} - \text{Date of 1st relapse/Death}] + 1)/30$

Analysis Population: The ITT set, which included all enrolled subjects, who received at least one dose of any study medication.

End point type	Secondary
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End point timeframe:

End of study up to approximately 3 years

End point values	Bevacizumab + mFOLFOX-6			
Subject group type	Reporting group			
Number of subjects analysed	77			
Units: months				
median (confidence interval 95%)	10.6 (5.7 to 13.8)			

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 as the time from the date of first study drug administration to the date of disease progression or death due to any cause, whichever came first. Progression was defined according to RECIST, v1.1 as at least a 20% increase in the sum of diameters of target lesions with an absolute increase of at least 5 mm or the appearance of one or more new lesions. Subjects, who did not progress were censored at the date of the last assessment. Subjects who withdrew from the study without

documented progression and for whom an electronic case report form (eCRF) existed as evidence that evaluations had been made, were censored at the date of the last tumour assessment when the subject was known to be progression-free. Subjects without post-baseline tumour assessments, but known to be alive were censored at the time of first study drug administration. PFS was calculated: $PFS\ (months) = ([Date\ of\ Event - Date\ of\ first\ study\ drug\ administration] + 1)/30$. Analysis population: ITT.

End point type	Secondary
End point timeframe:	
End of study up to approximately 3 years	

End point values	Bevacizumab + mFOLFOX-6			
Subject group type	Reporting group			
Number of subjects analysed	77 ^[3]			
Units: months				
median (confidence interval 95%)	11.7 (10.3 to 14.3)			

Notes:

[3] - The ITT set included all enrolled subjects, who received at least one dose of any study medication.

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 the date of first study drug administration to the date of death due to any cause. Subjects who were alive at the time of the analysis were censored at the last date the subject was known to be alive. OS was calculated as follows: $OS\ (months) = ([Date\ of\ Death - first\ study\ drug\ administration] + 1)/30$	
Analysis Population: The ITT set, which included all enrolled subjects, who received at least one dose of any study medication.	
999: The median overall survival time and its 95% confidence interval were not estimable because of the low number of events (less than 50%) and of the distribution of censored subjects over time.	
End point type	Secondary
End point timeframe:	
End of study up to approximately 3 years	

End point values	Bevacizumab + mFOLFOX-6			
Subject group type	Reporting group			
Number of subjects analysed	77			
Units: months				
number (confidence interval 95%)	999 (999 to 999)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

End of study up to approximately 3 years

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	18.1
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Reporting groups

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

Subjects received combination therapy of bevacizumab 5 mg/kg intravenously (IV) and mFOLFOX-6 (Levofolonic acid, 5-FU and oxaliplatin) on Day 1 of every 2 weeks' cycle for 5 cycles (Cycle 1-5), followed by 1 cycle (Cycle 6) of mFOLFOX6 alone (preoperative treatment phase). After 3 weeks of preoperative treatment phase, participants satisfying the surgical criteria for hepatic resectability underwent a liver metastasectomy. Thereafter participants received combination therapy of mFOLFOX-6 + bevacizumab for another 6 cycles (Cycle 7-12); (post-operative treatment phase) followed by bevacizumab alone for 52 weeks (26 cycles) (maintenance therapy).

Analysis Population: The safety analysis set (SAF) included all enrolled participants, who received at least one dose of any study medication. If there was any doubt whether a subject was treated or not, they were to be assumed treated for the purposes of analysis.

Serious adverse events	Bevacizumab + mFOLFOX-6		
Total subjects affected by serious adverse events			
subjects affected / exposed	29 / 77 (37.66%)		
number of deaths (all causes)	19		
number of deaths resulting from adverse events	1		
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 77 (1.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Haemorrhage			
subjects affected / exposed	1 / 77 (1.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypertension			
subjects affected / exposed	1 / 77 (1.30%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Surgical and medical procedures			
Biliary drainage			
subjects affected / exposed	1 / 77 (1.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Colectomy			
subjects affected / exposed	1 / 77 (1.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Death			
subjects affected / exposed	1 / 77 (1.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Pyrexia			
subjects affected / exposed	2 / 77 (2.60%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 77 (1.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pleural effusion			
subjects affected / exposed	1 / 77 (1.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	1 / 77 (1.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonitis			

subjects affected / exposed	1 / 77 (1.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary embolism			
subjects affected / exposed	3 / 77 (3.90%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		
Investigations			
Neutrophil count decreased			
subjects affected / exposed	1 / 77 (1.30%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
White blood cell count decreased			
subjects affected / exposed	1 / 77 (1.30%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Chemical peritonitis			
subjects affected / exposed	1 / 77 (1.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 77 (1.30%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Atrial fibrillation			
subjects affected / exposed	1 / 77 (1.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac arrest			
subjects affected / exposed	3 / 77 (3.90%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	1 / 3		

Cardiac failure acute			
subjects affected / exposed	1 / 77 (1.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Nervous system disorders			
Transient ischaemic attack			
subjects affected / exposed	1 / 77 (1.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	1 / 77 (1.30%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Neutropenia			
subjects affected / exposed	1 / 77 (1.30%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 77 (2.60%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Constipation			
subjects affected / exposed	1 / 77 (1.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			
subjects affected / exposed	2 / 77 (2.60%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Intestinal obstruction			

subjects affected / exposed	1 / 77 (1.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	1 / 77 (1.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Biliary tract disorder			
subjects affected / exposed	1 / 77 (1.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Biloma			
subjects affected / exposed	1 / 77 (1.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatic failure			
subjects affected / exposed	1 / 77 (1.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Fistula			
subjects affected / exposed	1 / 77 (1.30%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Abscess			
subjects affected / exposed	1 / 77 (1.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Device related infection			
subjects affected / exposed	1 / 77 (1.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Liver abscess			
subjects affected / exposed	1 / 77 (1.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 77 (1.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Bevacizumab + mFOLFOX-6		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	76 / 77 (98.70%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	26 / 77 (33.77%)		
occurrences (all)	40		
Nervous system disorders			
Neuropathy peripheral			
subjects affected / exposed	4 / 77 (5.19%)		
occurrences (all)	5		
Neurotoxicity			
subjects affected / exposed	4 / 77 (5.19%)		
occurrences (all)	8		
Paraesthesia			
subjects affected / exposed	43 / 77 (55.84%)		
occurrences (all)	150		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	6 / 77 (7.79%)		
occurrences (all)	7		
Leukopenia			
subjects affected / exposed	8 / 77 (10.39%)		
occurrences (all)	9		

Neutropenia			
subjects affected / exposed	32 / 77 (41.56%)		
occurrences (all)	48		
Thrombocytopenia			
subjects affected / exposed	10 / 77 (12.99%)		
occurrences (all)	16		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	29 / 77 (37.66%)		
occurrences (all)	63		
Fatigue			
subjects affected / exposed	7 / 77 (9.09%)		
occurrences (all)	13		
Mucosal inflammation			
subjects affected / exposed	9 / 77 (11.69%)		
occurrences (all)	13		
Pyrexia			
subjects affected / exposed	13 / 77 (16.88%)		
occurrences (all)	19		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	8 / 77 (10.39%)		
occurrences (all)	11		
Abdominal pain upper			
subjects affected / exposed	6 / 77 (7.79%)		
occurrences (all)	6		
Constipation			
subjects affected / exposed	14 / 77 (18.18%)		
occurrences (all)	17		
Diarrhoea			
subjects affected / exposed	16 / 77 (20.78%)		
occurrences (all)	35		
Haemorrhoids			
subjects affected / exposed	4 / 77 (5.19%)		
occurrences (all)	4		
Nausea			

<p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Stomatitis</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Vomiting</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>38 / 77 (49.35%)</p> <p>103</p> <p>14 / 77 (18.18%)</p> <p>26</p> <p>13 / 77 (16.88%)</p> <p>22</p>		
<p>Respiratory, thoracic and mediastinal disorders</p> <p>Cough</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Epistaxis</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>6 / 77 (7.79%)</p> <p>7</p> <p>13 / 77 (16.88%)</p> <p>21</p>		
<p>Skin and subcutaneous tissue disorders</p> <p>Erythema</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Palmar-plantar erythrodysaesthesia syndrome</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>4 / 77 (5.19%)</p> <p>4</p> <p>4 / 77 (5.19%)</p> <p>5</p>		
<p>Metabolism and nutrition disorders</p> <p>Decreased appetite</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>7 / 77 (9.09%)</p> <p>9</p>		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 October 2012	<p>Some inclusion and exclusion criteria were modified to better align the protocol with clinical practice and Response Evaluation Criteria In Solid Tumors (RECIST). Screening procedures performed as part of the routine clinical practice before the informed consent signature did not need to be repeated in case they had been performed recently and in the same facility where the subsequent assessments were expected to be performed. During the follow-up phase, visit and evaluations (physical, haematology and tumour) could be performed \pm 3 weeks from the scheduled dates. All AEs for which the intensity grade changed from the onset to the outcome, were to be registered in Electronic Case Report Form (eCRF) with the Start date and the End Date of the whole period during which they occurred and only the highest intensity detected for the AE in the whole period should have been registered. The postoperative chemotherapy + bevacizumab restart could be delayed, only for medical reasons, till a maximum of total 8 weeks after surgery. If chemotherapy + bevacizumab treatment did not restart within 8 weeks after surgery, subject had to be discontinued from the study. Defined the acceptable timeframe occurring between the end of the adjuvant treatment and the enrolment. Clarified target and non-target lesions and data requested in the eCRF. Timeline for the reporting of Serious Adverse Events and Pregnancies was modified to 'within 24 hours' in order to align the protocol to EU "Detailed Guidance on the collection, verification and presentation of adverse event/reaction reports arising from clinical trials on medicinal products for human use" ("CT-3") published in June 2011. A per-protocol analysis set (PPAS) has been defined in the statistical methods. Statistical methods for laboratory data were updated according to the criteria for collecting laboratory data at post-baseline visits. Change from folinic acid to levofolinic acid was applied to specify the correct chemical structure.</p>
25 October 2013	<p>The length of the study and the expected end of the study were updated. Risk-management plans were to be continually modified and updated throughout the lifetime of the medicine as new information became available, according to European Medicines Agency (EMA) requirements. The protocol section "Reporting of Serious Adverse Events (immediately reportable)" was updated to define the correct timelines of report. Moreover, Adverse Events of Special Interest (AESI) were added. The section "FOLFOX-6 and mFOLFOX-6 + Bevacizumab: Dose Modifications" was updated to clarify the management of drug related haematological toxicities. Changes of planned analyses: 1) Magnetic Resonance Imaging (MRI) exploratory evaluation: only subjects with assessments at both baseline and Day 14 were evaluated; 2) Haematology and Blood Chemistry Laboratory analysis: no shift table in the laboratory values according to normal range criteria was provided; 3) Unplanned analysis on primary endpoint: the final analysis was planned at the end of the study defined in the protocol as "the last subject last visit at the end of the follow-up period". However, after the Sponsor request the final primary efficacy analysis was foreseen and provided within the first quarter of 2016. The analysis was also focused on the first 12 cycles of study. The following changes to analyses planned in the final Statistical Analysis Plan (SAP) were made effective: A post-hoc analysis of the duration of follow-up was performed.</p>

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported