Clinical trial results:
Randomized, Blinded, Multicenter, Phase 2 Study Comparing Veliparib Plus FOLFIRI ± Bevacizumab Versus Placebo Plus FOLFIRI ± Bevacizumab in Previously Untreated Metastatic Colorectal Cancer

Summary

EudraCT number	2014-002866-65
Trial protocol	AT HU DE BE ES GB
Global end of trial date	22 September 2017

Results information

Result version number	v1 (current)
This version publication date	26 September 2018
First version publication date	26 September 2018

Trial information

Trial identification

Sponsor protocol code	M14-217

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02305758
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AbbVie Deutschland GmbH & Co. KG
Sponsor organisation address	AbbVie House, Vanwall Business Park, Vanwall Road, Maidenhead, Berkshire, United Kingdom, SL6-4UB
Public contact	Global Medical Services, AbbVie, 001 800-633-9110,
Scientific contact	Yan Luo, AbbVie, yan.luo@abbvie.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	22 September 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	22 September 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This was a blinded, randomized, placebo-controlled Phase 2 multicenter study evaluating the efficacy and tolerability of veliparib plus irinotecan, fluorouracil, and leucovorin chemotherapy regimen (FOLFIRI) compared to placebo plus FOLFIRI in participants with previously untreated metastatic colorectal cancer. Participants could also have been treated with bevacizumab at the discretion of the Investigator.

Protection of trial subjects:

The Investigator or his/her representative explained the nature of the study to the subject, and answered all questions regarding this study. Prior to any study-related screening procedures being performed on the subject, the informed consent statement was reviewed, signed, and dated by the subject, the person who administered the informed consent, and any other signatories according to local requirements. Pharmacogenetic analysis was only performed if the subject had voluntarily signed and dated a separate pharmacogenetic informed consent approved by an IRB/IEC, after the nature of the testing was explained and the subject has had an opportunity to ask questions. The separate pharmacogenetic informed consent was signed before the pharmacogenetic testing was performed. If the subject did not consent to the pharmacogenetic testing, it did not impact the subject's participation in the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	02 December 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 10
Country: Number of subjects enrolled	Austria: 6
Country: Number of subjects enrolled	Belgium: 10
Country: Number of subjects enrolled	Germany: 8
Country: Number of subjects enrolled	Hungary: 14
Country: Number of subjects enrolled	Russian Federation: 29
Country: Number of subjects enrolled	Spain: 27
Country: Number of subjects enrolled	United Kingdom: 9
Country: Number of subjects enrolled	United States: 17
Worldwide total number of subjects	130
EEA total number of subjects	74

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)	78
From 65 to 84 years	52
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study population consisted of adult subjects with histologically or cytologically documented adenocarcinoma of the colon or rectum with metastatic disease, who had not received prior chemotherapy for their metastatic colorectal cancer.

Pre-assignment

Screening details:

Screening procedures and baseline radiographic tumor assessments were to be performed within 28 days prior to the first dose of veliparib/placebo on Cycle 1 Day –2.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Veliparib + modified FOLFIRI ± bevacizumab

Arm description:

Dosing of oral veliparib (200 mg) began 2 days prior to the start of FOLFIRI and continued twice a day (BID) for a total of 7 consecutive days. At the discretion of the Investigator, bevacizumab (5 mg/kg) could be administered intravenously (IV) immediately preceding FOLFIRI. Modified FOLFIRI was administered as irinotecan 180 mg/m^2 (90-minute infusion ± 30 minutes); leucovorin 400 mg/m^2 (90-minute infusion ± 30 minutes); and saline bolus (up to 15-minute infusion) immediately followed by fluorouracil 2400 mg/m^2 (46-hour continuous infusion ± 4 hours) starting on Day 1 of each 14-day cycle.

Arm type	Experimental
Investigational medicinal product name	Veliparib
Investigational medicinal product code	
Other name	ABT-888
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

200 mg oral dose beginning 2 days prior to the start of FOLFIRI and continuing twice a day (BID) for a total of 7 consecutive days

Investigational medicinal product name	Modified FOLFIRI
Investigational medicinal product code	
Other name	Irinotecan; leucovorin; saline bolus
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Irinotecan 180 mg/m^2 (90-minute infusion ± 30 minutes); leucovorin 400 mg/m^2 (90-minute infusion ± 30 minutes); and saline bolus (up to 15-minute infusion) on Day 1 of each 14-day cycle

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

Dosage and administration details:

At the discretion of the Investigator, 5 mg/kg may be administered intravenously immediately preceding FOLFIRI dosing

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

Dosage and administration details:

2400 mg/m^2 (46-hour continuous infusion ± 4 hours) starting on Day 1 of each 14-day cycle

Arm title	Placebo + FOLFIRI ± bevacizumab

Arm description:

Dosing of oral placebo (200 mg) began 2 days prior to the start of FOLFIRI and continued twice a day (BID) for a total of 7 consecutive days. At the discretion of the Investigator, bevacizumab (5 mg/kg) could be administered intravenously (IV) immediately preceding FOLFIRI. Standard FOLFIRI was administered as irinotecan 180 mg/m^2 (90-minute infusion ± 30 minutes); leucovorin 400 mg/m^2 (90-minute infusion ± 30 minutes); and fluorouracil bolus 400 mg/m^2 (up to 15-minute infusion) immediately followed by fluorouracil 2400 mg/m^2 (46-hour continuous infusion ± 4 hours) on Day 1 of each 14-day cycle.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

200 mg oral dose beginning 2 days prior to the start of FOLFIRI and continuing twice a day (BID) for a total of 7 consecutive days

Investigational medicinal product name	FOLFIRI
Investigational medicinal product code	
Other name	Irinotecan; leucovorin; fluorouracil
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Irinotecan 180 mg/m^2 (90-minute infusion ± 30 minutes); leucovorin 400 mg/m^2 (90-minute infusion ± 30 minutes); and fluorouracil bolus 400 mg/m^2 (up to 15-minute infusion) on Day 1 of each 14-day cycle

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

Dosage and administration details:

At the discretion of the Investigator, 5 mg/kg may be administered intravenously immediately preceding FOLFIRI dosing

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

Dosage and administration details:

2400 mg/m^2 (46-hour continuous infusion ± 4 hours) starting on Day 1 of each 14-day cycle

Number of subjects in period 1	Veliparib + modified FOLFIRI ± bevacizumab	Placebo + FOLFIRI ± bevacizumab
Started	65	65
Completed	0	0
Not completed	65	65
Consent withdrawn by subject	9	2
Death	27	27
Other, not specified	2	1
Study terminated by sponsor	21	34
Lost to follow-up	6	1

Baseline characteristics

Reporting groups	
Reporting group title	Veliparib + modified FOLFIRI ± bevacizumab

Reporting group description:

Dosing of oral veliparib (200 mg) began 2 days prior to the start of FOLFIRI and continued twice a day (BID) for a total of 7 consecutive days. At the discretion of the Investigator, bevacizumab (5 mg/kg) could be administered intravenously (IV) immediately preceding FOLFIRI. Modified FOLFIRI was administered as irinotecan 180 mg/m^2 (90-minute infusion ± 30 minutes); leucovorin 400 mg/m^2 (90-minute infusion ± 30 minutes); and saline bolus (up to 15-minute infusion) immediately followed by fluorouracil 2400 mg/m^2 (46-hour continuous infusion ± 4 hours) starting on Day 1 of each 14-day cycle.

Reporting group title	Placebo + FOLFIRI ± bevacizumab

Reporting group description:

Dosing of oral placebo (200 mg) began 2 days prior to the start of FOLFIRI and continued twice a day (BID) for a total of 7 consecutive days. At the discretion of the Investigator, bevacizumab (5 mg/kg) could be administered intravenously (IV) immediately preceding FOLFIRI. Standard FOLFIRI was administered as irinotecan 180 mg/m^2 (90-minute infusion ± 30 minutes); leucovorin 400 mg/m^2 (90-minute infusion ± 30 minutes); and fluorouracil bolus 400 mg/m^2 (up to 15-minute infusion) immediately followed by fluorouracil 2400 mg/m^2 (46-hour continuous infusion ± 4 hours) on Day 1 of each 14-day cycle.

Reporting group values	Veliparib + modified FOLFIRI ± bevacizumab	Placebo + FOLFIRI ± bevacizumab	Total
Number of subjects	65	65	130
Age categorical			
Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			0
Newborns (0-27 days)			0
Infants and toddlers (28 days-23 months)			0
Children (2-11 years)			0
Adolescents (12-17 years)			0
Adults (18-64 years)			0
From 65-84 years			0
85 years and over			0
Age continuous			
Units: years			
arithmetic mean	58.9	63.8	
standard deviation	± 13.06	± 9.04	-
Gender categorical			
Units: Subjects			
Female	21	25	46
Male	44	40	84

End points

End points reporting groups

Reporting group title	Veliparib + modified FOLFIRI ± bevacizumab

Reporting group description:

Dosing of oral veliparib (200 mg) began 2 days prior to the start of FOLFIRI and continued twice a day (BID) for a total of 7 consecutive days. At the discretion of the Investigator, bevacizumab (5 mg/kg) could be administered intravenously (IV) immediately preceding FOLFIRI. Modified FOLFIRI was administered as irinotecan 180 mg/m^2 (90-minute infusion ± 30 minutes); leucovorin 400 mg/m^2 (90-minute infusion ± 30 minutes); and saline bolus (up to 15-minute infusion) immediately followed by fluorouracil 2400 mg/m^2 (46-hour continuous infusion ± 4 hours) starting on Day 1 of each 14-day cycle.

Reporting group title	Placebo + FOLFIRI ± bevacizumab

Reporting group description:

Dosing of oral placebo (200 mg) began 2 days prior to the start of FOLFIRI and continued twice a day (BID) for a total of 7 consecutive days. At the discretion of the Investigator, bevacizumab (5 mg/kg) could be administered intravenously (IV) immediately preceding FOLFIRI. Standard FOLFIRI was administered as irinotecan 180 mg/m^2 (90-minute infusion ± 30 minutes); leucovorin 400 mg/m^2 (90-minute infusion ± 30 minutes); and fluorouracil bolus 400 mg/m^2 (up to 15-minute infusion) immediately followed by fluorouracil 2400 mg/m^2 (46-hour continuous infusion ± 4 hours) on Day 1 of each 14-day cycle.

Primary: Progression-Free Survival (PFS): Time to Event

End point title	Progression-Free Survival (PFS): Time to Event

End point description:

PFS was defined as the number of days from the date the participant was randomized to the date the participant experienced an event of disease progression or death, whichever occurred first. All events of disease progression were included, whether the participant was still taking or had discontinued study drug. Events of death were included for participants who had not experienced an event of disease progression, if the death occurred within 8 weeks of the last evaluable disease progression assessment. If the participant did not have an event of disease progression and the participant had not died as defined above, data were censored at the date of the participant's last evaluable disease progression assessment. The PFS distribution was estimated using Kaplan-Meier methodology. Point estimates and 95% confidence intervals (95% CIs) for the PFS distribution quartiles are provided.

End point type	Primary

End point timeframe:

Every 8 weeks from Cycle 1, Day 1 until radiographic progression was observed. The maximum observed follow up duration at the progression-free survival analysis time was 579 days.

End point values	Veliparib + modified FOLFIRI ± bevacizumab	Placebo + FOLFIRI ± bevacizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	65[1]	65[2]		
Units: days				
number (confidence interval 95%)				
25th Quartile	221 (120 to 295)	213 (121 to 233)		
50th Quartile	361 (289 to 453)	337 (233 to 421)		

75th Quartile	534 (453 to 999)	512 (421 to 999)		

Notes:

[1] - 999= upper 95% CI limit not estimable due to an insufficient number of subjects with events

[2] - 999= upper 95% CI limit not estimable due to an insufficient number of subjects with events

Statistical analyses

Statistical analysis title	Progression-Free Survival (PFS): Time to Event

Statistical analysis description:

Comparisons between treatment groups were performed using the Cox Proportional Hazard Model, stratified by planned bevacizumab use (planned use versus no planned use).

Comparison groups	Veliparib + modified FOLFIRI ± bevacizumab v Placebo + FOLFIRI ± bevacizumab
Number of subjects included in analysis	130
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	0.939
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.596
upper limit	1.48

Secondary: Overall Survival (OS): Time to Event

End point title	Overall Survival (OS): Time to Event

End point description:

Overall survival was defined as the number of days from the date that the participant was randomized to the date of the participant's death. All events of death were included, regardless of whether the event occurred while the participant was still taking or had discontinued study drug. If a participant had not died, the data were censored at the date last known to be alive. The OS distribution was estimated using Kaplan-Meier methodology. Point estimates and 95% confidence intervals (95% CIs) for the OS distribution quartiles are provided.

End point type	Secondary

End point timeframe:

Survival information was to be collected 4 wks after the last study visit, continuing every 4 wks for 1 yr, then every 8 wks for up to 2 more yrs or until death. The maximum observed follow up duration at the overall survival analysis time was 914 days.

End point values	Veliparib + modified FOLFIRI ± bevacizumab	Placebo + FOLFIRI ± bevacizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	65[3]	65[4]		
Units: days				
number (confidence interval 95%)				

25th Quartile	557 (391 to 616)	512 (326 to 655)		
50th Quartile	770 (609 to 999)	811 (678 to 999)		
75th Quartile	999 (784 to 999)	999 (811 to 999)		

Notes:

[3] - 999 = not calculable/estimable due to an insufficient number of subjects with events

[4] - 999 = not calculable/estimable due to an insufficient number of subjects with events

Statistical analyses

Statistical analysis title	Overall Survival (OS): Time to Event

Statistical analysis description:

Comparisons between treatment groups were performed using the Cox Proportional Hazard Model, stratified by planned bevacizumab use (planned use versus no planned use).

Comparison groups	Veliparib + modified FOLFIRI ± bevacizumab v Placebo + FOLFIRI ± bevacizumab
Number of subjects included in analysis	130
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	1.261
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.738
upper limit	2.156

Secondary: Objective Response Rate (ORR)

End point title	Objective Response Rate (ORR)

End point description:

ORR was defined as the proportion of participants with a complete (CR) or partial response (PR) based on Response Evaluation Criteria in Solid Tumors (RECIST, version 1.1) for target lesions, assessed by computed tomography (CT). Complete response (CR) was defined as disappearance of all target lesions; partial response (PR) ≥30% decrease in the the sum of diameters of target lesions, taking as reference the baseline sum diameters. For participants who underwent surgery, ORR was not evaluated after surgery.

End point type	Secondary

End point timeframe:

Per protocol, post-baseline tumor assessment was conducted every 8 weeks from Cycle 1 Day 1 until radiographic progression. The maximum observed follow up duration at the progression-free survival analysis time was 579 days.

End point values	Veliparib + modified FOLFIRI ± bevacizumab	Placebo + FOLFIRI ± bevacizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	65[5]	65[6]		
Units: Participants	37	40		

Notes:

[5] - All randomized participants

[6] - All randomized participants

Statistical analyses

Statistical analysis title	Objective Response Rate (ORR)

Statistical analysis description:

Comparisons between treatment groups were performed using the Mantel-Haenszel method, stratified by planned bevacizumab use (planned use versus no planned use).

Comparison groups	Veliparib + modified FOLFIRI ± bevacizumab v Placebo + FOLFIRI ± bevacizumab
Number of subjects included in analysis	130
Analysis specification	Pre-specified
Analysis type	superiority[7]
Method	Mantel-Haenszel
Parameter estimate	Mean difference (final values)
Point estimate	-4.62
Confidence interval	
level	95 %
sides	2-sided
lower limit	-21.4
upper limit	12.1

Notes:

[7] - Difference in proportions

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Treatment-emergent adverse events (TEAEs) and serious adverse events (TESAEs) were collected from the time of veliparib/placebo administration until 30 days after the last dose of veliparib/placebo (up to 396 days).

Adverse event reporting additional description:

TEAEs and TESAEs are defined as any adverse event (AE) with an onset date that is after the first dose of veliparib/placebo until 30 days after the last dose of veliparib/placebo and were collected whether elicited or spontaneously reported by the participant.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20

Reporting groups

Reporting group title	Placebo + FOLFIRI ± Bevacizumab

Reporting group description:

Dosing of oral placebo (200 mg) began 2 days prior to the start of FOLFIRI and continued twice a day (BID) for a total of 7 consecutive days. At the discretion of the Investigator, bevacizumab (5 mg/kg) could be administered intravenously (IV) immediately preceding FOLFIRI. Standard FOLFIRI was administered as irinotecan 180 mg/m^2 (90-minute infusion ± 30 minutes); leucovorin 400 mg/m^2 (90-minute infusion ± 30 minutes); and fluorouracil bolus 400 mg/m^2 (up to 15-minute infusion) immediately followed by fluorouracil 2400 mg/m^2 (46-hour continuous infusion ± 4 hours) on Day 1 of each 14-day cycle.

Reporting group title	Veliparib + Modified FOLFIRI ± Bevacizumab

Reporting group description:

Dosing of oral veliparib (200 mg) began 2 days prior to the start of FOLFIRI and continued twice a day (BID) for a total of 7 consecutive days. At the discretion of the Investigator, bevacizumab (5 mg/kg) could be administered intravenously (IV) immediately preceding FOLFIRI. Modified FOLFIRI was administered as irinotecan 180 mg/m^2 (90-minute infusion ± 30 minutes); leucovorin 400 mg/m^2 (90-minute infusion ± 30 minutes); and saline bolus (up to 15-minute infusion) immediately followed by fluorouracil 2400 mg/m^2 (46-hour continuous infusion ± 4 hours) starting on Day 1 of each 14-day cycle.

Serious adverse events	Placebo + FOLFIRI ± Bevacizumab	Veliparib + Modified FOLFIRI ± Bevacizumab	
Total subjects affected by serious adverse events			
subjects affected / exposed	33 / 65 (50.77%)	30 / 65 (46.15%)	
number of deaths (all causes)	27	27	
number of deaths resulting from adverse events	2	2	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
MALIGNANT NEOPLASM PROGRESSION			
subjects affected / exposed	2 / 65 (3.08%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

METASTASES TO CENTRAL NERVOUS SYSTEM			
subjects affected / exposed	1 / 65 (1.54%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
DEEP VEIN THROMBOSIS			
subjects affected / exposed	1 / 65 (1.54%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
CHEST PAIN			
subjects affected / exposed	0 / 65 (0.00%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
EXTRAVASATION			
subjects affected / exposed	0 / 65 (0.00%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PYREXIA			
subjects affected / exposed	0 / 65 (0.00%)	2 / 65 (3.08%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
FEMALE GENITAL TRACT FISTULA			
subjects affected / exposed	0 / 65 (0.00%)	1 / 65 (1.54%)	
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			
DYSPNOEA			
subjects affected / exposed	2 / 65 (3.08%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HICCUPS			

subjects affected / exposed	1 / 65 (1.54%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PLEURAL EFFUSION			
subjects affected / exposed	1 / 65 (1.54%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PULMONARY EMBOLISM			
subjects affected / exposed	2 / 65 (3.08%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Device dislocation			
subjects affected / exposed	1 / 65 (1.54%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
BLOOD CREATININE INCREASED			
subjects affected / exposed	1 / 65 (1.54%)	0 / 65 (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			
FEMORAL NECK FRACTURE			
subjects affected / exposed	0 / 65 (0.00%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HIP FRACTURE			
subjects affected / exposed	1 / 65 (1.54%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
ATRIAL FLUTTER			

subjects affected / exposed	0 / 65 (0.00%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CARDIAC ARREST			
subjects affected / exposed	2 / 65 (3.08%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
LEFT VENTRICULAR DYSFUNCTION			
subjects affected / exposed	1 / 65 (1.54%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
MYOCARDIAL ISCHAEMIA			
subjects affected / exposed	1 / 65 (1.54%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
TACHYARRHYTHMIA			
subjects affected / exposed	0 / 65 (0.00%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
TACHYCARDIA			
subjects affected / exposed	1 / 65 (1.54%)	0 / 65 (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			
CEREBROVASCULAR ACCIDENT			
subjects affected / exposed	1 / 65 (1.54%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
LACUNAR INFARCTION			
subjects affected / exposed	1 / 65 (1.54%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SYNCOPE			

subjects affected / exposed	1 / 65 (1.54%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
FEBRILE NEUTROPENIA			
subjects affected / exposed	3 / 65 (4.62%)	3 / 65 (4.62%)	
occurrences causally related to treatment / all	2 / 3	4 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
NEUTROPENIA			
subjects affected / exposed	1 / 65 (1.54%)	2 / 65 (3.08%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
ABDOMINAL PAIN			
subjects affected / exposed	2 / 65 (3.08%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CONSTIPATION			
subjects affected / exposed	0 / 65 (0.00%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
DIARRHOEA			
subjects affected / exposed	2 / 65 (3.08%)	9 / 65 (13.85%)	
occurrences causally related to treatment / all	2 / 2	1 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
ENTERITIS			
subjects affected / exposed	0 / 65 (0.00%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTROINTESTINAL OBSTRUCTION			
subjects affected / exposed	0 / 65 (0.00%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
INTESTINAL OBSTRUCTION			

subjects affected / exposed	3 / 65 (4.62%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
INTESTINAL PERFORATION			
subjects affected / exposed	0 / 65 (0.00%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
INTRA-ABDOMINAL FLUID COLLECTION			
subjects affected / exposed	0 / 65 (0.00%)	1 / 65 (1.54%)	
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 / 65 (1.54%)	2 / 65 (3.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
NAUSEA			
subjects affected / exposed	0 / 65 (0.00%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PROCTITIS			
subjects affected / exposed	0 / 65 (0.00%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
RECTAL HAEMORRHAGE			
subjects affected / exposed	0 / 65 (0.00%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SMALL INTESTINAL OBSTRUCTION			
subjects affected / exposed	1 / 65 (1.54%)	0 / 65 (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	0 / 65 (0.00%)	2 / 65 (3.08%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
BILE DUCT STENOSIS			
subjects affected / exposed	0 / 65 (0.00%)	2 / 65 (3.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
HEPATOTOXICITY			
subjects affected / exposed	0 / 65 (0.00%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
ACUTE KIDNEY INJURY			
subjects affected / exposed	1 / 65 (1.54%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
NEPHROLITHIASIS			
subjects affected / exposed	0 / 65 (0.00%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
RENAL FAILURE			
subjects affected / exposed	1 / 65 (1.54%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
subjects affected / exposed	0 / 65 (0.00%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
FLANK PAIN			
subjects affected / exposed	1 / 65 (1.54%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

MUSCULAR WEAKNESS			
subjects affected / exposed	1 / 65 (1.54%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
MUSCULOSKELETAL PAIN			
subjects affected / exposed	1 / 65 (1.54%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
OSTEONECROSIS OF JAW			
subjects affected / exposed	0 / 65 (0.00%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PAIN IN JAW			
subjects affected / exposed	0 / 65 (0.00%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
ABDOMINAL ABSCESS			
subjects affected / exposed	1 / 65 (1.54%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CAMPYLOBACTER INFECTION			
subjects affected / exposed	0 / 65 (0.00%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
LOWER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	1 / 65 (1.54%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
LUNG INFECTION			
subjects affected / exposed	1 / 65 (1.54%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

PNEUMONIA			
subjects affected / exposed	1 / 65 (1.54%)	2 / 65 (3.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
SERRATIA INFECTION			
subjects affected / exposed	1 / 65 (1.54%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
STREPTOCOCCAL INFECTION			
subjects affected / exposed	0 / 65 (0.00%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
URINARY TRACT INFECTION			
subjects affected / exposed	1 / 65 (1.54%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
UROSEPSIS			
subjects affected / exposed	1 / 65 (1.54%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
VIRAL INFECTION			
subjects affected / exposed	0 / 65 (0.00%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
VIRAL UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	1 / 65 (1.54%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
DEHYDRATION			
subjects affected / exposed	1 / 65 (1.54%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

HYPOKALAEMIA			
subjects affected / exposed	1 / 65 (1.54%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPOMAGNESAEMIA			
subjects affected / exposed	0 / 65 (0.00%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPONATRAEMIA			
subjects affected / exposed	1 / 65 (1.54%)	0 / 65 (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	Placebo + FOLFIRI ± Bevacizumab	Veliparib + Modified FOLFIRI ± Bevacizumab	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	60 / 65 (92.31%)	59 / 65 (90.77%)	
Vascular disorders			
HYPERTENSION			
subjects affected / exposed	9 / 65 (13.85%)	6 / 65 (9.23%)	
occurrences (all)	10	12	
General disorders and administration site conditions			
ASTHENIA			
subjects affected / exposed	14 / 65 (21.54%)	16 / 65 (24.62%)	
occurrences (all)	41	34	
FATIGUE			
subjects affected / exposed	24 / 65 (36.92%)	25 / 65 (38.46%)	
occurrences (all)	65	38	
MUCOSAL INFLAMMATION			
subjects affected / exposed	14 / 65 (21.54%)	4 / 65 (6.15%)	
occurrences (all)	27	7	
OEDEMA PERIPHERAL			

subjects affected / exposed	7 / 65 (10.77%)	5 / 65 (7.69%)	
occurrences (all)	7	5	
PYREXIA			
subjects affected / exposed	11 / 65 (16.92%)	8 / 65 (12.31%)	
occurrences (all)	13	15	
Respiratory, thoracic and mediastinal disorders			
COUGH			
subjects affected / exposed	7 / 65 (10.77%)	3 / 65 (4.62%)	
occurrences (all)	8	3	
DYSPHONIA			
subjects affected / exposed	5 / 65 (7.69%)	3 / 65 (4.62%)	
occurrences (all)	5	3	
DYSPNOEA			
subjects affected / exposed	8 / 65 (12.31%)	5 / 65 (7.69%)	
occurrences (all)	9	5	
EPISTAXIS			
subjects affected / exposed	17 / 65 (26.15%)	6 / 65 (9.23%)	
occurrences (all)	22	8	
NASAL DRYNESS			
subjects affected / exposed	2 / 65 (3.08%)	4 / 65 (6.15%)	
occurrences (all)	2	4	
OROPHARYNGEAL PAIN			
subjects affected / exposed	2 / 65 (3.08%)	4 / 65 (6.15%)	
occurrences (all)	2	4	
PRODUCTIVE COUGH			
subjects affected / exposed	4 / 65 (6.15%)	1 / 65 (1.54%)	
occurrences (all)	4	1	
PULMONARY EMBOLISM			
subjects affected / exposed	6 / 65 (9.23%)	3 / 65 (4.62%)	
occurrences (all)	6	3	
RHINORRHOEA			
subjects affected / exposed	3 / 65 (4.62%)	5 / 65 (7.69%)	
occurrences (all)	4	5	
Psychiatric disorders			

INSOMNIA			
subjects affected / exposed	8 / 65 (12.31%)	10 / 65 (15.38%)	
occurrences (all)	9	10	
Investigations			
BLOOD ALKALINE PHOSPHATASE INCREASED			
subjects affected / exposed	4 / 65 (6.15%)	1 / 65 (1.54%)	
occurrences (all)	8	3	
WEIGHT DECREASED			
subjects affected / exposed	5 / 65 (7.69%)	6 / 65 (9.23%)	
occurrences (all)	9	6	
Nervous system disorders			
DIZZINESS			
subjects affected / exposed	4 / 65 (6.15%)	0 / 65 (0.00%)	
occurrences (all)	5	0	
DYSGEUSIA			
subjects affected / exposed	6 / 65 (9.23%)	11 / 65 (16.92%)	
occurrences (all)	6	11	
HEADACHE			
subjects affected / exposed	5 / 65 (7.69%)	10 / 65 (15.38%)	
occurrences (all)	12	11	
PARAESTHESIA			
subjects affected / exposed	5 / 65 (7.69%)	5 / 65 (7.69%)	
occurrences (all)	6	6	
PERIPHERAL SENSORY NEUROPATHY			
subjects affected / exposed	7 / 65 (10.77%)	3 / 65 (4.62%)	
occurrences (all)	7	3	
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	12 / 65 (18.46%)	25 / 65 (38.46%)	
occurrences (all)	28	59	
LEUKOPENIA			
subjects affected / exposed	4 / 65 (6.15%)	11 / 65 (16.92%)	
occurrences (all)	8	24	
LYMPHOPENIA			
subjects affected / exposed	2 / 65 (3.08%)	4 / 65 (6.15%)	
occurrences (all)	3	5	

NEUTROPENIA			
subjects affected / exposed	23 / 65 (35.38%)	41 / 65 (63.08%)	
occurrences (all)	54	108	
Gastrointestinal disorders			
ABDOMINAL PAIN			
subjects affected / exposed	22 / 65 (33.85%)	12 / 65 (18.46%)	
occurrences (all)	37	16	
ABDOMINAL PAIN UPPER			
subjects affected / exposed	8 / 65 (12.31%)	2 / 65 (3.08%)	
occurrences (all)	9	7	
CONSTIPATION			
subjects affected / exposed	21 / 65 (32.31%)	9 / 65 (13.85%)	
occurrences (all)	29	16	
DIARRHOEA			
subjects affected / exposed	35 / 65 (53.85%)	29 / 65 (44.62%)	
occurrences (all)	103	73	
DRY MOUTH			
subjects affected / exposed	1 / 65 (1.54%)	4 / 65 (6.15%)	
occurrences (all)	1	5	
FLATULENCE			
subjects affected / exposed	2 / 65 (3.08%)	4 / 65 (6.15%)	
occurrences (all)	2	4	
GASTROOESOPHAGEAL REFLUX DISEASE			
subjects affected / exposed	4 / 65 (6.15%)	1 / 65 (1.54%)	
occurrences (all)	5	1	
HAEMORRHOIDS			
subjects affected / exposed	4 / 65 (6.15%)	4 / 65 (6.15%)	
occurrences (all)	6	5	
NAUSEA			
subjects affected / exposed	40 / 65 (61.54%)	35 / 65 (53.85%)	
occurrences (all)	66	69	
STOMATITIS			
subjects affected / exposed	10 / 65 (15.38%)	15 / 65 (23.08%)	
occurrences (all)	14	25	
TOOTHACHE			

subjects affected / exposed	4 / 65 (6.15%)	1 / 65 (1.54%)	
occurrences (all)	6	1	
VOMITING			
subjects affected / exposed	26 / 65 (40.00%)	26 / 65 (40.00%)	
occurrences (all)	38	48	
Skin and subcutaneous tissue disorders			
ALOPECIA			
subjects affected / exposed	18 / 65 (27.69%)	25 / 65 (38.46%)	
occurrences (all)	30	28	
DRY SKIN			
subjects affected / exposed	3 / 65 (4.62%)	5 / 65 (7.69%)	
occurrences (all)	3	12	
PRURITUS			
subjects affected / exposed	4 / 65 (6.15%)	4 / 65 (6.15%)	
occurrences (all)	5	8	
Renal and urinary disorders			
DYSURIA			
subjects affected / exposed	3 / 65 (4.62%)	5 / 65 (7.69%)	
occurrences (all)	3	8	
HAEMATURIA			
subjects affected / exposed	5 / 65 (7.69%)	2 / 65 (3.08%)	
occurrences (all)	6	2	
PROTEINURIA			
subjects affected / exposed	4 / 65 (6.15%)	3 / 65 (4.62%)	
occurrences (all)	6	4	
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
subjects affected / exposed	5 / 65 (7.69%)	5 / 65 (7.69%)	
occurrences (all)	7	6	
BACK PAIN			
subjects affected / exposed	8 / 65 (12.31%)	8 / 65 (12.31%)	
occurrences (all)	11	10	
MUSCULOSKELETAL PAIN			
subjects affected / exposed	4 / 65 (6.15%)	3 / 65 (4.62%)	
occurrences (all)	4	3	
MYALGIA			

subjects affected / exposed	5 / 65 (7.69%)	3 / 65 (4.62%)	
occurrences (all)	5	3	
Infections and infestations			
BRONCHITIS			
subjects affected / exposed	5 / 65 (7.69%)	2 / 65 (3.08%)	
occurrences (all)	5	7	
UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	5 / 65 (7.69%)	2 / 65 (3.08%)	
occurrences (all)	5	5	
URINARY TRACT INFECTION			
subjects affected / exposed	4 / 65 (6.15%)	6 / 65 (9.23%)	
occurrences (all)	6	8	
VIRAL UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	2 / 65 (3.08%)	6 / 65 (9.23%)	
occurrences (all)	2	7	
Metabolism and nutrition disorders			
DECREASED APPETITE			
subjects affected / exposed	19 / 65 (29.23%)	15 / 65 (23.08%)	
occurrences (all)	36	21	
DEHYDRATION			
subjects affected / exposed	6 / 65 (9.23%)	6 / 65 (9.23%)	
occurrences (all)	7	9	
HYPERGLYCAEMIA			
subjects affected / exposed	9 / 65 (13.85%)	4 / 65 (6.15%)	
occurrences (all)	15	5	
HYPERURICAEMIA			
subjects affected / exposed	0 / 65 (0.00%)	4 / 65 (6.15%)	
occurrences (all)	0	9	
HYPOKALAEMIA			
subjects affected / exposed	3 / 65 (4.62%)	10 / 65 (15.38%)	
occurrences (all)	3	18	
HYPOMAGNESAEMIA			
subjects affected / exposed	4 / 65 (6.15%)	1 / 65 (1.54%)	
occurrences (all)	5	1	
HYPONATRAEMIA			

subjects affected / exposed occurrences (all)	3 / 65 (4.62%) 4	4 / 65 (6.15%) 8	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 September 2014	Protocol Amendment 1: This study did not begin under the original protocol. Sites needed to obtain amendment approval before study initiation. The purpose of this amendment was to: ● Revise study design such that subjects randomized to the placebo arm will receive a fluorouracil bolus (400 mg/m^2) prior to the 46-hr (2400 mg/m^2) infusion, i.e., these subjects will receive the standard FOLFIRI regimen. This change was made in response to FDA's comments. ● Add new information regarding unblinded site pharmacy personnel responsible for the preparation of a fluorouracil or saline bolus in response to FDA's comments. ● Clarify that a female subject must be postmenopausal for at least 1 yr. ● Update the informed consent inclusion criterion in the Synopsis and Section 5.2.2 and remove the references to the "subject's legally acceptable representative" as subjects in the study are required to consent for themselves. ● Clarify a discrepancy in the Main Exclusion Criteria of the synopsis to indicate that subjects must be disease-free from previous or concurrent malignancies for a minimum of 3 yrs. ● Clarify a discrepancy in the Main Exclusion Criteria of the synopsis and Section 5.2.2 to indicate that "symptomatic congestive heart failure" is an exclusion criterion for all subjects, not only subjects receiving bevacizumab. ● Clarify that leucovorin will be administered for 90 minutes concurrently with irinotecan per National Comprehensive Cancer Network (NCCN) Guidelines. ● Increase frequency of radiographic tumor assessments to ensure adequate evaluation of subjects and maintain consistency throughout the duration of the study. ● Update Clinical Experience Section 3.8 to include the rationale for excluding the 5-fluorouracil (5-FU) bolus with veliparib treatment based on published Phase 1 trial data. ● Move Benefits and Risks Section 3.9 to the end of the Introduction to improve overall clarity.

23 September 2014	Protocol Amendment 1, continued: ● Update the Benefits and Risks Section 3.9 to include potential risk of excluding fluorouracil bolus from the veliparib arm. ● Add an exclusion criterion to the Synopsis and Section 5.2.2 to exclude subjects that have received an investigational product within the 28 days prior to Screening. ● Add an exclusion criterion to the Synopsis and Section 5.2.2 to cover local laws and regulations where certain patient groups would be prohibited from participation. ● Update Table 2 Excluded Medications for clarity to specify the appropriate patient population. ● Clarify in Section 5.3.1.1 that body weight measurement is not a necessary component for every physical exam, only for those visits as indicated in Table 4. ● Update Table 4 Study Assessments to include Adverse Event (AE) assessments and Prior and Concomitant Therapy assessments. ● Clarify in Section 5.3.1.1 that radiographic tumor assessments may be performed up to 4 days before scheduled date, but not after, and should be performed prior to the next cycle of FOLFIRI to ensure subjects are evaluated before receiving additional chemotherapy. ● Add in Section 5.3.1.1 that AbbVie may require sites to electronically transfer copies of CT or MRI scans to facilitate third party review of disease progression. ● Update Section 5.3.1.1 to remove the statement that Australia should select "Europe" in the Interactive Response Technology (IRT) system at randomization as the IRT system only includes "Rest of World" and "North America" classifications. ● Clarify in Table 5 that the subject's morning dose of veliparib on the pharmacokinetic (PK) sampling days of C2D1 and C3D1 should be taken on site. ● Clarify the timing of the safety data analysis in Section 5.3.4. ● Provide additional clarity in Section 5.4.1 and Section 8.1.2.2 for subjects that undergo surgical resection while on the study.
23 September 2014	Protocol Amendment 1, continued: ● Clarify in Section 5.5.9 that AbbVie must be notified before the blind is broken by the Investigator. ● Add Section 8.1.7, Interim Analysis, to indicate that AbbVie will perform at least 2 efficacy and 2 safety interim analyses to ensure subject safety and assess efficacy of veliparib. ● Clarify language in Completion of Study Section 13.0. ● Revise guidelines for dose reduction and toxicity management (Appendix G and Appendix I) for fluorouracil to adjust for inclusion of the bolus in the placebo arm. ● Add the central back-up phone number under Section 6.7 Adverse Event. ● Reporting as required per the current version of the protocol template. ● Incorporate minor linguistic and administrative changes throughout the document for clarification.

16 July 2015	Protocol Amendment 2: The purpose of this amendment was to: ● Update contact information for the AbbVie Study Designated Physician. ● Provide timing windows around the infusion duration of fluorouracil, irinotecan, leucovorin and bevacizumab. ● Section 1.2, Synopsis, add bevacizumab as a reference therapy in the table. ● Section 1.2, Synopsis, and Section 5.2.2, Exclusion Criteria, clarify that Exclusion Criterion 3 pertains to neoadjuvant chemotherapy in addition to adjuvant therapy and change "prior to colorectal cancer recurrence" to "prior to C1D–2." ● Section 1.2, Synopsis, and Section 5.2.2, Exclusion Criteria, add a definition to symptomatic congestive heart failure. ● Section 3.8, Clinical Experience, correct inaccurate adverse event frequencies from Study M10-977, Phase 1 dose escalation study. ● Section 5.1, Overall Study Design and Plan: Description, update Figure 1 to reflect that subjects will receive either fluorouracil or saline bolus and illustrate that the 46-hour fluorouracil infusion will continue into Day 3. ● Section 5.1, Overall Study Design and Plan: Description, and Section 5.4.5, Timing and Collection of Survival and Post-Treatment Cancer Information, clarify that the survival information and post-treatment cancer information will be collected beginning 4 weeks after the last clinical assessment. ● Section 5.3.1, Efficacy and Safety Measurements Assessed and Flow Chart, remove physical exam requirement at C1D1. ● Section 5.3.1.1, Study Procedures, clarify that RAS, BRAF and MSI status only need to be captured in Medical History if known. ● Section 5.3.1.1, Study Procedures, Table 7, Clinical Laboratory Tests, update clinical chemistry terminology. ● Section 5.3.2.1, Blood Samples for Pharmacokinetic Analysis, update the information that is to be captured. ● Section 5.3.2.2, Measurement Methods, revise "non-GLP" to "non-validated."

16 July 2015	Protocol Amendment 2, continued: ● Section 5.3.2.3, Blood Samples for Pharmacogenetic Analysis, revise the label for the pharmacogenetic sample collection tube from "PG-DNA" to "PG-DNA blood." ● Section 5.3.7, Pharmacodynamic Variables, and Section 5.4, Removal (Discontinuation) of Subjects from Protocol Therapy and Study Visits, update storage and retention language for the pharmacodynamics samples. ● Section 5.4, Removal (Discontinuation) of Subjects from Protocol Therapy and Study Visits, update language regarding consent withdrawal and the pharmacodynamic samples. ● Section 5.5.1, Protocol Therapy Administered, specify that sites can use their own method for calculating body surface area (BSA), and dose re-calculations must be made if a subject's weight increases or decreases by more than 10%. ● Section 5.5.1, Protocol Therapy Administered, update protocol therapy administration to allow for sequential infusion of irinotecan followed by leucovorin. ● Section 5.5.9, Blinding, update language regarding unblinded AbbVie study personnel. ● Section 6.7, Adverse Event Reporting, update information regarding reporting SAEs if the site does not have access to Electronic Data Capture (EDC) or the system is not operable and update the 24-hour AbbVie Medical Escalation Hotline information. ● Section 7.0, Protocol Deviations, update language regarding intentional/prospective deviations from the protocol. ● Section 8.1.7, Interim Analysis, update interim analysis plan. ● Appendix I, Toxicity Management Guidelines for Protocol Therapy, update language regarding dose modifications and unresolved toxicity. ● Additional minor corrections and clarifications.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported