Clinical trial results:
An Uncontrolled, open-label, phase II study in subjects with Metastatic Adenocarcinoma of the colon or rectum who are Receiving first line Chemotherapy with mFOLFOX6 (oxaliplatin/ folinic acid/5-fluorouracil [5-FU]) in combination with regorafenib

Summary

EudraCT number	2010-020121-41
Trial protocol	GB DE BE ES IT
Global end of trial date	30 June 2014

Results information

Result version number	v2 (current)
This version publication date	04 September 2016
First version publication date	26 July 2015
Version creation reason	• New data added to full data set • Correction of full data set Bayer sponsor contact information to be updated

Trial information

Trial identification

Sponsor protocol code	BAY73-4506/11728

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01289821
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Bayer AG
Sponsor organisation address	Kaiser Wilhelm Allee, Leverkusen, Germany, D-51368
Public contact	Therapeutic Area Head, Bayer AG, clinical-trials-contact@bayer.com
Scientific contact	Therapeutic Area Head, Bayer AG, clinical-trials-contact@bayer.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	30 June 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	30 June 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

•Objective tumor response rate (ORR), centrally assessed

Protection of trial subjects:

The conduct of this clinical study met all local legal and regulatory requirements. The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and the International Conference on Harmonization (ICH) guideline E6: Good Clinical Practice. Before entering the study, the ICF was read by and explained to all subjects or their legally authorized representative. Participating subjects signed informed consent form and could withdraw from the study at any time without any disadvantage and without having to provide a reason for this decision. Only investigators qualified by training and experience were selected as appropriate experts to investigate the study drug.

Background therapy:

mFOLFOX6: On Day 1, subjects received 85 milligram per square meter (mg/m^2) oxaliplatin as a 2 hour intravenous (IV) infusion and folinic acid (either 400 mg/m^2 D/L folinic acid or 200 mg/m^2 L folinic acid) as a 2 hour IV infusion. Once the initial infusion was completed, subjects received 5-FU 400 mg/m^2 IV bolus injection immediately followed by a 5-FU 2400 mg/m^2 IV infusion for 46 hours. Thus, all mFOLFOX6 components were delivered over a total administration period of 48 hours. The next cycle of mFOLFOX6 was administered on Days 15 to 17.

Evidence for comparator: -	
Actual start date of recruitment	07 February 2011
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy
Long term follow-up duration	40 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Belgium: 3
Country: Number of subjects enrolled	United States: 4
Country: Number of subjects enrolled	Italy: 15
Country: Number of subjects enrolled	United Kingdom: 11
Country: Number of subjects enrolled	Germany: 7
Country: Number of subjects enrolled	Spain: 14
Worldwide total number of subjects	54
EEA total number of subjects	50

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)	33
From 65 to 84 years	21
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Male or female subjects with histological or cytological documentation of metastatic adenocarcinoma of the colon or rectum that was unresectable or unlikely of becoming resectable, who were at least 18 years of age and were suitable to receive mFOLFOX6 regimen as first line treatment could participate in this study at 16 centers in 7 countries.

Pre-assignment

Screening details:

Of 66 enrolled subjects, 54 received study medication, 4 withdrew consent during screening, and 8 were screen failures due to no measurable lesion, not suitable to receive mFOLFOX as 1st line regimen (2), uncontrolled hypertension, symptoms/signs/history of brain metastases, glomerular filtration rate too low (2), and protein in spot urine.

Period 1

Period 1 title	Treatment Period
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Regorafenib + Oxaliplatin/Folinic Acid/5-FU (mFOLFOX6)

Arm description:

On Day 1, subjects received 85 milligram per square meter (mg/m^2) oxaliplatin as a 2-hour intravenous (IV) infusion and folinic acid (either 400 mg/m^2 D/L-folinic acid or 200 mg/m^2 L-folinic acid) as a 2-hour IV infusion. Once the initial infusion was completed, subjects received 5-FU 400 mg/m^2 IV bolus injection immediately followed by a 5-FU 2400 mg/m^2 IV infusion for 46 hours. The next cycle of mFOLFOX6 was administered on Day 15 to 17. Subjects received Regorafenib (Stivarga, BAY73-4506) 160 mg orally once daily on Days 4 to 10 and Days 18 to 24. One cycle comprised 28 days.

Arm type	Experimental
Investigational medicinal product name	Regorafenib
Investigational medicinal product code	BAY73-4506
Other name	Stivarga
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received regorafenib 160 mg orally once daily on Days 4 to 10 and Days 18 to 24. If regorafenib was administered as a monotherapy during the study, 160 mg once daily was administered for 3 weeks on/1 week off. Doses were self-administered as four 40 mg tablets taken with 8 ounces of fluid after a low-fat breakfast.

Investigational medicinal product name	mFOLFOX6
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous bolus use , Intravenous use

Dosage and administration details:

On Day 1, subjects were administered 85 mg/m^2 oxaliplatin and folinic acid (either 400 mg/m^2 D/L-folinic acid or 200 mg/m^2 L-folinic acid) as a 2-hour IV infusion (sequential or concurrent administration was possible). Once the initial infusion was complete, subjects received a 5-FU 400 mg/m^2 IV bolus injection immediately followed by 5-FU 2400 mg/m^2 IV for 46 hours. Thus, all mFOLFOX6 components were delivered over a total administration period of 48 hours. The next cycle of mFOLFOX6 was administered on Day 15 to 17.

Number of subjects in period 1	Regorafenib + Oxaliplatin/Folinic Acid/5-FU (mFOLFOX6)
Started	54
Subjects Received Regorafenib	54
Completed	0
Not completed	54
Progressive disease - Radiological progression	43
Consent withdrawn by subject	1
Physician decision	3
Progressive disease - Clinical progression	2
Adverse event	4
Therapeutic procedure required	1

Period 2

Period 2 title	Safety Follow-up Period
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Regorafenib + Oxaliplatin/Folinic Acid/5-FU (mFOLFOX6)

Arm description:

On Day 1, subjects received 85 mg/m^2 oxaliplatin as a 2-hour IV infusion and folinic acid (either 400 mg/m^2 D/L-folinic acid or 200 mg/m^2 L-folinic acid) as a 2-hour IV infusion. Once the initial infusion was completed, subjects received 5-FU 400 mg/m^2 IV bolus injection immediately followed by a 5-FU 2400 mg/m^2 IV infusion for 46 hours. The next cycle of mFOLFOX6 was administered on Day 15 to 17. Subjects received Regorafenib (Stivarga, BAY73-4506) 160 mg orally once daily on Days 4 to 10 and Days 18 to 24. One cycle comprised 28 days.
Subjects who had not started another anti-tumor treatment within 30 days after the last dose of study treatment, a safety follow-up visit was performed after 30 days after the last dose of study treatment.

Arm type	Experimental
Investigational medicinal product name	mFOLFOX6
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous bolus use , Intravenous use

Dosage and administration details:

On Day 1, subjects were administered 85 mg/m^2 oxaliplatin and folinic acid (either 400 mg/m^2 D/L-folinic acid or 200 mg/m^2 L-folinic acid) as a 2-hour IV infusion (sequential or concurrent administration was possible). Once the initial infusion was complete, subjects received a 5-FU 400 mg/m^2 IV bolus injection immediately followed by 5-FU 2400 mg/m^2 IV for 46 hours. Thus, all mFOLFOX6 components were delivered over a total administration period of 48 hours. The next cycle of mFOLFOX6 was administered on Day 15 to 17.

Investigational medicinal product name	Regorafenib
Investigational medicinal product code	BAY73-4506
Other name	Stivarga

Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received Regorafenib 160 mg orally once daily on Days 4 to 10 and Days 18 to 24. If Regorafenib was administered as a monotherapy during the study, 160 mg orally was administered for 3 weeks on/1 week off. Doses were self-administered as four 40 mg tablets taken with 8 ounces of fluid after a low-fat breakfast.

Number of subjects in period 2	Regorafenib + Oxaliplatin/Folinic Acid/5-FU (mFOLFOX6)
Started	54
Completed	49
Not completed	5
Consent withdrawn by subject	1
Protocol violation	3
Unspecified reason	1

Period 3

Period 3 title	Survival Follow-up Period
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Regorafenib + Oxaliplatin/Folinic Acid/5-FU (mFOLFOX6)

Arm description:

On Day 1, subjects received 85 mg/m^2 oxaliplatin as a 2-hour IV infusion and folinic acid (either 400 mg/m^2 D/L-folinic acid or 200 mg/m^2 L-folinic acid) as a 2-hour IV infusion. Once the initial infusion was completed, subjects received 5-FU 400 mg/m^2 IV bolus injection immediately followed by a 5-FU 2400 mg/m^2 IV infusion for 46 hours. The next cycle of mFOLFOX6 was administered on Day 15 to 17. Subjects received Regorafenib (Stivarga, BAY73-4506) 160 mg orally once daily on Days 4 to 10 and Days 18 to 24. One cycle comprised 28 days.
Subjects were evaluated bimonthly to determine their survival status up to data cut off date 30 June 2014.

Arm type	Experimental
Investigational medicinal product name	Regorafenib
Investigational medicinal product code	BAY73-4506
Other name	Stivarga
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received regorafenib 160 mg orally once daily on Days 4 to 10 and Days 18 to 24. If regorafenib was administered as a monotherapy during the study, 160 mg once daily was administered for 3 weeks on/1 week off. Doses were self-administered as four 40 mg tablets taken with 8 ounces of fluid after a low-fat breakfast.

Investigational medicinal product name	mFOLFOX6
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous bolus use , Intravenous use

Dosage and administration details:

On Day 1, subjects were administered 85 mg/m^2 oxaliplatin and folinic acid (either 400 mg/m^2 D/L-folinic acid or 200 mg/m^2 L-folinic acid) as a 2-hour IV infusion (sequential or concurrent administration was possible). Once the initial infusion was complete, subjects received a 5-FU 400 mg/m^2 IV bolus injection immediately followed by 5-FU 2400 mg/m^2 IV for 46 hours. Thus, all mFOLFOX6 components were delivered over a total administration period of 48 hours. The next cycle of mFOLFOX6 was administered on Day 15 to 17.

Number of subjects in period 3	Regorafenib + Oxaliplatin/Folinic Acid/5-FU (mFOLFOX6)
Started	52
Completed	0
Not completed	52
Lost to follow up	1
Clinical endpoint reached	16
Protocol violation	1
Death	34

Baseline characteristics

Reporting groups	
Reporting group title	Treatment Period

Reporting group description:

On Day 1, subjects received 85 mg/m^2 oxaliplatin as a 2-hour IV infusion and folinic acid (either 400 mg/m^2 D/L-folinic acid or 200 mg/m^2 L-folinic acid) as a 2-hour IV infusion. Once the initial infusion was completed, subjects received 5-FU 400 mg/m^2 IV bolus injection immediately followed by a 5-FU 2400 mg/m^2 IV infusion for 46 hours. The next cycle of mFOLFOX6 was administered on Day 15 to 17. Subjects received Regorafenib (Stivarga, BAY73-4506) 160 mg orally once daily on Days 4 to 10 and Days 18 to 24. One cycle comprised 28 days.

Reporting group values	Treatment Period	Total	
Number of subjects	54	54	
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	 60.6 ± 10.5	 -	
Gender categorical Units: Subjects			
Female	26	26	
Male	28	28	
Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) at study entry			
The ECOG PS required for the study was 0 (fully active) or 1 (restricted in physically strenous activity but ambulatory and able to carry out work of a light or sedentary nature).			
Units: Subjects			
Zero	35	35	
One	19	19	
Stage at Initial Diagnosis			
The TNM classification of malignant tumors (TNM) is a cancer staging system that describes the extent of a person's cancer. T describes the size of the original (primary) tumor and whether it has invaded nearby tissue, N describes nearby (regional) lymph nodes that are involved, M describes distant metastasis. For colon carcinoma, this is translated into stages I-IV. Stages II-IV can be further subdivided in subgroups (for example A, B, or C).			
Units: Subjects			
Stage: 1	1	1	
Stage: 2A	5	5	
Stage: 3B	3	3	
Stage: 3C	4	4	
Stage: 4	41	41	
Race Units: Subjects			
Caucasian	54	54	

End points

End points reporting groups

Reporting group title	Regorafenib + Oxaliplatin/Folinic Acid/5-FU (mFOLFOX6)

Reporting group description:

On Day 1, subjects received 85 milligram per square meter (mg/m^2) oxaliplatin as a 2-hour intravenous (IV) infusion and folinic acid (either 400 mg/m^2 D/L-folinic acid or 200 mg/m^2 L-folinic acid) as a 2-hour IV infusion. Once the initial infusion was completed, subjects received 5-FU 400 mg/m^2 IV bolus injection immediately followed by a 5-FU 2400 mg/m^2 IV infusion for 46 hours. The next cycle of mFOLFOX6 was administered on Day 15 to 17. Subjects received Regorafenib (Stivarga, BAY73-4506) 160 mg orally once daily on Days 4 to 10 and Days 18 to 24. One cycle comprised 28 days.

Reporting group title	Regorafenib + Oxaliplatin/Folinic Acid/5-FU (mFOLFOX6)

Reporting group description:

On Day 1, subjects received 85 mg/m^2 oxaliplatin as a 2-hour IV infusion and folinic acid (either 400 mg/m^2 D/L-folinic acid or 200 mg/m^2 L-folinic acid) as a 2-hour IV infusion. Once the initial infusion was completed, subjects received 5-FU 400 mg/m^2 IV bolus injection immediately followed by a 5-FU 2400 mg/m^2 IV infusion for 46 hours. The next cycle of mFOLFOX6 was administered on Day 15 to 17. Subjects received Regorafenib (Stivarga, BAY73-4506) 160 mg orally once daily on Days 4 to 10 and Days 18 to 24. One cycle comprised 28 days.
Subjects who had not started another anti-tumor treatment within 30 days after the last dose of study treatment, a safety follow-up visit was performed after 30 days after the last dose of study treatment.

Reporting group title	Regorafenib + Oxaliplatin/Folinic Acid/5-FU (mFOLFOX6)

Reporting group description:

On Day 1, subjects received 85 mg/m^2 oxaliplatin as a 2-hour IV infusion and folinic acid (either 400 mg/m^2 D/L-folinic acid or 200 mg/m^2 L-folinic acid) as a 2-hour IV infusion. Once the initial infusion was completed, subjects received 5-FU 400 mg/m^2 IV bolus injection immediately followed by a 5-FU 2400 mg/m^2 IV infusion for 46 hours. The next cycle of mFOLFOX6 was administered on Day 15 to 17. Subjects received Regorafenib (Stivarga, BAY73-4506) 160 mg orally once daily on Days 4 to 10 and Days 18 to 24. One cycle comprised 28 days.
Subjects were evaluated bimonthly to determine their survival status up to data cut off date 30 June 2014.

Subject analysis set title	Per Protocol Set (PPS)
Subject analysis set type	Per protocol

Subject analysis set description:

PPS (N=48) included all FAS subjects with no major protocol deviations affecting tumor evaluation. At least one post-baseline tumor assessment was required in order to consider the subject evaluable. Subjects who were not evaluable for tumor response and who discontinued due to a drug-related toxicity, progression by clinical judgment before disease was re-evaluated, or death were also to be considered evaluable.

Subject analysis set title	Full Analysis Set (FAS)
Subject analysis set type	Full analysis

Subject analysis set description:

FAS (N=54) included all subjects who received treatment.

Subject analysis set title	Primary Analysis Set (PAS)
Subject analysis set type	Per protocol

Subject analysis set description:

PAS (N=41) was a subset of the PPS and included the first 41 subjects, who were assigned to treatment.

Primary: Objective Response (OR)

End point title	Objective Response (OR)[1]

End point description:

OR was defined as the best tumor response (confirmed complete response [CR] or partial response [PR]) observed by magnetic resonance imaging (MRI) or computed tomography (CT) scan assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST) criteria, version 1.1. CR and PR were confirmed not earlier than 4 weeks following the initial detection of response. CR = Disappearance of all clinical and radiological evidence of tumor (both target and no-target). Any pathological lymph nodes (whether target or non target) must have a reduction in short axis to less than (<) 10 millimeter

(mm). PR = At least a 30 percent (%) decrease in the sum of diameters of target lesions taking as reference the baseline sum, no unequivocal progression of existing non-target lesions and no appearance of new lesions.

End point type	Primary

End point timeframe:

From start of treatment until 30 days after the last dose of study treatment, assessed by every 8 weeks

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: EudraCT database does not allow to report only one treatment group in statistical analyses section. Due to this format constraint, charts have been uploaded with the accurate details of statistical analyses for this endpoint. Please find the statistical analyses in the attachment below.

End point values	Regorafenib + Oxaliplatin/Folinic Acid/5-FU (mFOLFOX6)			
Subject group type	Reporting group			
Number of subjects analysed	41[2]			
Units: Proportion of Subjects				
number (not applicable)	43.9			

Notes:

[2] - PAS

Attachments (see zip file)	Statistical analysis_Primary_Objective

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

OS was calculated as the time from first date of receiving study treatment to date of death due to any cause. Subjects alive at the time of analysis were censored at their last date of follow-up.

End point type	Secondary

End point timeframe:

From start of treatment until 30 days after the last dose of study treatment, assessed by every 8 weeks

End point values	Regorafenib + Oxaliplatin/Folinic Acid/5-FU (mFOLFOX6)			
Subject group type	Reporting group			
Number of subjects analysed	54[3]			
Units: Days				
median (confidence interval 95%)	772 (646 to 1089)			

Notes:

[3] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free Survival (PFS)

End point title	Progression-free Survival (PFS)

End point description:

PFS was defined as time from the date of start of study treatment to the date of first observed disease progression (radiological according to central assessment or clinical), or death due to any cause, if death occurred before progression was documented. PFS for subjects without disease progression or death at the date of database cutoff were right-censored at the last date of tumor assessment. Subjects who had no tumor evaluation after baseline and no clinical progression post baseline and who did not die were censored at Day 1 in the analysis. PD = At least a 20% increase in the sum of diameters of target lesions taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. Unequivocal progression of existing non target lesions or the appearance of one or more new lesions will also constitute PD.

End point type	Secondary

End point timeframe:

From start of treatment until 30 days after the last dose of study treatment, assessed by every 8 weeks

End point values	Regorafenib + Oxaliplatin/Folinic Acid/5-FU (mFOLFOX6)			
Subject group type	Reporting group			
Number of subjects analysed	54[4]			
Units: Days				
median (confidence interval 95%)	258 (222 to 334)			

Notes:

[4] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Control (DC)

End point title	Disease Control (DC)

End point description:

DC was defined as the proportion of subjects who had a best response rating of CR, PR, or stable disease (SD) according to RECIST criteria that was achieved during treatment or within 30 days after termination of study treatment. CR and PR were confirmed not earlier than 4 weeks following the initial detection of response. A minimum of 8 weeks (allowing a minus 7-day time window) between start of study treatment and the first follow-up tumor assessment with SD as response was required to assign SD as best overall response.

End point type	Secondary

End point timeframe:

From start of treatment until 30 days after the last dose of study treatment, assessed by every 8 weeks

End point values	Regorafenib + Oxaliplatin/Folinic Acid/5-FU (mFOLFOX6)			
Subject group type	Reporting group			
Number of subjects analysed	41[5]			
Units: Proportion of Subjects				
number (not applicable)	85.37			

Notes:

[5] - PAS

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR)

End point title	Duration of Response (DOR)

End point description:

DOR was defined as the time from the date of first documented objective response of PR or CR, whichever was noted earlier, to first subsequent disease progression or death (if death occurred before progression was documented). DOR was defined for responders only (that is, subjects with CR or PR). DOR for subjects without disease progression or death before progression was right censored at the date of their last tumor assessment.

End point type	Secondary

End point timeframe:

From start of treatment until 30 days after the last dose of study treatment, assessed by every 8 weeks

End point values	Regorafenib + Oxaliplatin/Folinic Acid/5-FU (mFOLFOX6)			
Subject group type	Reporting group			
Number of subjects analysed	20[6]			
Units: Days				
median (confidence interval 95%)	257 (176 to 349)			

Notes:

[6] - PPS

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Stable Disease (DOSD)

End point title	Duration of Stable Disease (DOSD)

End point description:

DOSD was only evaluated in subjects failing to achieve a best response of CR or PR, but who achieved SD. DOSR was defined as the time (in days) from date of start of study treatment to the date at which disease progression or death (if death occurred before progression was first documented). The date the tumor scan was performed was used for this calculation. DOSD for subjects without disease progression or death before progression at the time of analysis were censored at the date of their last tumor assessment.

End point type	Secondary

End point timeframe:

From start of treatment until 30 days after the last dose of study treatment, assessed by every 8 weeks

End point values	Regorafenib + Oxaliplatin/Folinic Acid/5-FU (mFOLFOX6)			
Subject group type	Reporting group			
Number of subjects analysed	22[7]			
Units: Days				
median (confidence interval 95%)	231 (167 to 259)			

Notes:

[7] - PPS

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From start of study treatment until 4 weeks following the last dose of study treatment

Assessment type	Non-systematic

Dictionary used

Dictionary name	NCI_CTCAE
Dictionary version	4.0

Reporting groups

Reporting group title	Regorafenib + Oxaliplatin/Folinic Acid/5-FU (mFOLFOX6)

Reporting group description:

On Day 1, participants received 85 mg/m2 oxaliplatin as a 2-hour intravenous (IV) infusion and folinic acid (either 400 mg/m2 D/L folinic acid or 200 mg/m2 L-folinic acid) as a 2-hour IV infusion. Once the initial infusion was completed, participants received 5-FU 400 mg/m2 IV bolus injection immediately followed by a 5-FU 2400 mg/m2 IV infusion for 46 hours. The next cycle of mFOLFOX6 was administered on Day 15 to 17. Participants received Regorafenib (Stivarga, BAY73-4506) 160 mg orally (po) once daily (qd) on Days 4 to 10 and Days 18 to 24. One cycle comprised 28 days.

Serious adverse events	Regorafenib + Oxaliplatin/Folinic Acid/5-FU (mFOLFOX6)		
Total subjects affected by serious adverse events			
subjects affected / exposed	25 / 53 (47.17%)		
number of deaths (all causes)	34		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant melanoma			
subjects affected / exposed	1 / 53 (1.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metastases to liver			
subjects affected / exposed	1 / 53 (1.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Rectosigmoid cancer			
subjects affected / exposed	1 / 53 (1.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tumour pain			

subjects affected / exposed	1 / 53 (1.89%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Metastases to peritoneum				
subjects affected / exposed	1 / 53 (1.89%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Metastases to spleen				
subjects affected / exposed	1 / 53 (1.89%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Tumour associated fever				
subjects affected / exposed	1 / 53 (1.89%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Colorectal adenocarcinoma				
subjects affected / exposed	1 / 53 (1.89%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Vascular disorders				
Hypertension				
subjects affected / exposed	1 / 53 (1.89%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pelvic venous thrombosis				
subjects affected / exposed	1 / 53 (1.89%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Surgical and medical procedures				
Resection of rectum				
subjects affected / exposed	1 / 53 (1.89%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Therapeutic embolisation				

subjects affected / exposed	1 / 53 (1.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Stoma care			
subjects affected / exposed	1 / 53 (1.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sigmoidectomy			
subjects affected / exposed	1 / 53 (1.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cancer surgery			
subjects affected / exposed	1 / 53 (1.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 53 (1.89%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pyrexia			
subjects affected / exposed	2 / 53 (3.77%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	2 / 53 (3.77%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Investigations			
Electrocardiogram abnormal			

subjects affected / exposed	1 / 53 (1.89%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	1 / 53 (1.89%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorder postoperative			
subjects affected / exposed	1 / 53 (1.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 53 (1.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Arrhythmia			
subjects affected / exposed	1 / 53 (1.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Acute coronary syndrome			
subjects affected / exposed	1 / 53 (1.89%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 53 (1.89%)		
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 / 53 (1.89%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Retroperitoneal lymphadenopathy				
subjects affected / exposed	1 / 53 (1.89%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Abdominal pain				
subjects affected / exposed	1 / 53 (1.89%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Constipation				
subjects affected / exposed	1 / 53 (1.89%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Diarrhoea				
subjects affected / exposed	3 / 53 (5.66%)			
occurrences causally related to treatment / all	3 / 3			
deaths causally related to treatment / all	0 / 0			
Intestinal obstruction				
subjects affected / exposed	2 / 53 (3.77%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Small intestinal obstruction				
subjects affected / exposed	1 / 53 (1.89%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pancreatitis				
subjects affected / exposed	1 / 53 (1.89%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Large intestinal obstruction				

subjects affected / exposed	1 / 53 (1.89%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Vomiting				
subjects affected / exposed	1 / 53 (1.89%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
Hyperbilirubinaemia				
subjects affected / exposed	1 / 53 (1.89%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cholecystitis				
subjects affected / exposed	1 / 53 (1.89%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Cellulitis				
subjects affected / exposed	1 / 53 (1.89%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Abdominal sepsis				
subjects affected / exposed	1 / 53 (1.89%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Colonic abscess				
subjects affected / exposed	1 / 53 (1.89%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Device related infection				
subjects affected / exposed	1 / 53 (1.89%)			
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 / 53 (1.89%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hypokalaemia			
subjects affected / exposed	1 / 53 (1.89%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Regorafenib + Oxaliplatin/Folinic Acid/5-FU (mFOLFOX6)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	53 / 53 (100.00%)		
Vascular disorders			
Flushing			
subjects affected / exposed	6 / 53 (11.32%)		
occurrences (all)	9		
Hypotension			
subjects affected / exposed	5 / 53 (9.43%)		
occurrences (all)	5		
Phlebitis			
subjects affected / exposed	3 / 53 (5.66%)		
occurrences (all)	3		
Hypertension			
subjects affected / exposed	28 / 53 (52.83%)		
occurrences (all)	118		
Prehypertension			
subjects affected / exposed	7 / 53 (13.21%)		
occurrences (all)	16		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	22 / 53 (41.51%)		
occurrences (all)	70		

Fatigue subjects affected / exposed occurrences (all)	14 / 53 (26.42%) 20		
Mucosal inflammation subjects affected / exposed occurrences (all)	11 / 53 (20.75%) 34		
Pyrexia subjects affected / exposed occurrences (all)	9 / 53 (16.98%) 16		
Immune system disorders Drug hypersensitivity subjects affected / exposed occurrences (all)	5 / 53 (9.43%) 5		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	5 / 53 (9.43%) 8		
Epistaxis subjects affected / exposed occurrences (all)	7 / 53 (13.21%) 12		
Oropharyngeal pain subjects affected / exposed occurrences (all)	5 / 53 (9.43%) 6		
Dysphonia subjects affected / exposed occurrences (all)	18 / 53 (33.96%) 35		
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	5 / 53 (9.43%) 5		
Investigations Amylase increased subjects affected / exposed occurrences (all)	5 / 53 (9.43%) 8		
Alanine aminotransferase increased			

subjects affected / exposed	10 / 53 (18.87%)		
occurrences (all)	27		
Gamma-glutamyltransferase increased			
subjects affected / exposed	8 / 53 (15.09%)		
occurrences (all)	17		
Aspartate aminotransferase increased			
subjects affected / exposed	12 / 53 (22.64%)		
occurrences (all)	29		
Blood bilirubin increased			
subjects affected / exposed	7 / 53 (13.21%)		
occurrences (all)	12		
Lipase increased			
subjects affected / exposed	13 / 53 (24.53%)		
occurrences (all)	18		
Neutrophil count decreased			
subjects affected / exposed	12 / 53 (22.64%)		
occurrences (all)	28		
Platelet count decreased			
subjects affected / exposed	13 / 53 (24.53%)		
occurrences (all)	24		
Weight decreased			
subjects affected / exposed	5 / 53 (9.43%)		
occurrences (all)	7		
Blood alkaline phosphatase increased			
subjects affected / exposed	3 / 53 (5.66%)		
occurrences (all)	3		
White blood cell count decreased			
subjects affected / exposed	3 / 53 (5.66%)		
occurrences (all)	3		
Injury, poisoning and procedural complications			
Stoma site haemorrhage			
subjects affected / exposed	3 / 53 (5.66%)		
occurrences (all)	3		
Nervous system disorders			

Aphonia subjects affected / exposed occurrences (all)	4 / 53 (7.55%) 10		
Dysaesthesia subjects affected / exposed occurrences (all)	10 / 53 (18.87%) 27		
Dizziness subjects affected / exposed occurrences (all)	6 / 53 (11.32%) 6		
Dysgeusia subjects affected / exposed occurrences (all)	16 / 53 (30.19%) 18		
Headache subjects affected / exposed occurrences (all)	8 / 53 (15.09%) 12		
Neurotoxicity subjects affected / exposed occurrences (all)	11 / 53 (20.75%) 16		
Lethargy subjects affected / exposed occurrences (all)	10 / 53 (18.87%) 30		
Neuropathy peripheral subjects affected / exposed occurrences (all)	8 / 53 (15.09%) 12		
Polyneuropathy subjects affected / exposed occurrences (all)	6 / 53 (11.32%) 6		
Paraesthesia subjects affected / exposed occurrences (all)	28 / 53 (52.83%) 66		
Somnolence subjects affected / exposed occurrences (all)	3 / 53 (5.66%) 4		
Blood and lymphatic system disorders Anaemia			

subjects affected / exposed	12 / 53 (22.64%)		
occurrences (all)	22		
Leukopenia			
subjects affected / exposed	4 / 53 (7.55%)		
occurrences (all)	5		
Neutropenia			
subjects affected / exposed	28 / 53 (52.83%)		
occurrences (all)	60		
Thrombocytopenia			
subjects affected / exposed	16 / 53 (30.19%)		
occurrences (all)	37		
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	17 / 53 (32.08%)		
occurrences (all)	26		
Abdominal pain			
subjects affected / exposed	24 / 53 (45.28%)		
occurrences (all)	38		
Abdominal pain upper			
subjects affected / exposed	9 / 53 (16.98%)		
occurrences (all)	11		
Dyspepsia			
subjects affected / exposed	6 / 53 (11.32%)		
occurrences (all)	7		
Nausea			
subjects affected / exposed	28 / 53 (52.83%)		
occurrences (all)	70		
Diarrhoea			
subjects affected / exposed	37 / 53 (69.81%)		
occurrences (all)	124		
Proctalgia			
subjects affected / exposed	3 / 53 (5.66%)		
occurrences (all)	3		
Stomatitis			
subjects affected / exposed	17 / 53 (32.08%)		
occurrences (all)	29		

Vomiting subjects affected / exposed occurrences (all)	16 / 53 (30.19%) 29		
Skin and subcutaneous tissue disorders Alopecia subjects affected / exposed occurrences (all) Dry skin subjects affected / exposed occurrences (all) Palmar-plantar erythrodysaesthesia syndrome subjects affected / exposed occurrences (all) Pruritus subjects affected / exposed occurrences (all) Rash subjects affected / exposed occurrences (all)	 15 / 53 (28.30%) 15 5 / 53 (9.43%) 6 18 / 53 (33.96%) 43 3 / 53 (5.66%) 4 10 / 53 (18.87%) 15		
Renal and urinary disorders Haematuria subjects affected / exposed occurrences (all)	 3 / 53 (5.66%) 4		
Endocrine disorders Hypothyroidism subjects affected / exposed occurrences (all)	 5 / 53 (9.43%) 7		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) Back pain subjects affected / exposed occurrences (all) Pain in extremity	 3 / 53 (5.66%) 4 11 / 53 (20.75%) 17		

subjects affected / exposed	4 / 53 (7.55%)		
occurrences (all)	4		
Myalgia			
subjects affected / exposed	3 / 53 (5.66%)		
occurrences (all)	4		
Musculoskeletal chest pain			
subjects affected / exposed	3 / 53 (5.66%)		
occurrences (all)	3		
Pain in jaw			
subjects affected / exposed	5 / 53 (9.43%)		
occurrences (all)	5		
Infections and infestations			
Conjunctivitis			
subjects affected / exposed	3 / 53 (5.66%)		
occurrences (all)	4		
Nasopharyngitis			
subjects affected / exposed	3 / 53 (5.66%)		
occurrences (all)	3		
Device related infection			
subjects affected / exposed	3 / 53 (5.66%)		
occurrences (all)	5		
Urinary tract infection			
subjects affected / exposed	5 / 53 (9.43%)		
occurrences (all)	7		
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	6 / 53 (11.32%)		
occurrences (all)	10		
Hyponatraemia			
subjects affected / exposed	4 / 53 (7.55%)		
occurrences (all)	4		
Hypokalaemia			
subjects affected / exposed	6 / 53 (11.32%)		
occurrences (all)	9		
Hypocalcaemia			

subjects affected / exposed	6 / 53 (11.32%)		
occurrences (all)	7		
Decreased appetite			
subjects affected / exposed	21 / 53 (39.62%)		
occurrences (all)	42		
Hypophosphataemia			
subjects affected / exposed	13 / 53 (24.53%)		
occurrences (all)	33		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 July 2011	Amendment 1 was instituted to: - Require additional monitoring of liver function (weekly monitoring of aspartate transaminase, alanine transaminase, and bilirubin during the first 2 cycles of regorafenib dosing was added) and to include a dose modification/interruption table specific to changes of liver function tests under treatment in accordance with the Safety Report for Health Authorities and Ethics Committees, dated 13 July 2011 - Add 2 inclusion criteria that ensured that subjects with adequate pancreatic and renal function were enrolled - Revise the description of withdrawal of subjects from study treatment to add clinical progression to radiological progression as a condition of disease progression - Add rules for the replacement of non-evaluable subjects for the primary endpoint - Clarify that the administration of oxaliplatin and folinic acid could be concurrent or sequential - Add a description of the reporting of adverse event of special interest - Revise the definition of the FAS population to align with the intent-to-treat principle - Rename the population analysis set to per-protocol analysis set - Change the display of population characteristics to reflect the FAS only - Provide miscellaneous corrections and clarifications to improved consistency throughout the document.
25 February 2014	Amendment 2 was instituted to specify that OS data collection would be halted as of 30 June 2014.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

'99999' in the posting indicates that data were not calculated. Decimal places were automatically truncated if last decimal equals zero.

Notes: