Clinical trial results:
A Multi-Center, Randomized, Placebo-Controlled Phase II Study of Regorafenib in Combination With FOLFIRI (Irinotecan, 5-Fluorouracil, and Leucovorin) Versus Placebo With FOLFIRI as Second-Line Therapy in Patients with Metastatic Colorectal Cancer.

Summary

EudraCT number	2012-000709-59
Trial protocol	IE GB
Global end of trial date	05 December 2018

Results information

Result version number	v1 (current)
This version publication date	23 June 2022
First version publication date	23 June 2022
Summary attachment (see zip file)	LCCC1029_CSR (LCCC1029 ClinicalTrials.gov Registration and Results Final download 2020 02 13 modwyer.pdf)

Trial information

Trial identification

Sponsor protocol code	LCCC1029

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01298570
WHO universal trial number (UTN)	-
Other trial identifiers	ICORG Study Number: ICORG 12-07

Notes:

Sponsors

Sponsor organisation name	Cancer Trials Ireland
Sponsor organisation address	Ardilaun House, Block B, 111 St Stephen's Green, Dublin 2, Ireland, D02 VN51
Public contact	Clinical Project Manager, Cancer Trials Ireland, 353 016677211, info@cancertrials.ie
Scientific contact	Clinical Project Manager, Cancer Trials Ireland, 353 016677211, info@cancertrials.ie
Sponsor organisation name	UNC Lineberger Comprehensive Cancer Centre
Sponsor organisation address	University of North Carolina, Chapel Hill, North Carolina, United States, 27599
Public contact	Maureen Tyan, RN, UNC Lineberger Comprehensive Cancer Centre, 919 8437039, maureen_tynan@med.unc.edu
Scientific contact	Maureen Tyan, RN, UNC Lineberger Comprehensive Cancer Centre, 919 8437039, maureen_tynan@med.unc.edu

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No

Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	28 June 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 November 2016
Global end of trial reached?	Yes
Global end of trial date	05 December 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare progression-free survival (PFS) between the two treatment arms (PFS: time from randomization until progression or death).

Protection of trial subjects:

This clinical study was designed, implemented, and reported in accordance with the International Conference on Harmonization (ICH) Harmonized Tripartite Guidelines for Good Clinical Practice (GCP), with applicable local regulations SI 190 of 2004 as amend and European Directive 2001/20/EC. The study was approved by the HPRA and Cork Teaching Hospitals Clinical Research Ethics Committee.

Background therapy:

N/A

Evidence for comparator:

Active Comparator: Regorafenib + FOLFIRI (ARM A)
Placebo Comparator: Placebo + FOLFIRI (ARM B)
The trial is designed to compare the Progression Free Survival of ARM A versus ARM B in patients with metastatic colorectal carcinoma (mCRC) previously treated with a FOLFOX (5-fluorouracil + leucovorin + oxaliplatin) regimen.

Actual start date of recruitment	01 March 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 127
Country: Number of subjects enrolled	Ireland: 54
Worldwide total number of subjects	181
EEA total number of subjects	54

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)	131
From 65 to 84 years	48
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

224 participants were consented to the study from 39 institutions in the United States and Ireland from 4July2011 - 8October2015.

Pre-assignment

Screening details:

The target population will be previously treated patients with Metastatic Colorectal Cancer who have had one prior oxaliplatin-containing regimen which failed. They must meet all of the inclusion criteria and none of the exclusion criteria.

Pre-assignment period milestones

Number of subjects started	224[1]
Number of subjects completed	181

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Ineligible: 30
Reason: Number of subjects	Consent withdrawn by subject: 7
Reason: Number of subjects	Study Closure: 3
Reason: Number of subjects	Financial Reasons: 2
Reason: Number of subjects	No reason given for non participation: 1

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: 224 participant were consented, however did not take part in the study for a number of reasons including ineligibility, withdrawn, study closure, financial reasons. 181 patients were enrolled and went onto treatment

Period 1

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

Blinding implementation details:

At the end of the screening period, eligible patients were randomly assigned in a 2:1 ratio to regorafenib + FOLFIRI or placebo + FOLFIRI in a double-blind fashion such that the Investigator, Sponsor, nor the patient knew which agent was administered. The randomization number was assigned by the UNC Cancer Network (UNCCN) or its designate. Regorafenib and placebo were be identical in appearance in order to preserve blinding

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm A

Arm description:

regorafenib 160 mg + FOLFIRI

Arm type	Active comparator

Investigational medicinal product name	Regorafenib
Investigational medicinal product code	BAY 73-4506
Other name	Stivarga
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

On Days 4-10 and 18-24 of each cycle, the patient should be instructed to take regorafenib PO once daily in the morning (close to the same time each day) with approximately 8 ounces of water after a low-fat (<30% fat) breakfast

Investigational medicinal product name	FOLFIRI
Investigational medicinal product code	
Other name	FOLFIRI (Irinotecan + 5-Fluorouracil + Leucovorin)
Pharmaceutical forms	Infusion
Routes of administration	Intravenous bolus use , Intravenous use

Dosage and administration details:

FOLFIRI : (Irinotecan,180 mg/m2 IV over 90 minutes; Leucovorin 200-400c mg/m2 IV over 2 hours; 5-Fluorouracil 400 mg/m2 IV bolus followed by 2400 mg/m2 IV over 46 hours;) Day 1 and Day 15 of each 28 day cycle
Both irinotecan and leucovorin should be administered prior to fluorouracil (5-FU)

Arm title	Arm B

Arm description:

Placebo + FOLFIRI

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

Dosage and administration details:

Placebo, 160 mg, PO oral administration, Days 4-10 and Days 18-24 of 28 day cycle

Investigational medicinal product name	FOLFIRI
Investigational medicinal product code	
Other name	FOLFIRI (Irinotecan + 5-Fluorouracil + Leucovorin)
Pharmaceutical forms	Infusion
Routes of administration	Intravenous bolus use , Intravenous use

Dosage and administration details:

FOLFIRI : (Irinotecan,180 mg/m2 IV over 90 minutes; Leucovorin 200-400c mg/m2 IV over 2 hours; 5-Fluorouracil 400 mg/m2 IV bolus followed by 2400 mg/m2 IV over 46 hours;) Day 1 and Day 15 of each 28 day cycle
Both irinotecan and leucovorin should be administered prior to fluorouracil (5-FU)

Number of subjects in period 1	Arm A	Arm B
Started	120	61
Completed	0	0
Not completed	120	61
Physician decision	4	2
Symptomatic Progression/deterioration	3	2
Treatment Delay > 4 weeks	4	5

Adverse Event	-	2
Adverse event, non-fatal	20	-
Death	-	1
Other complicating disease	-	1
Surgery	2	1
Ineligibility	-	1
Other complicating Disease	2	-
Disease Progression	64	40
Withdrawal by subject	21	6

Baseline characteristics

Reporting groups	
Reporting group title	Arm A
Reporting group description: regorafenib 160 mg + FOLFIRI	
Reporting group title	Arm B
Reporting group description: Placebo + FOLFIRI	

Reporting group values	Arm A	Arm B	Total
Number of subjects	120	61	181
Age categorical Units: Subjects			
Adults (18-64 years)	88	43	131
From 65-84 years	30	18	48
85 years and over	2	0	2
Age continuous Units: years			
median	62	62	
full range (min-max)	30 to 94	30 to 82	-
Gender categorical Units: Subjects			
Female	52	29	81
Male	68	32	100
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	0	0
Native Hawaiian or other Pacific Islander	0	0	0
Black or African American	20	11	31
White	99	48	147
More than one race	0	0	0
Unknown or not reported	1	2	3
Region of Enrollment Units: Subjects			
Ireland	84	43	127
United States	36	18	54
ECOG Performance Status			
Measure Description: A scale by the Eastern Cooperative Oncology Group (ECOG) from 0-5 to describe patient's selfcare ability and activity level. 0.Fully active 1.Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature 2.Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours 3.Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours 4.Completely disabled; cannot carry on any selfcare; totally confined to bed or chair 5.Dead			
Units: Subjects			

0 - Fully Active	52	23	75
1. (see description)	68	38	106
Stage at Diagnosis			
Measure Description: Stages I, II, III indicate that cancer is present, and the higher the number the larger the cancer tumor and the more it has spread into nearby tissues. Stage IV indicates that cancer has spread to distant parts of the body.			
Units: Subjects			
Stage I	3	0	3
Stage II	4	4	8
Stage III	24	11	35
Stage IV	86	46	132
Unknown	3	0	3
Prior Biological Agent Units: Subjects			
None	33	16	49
Bevacizumab	76	41	117
EGFR Inhibitor	11	4	15
Locally Reported RAS			
Measure Description: The 3 Ras genes in humans (HRas, KRas, and NRas) are the most common oncogenes in human cancer; some therapies are more effective with nonmutated wildtype genes.			
Units: Subjects			
Wildtype	49	18	67
Mutated	54	37	91
Unknown	17	6	23
Locally Reported BRAF			
Measure Description: Many mutations of the BRAF gene are associated with cancer. Some drugs are designed to work with mutated forms of the gene.			
Units: Subjects			
Wildtype	22	12	34
Mutated	10	2	12
Unknown	88	47	135

End points

End points reporting groups

Reporting group title	Arm A
Reporting group description: regorafenib 160 mg + FOLFIRI	
Reporting group title	Arm B
Reporting group description: Placebo + FOLFIRI	

Primary: Progression Free Survival (PFS)

End point title	Progression Free Survival (PFS)

End point description:

To compare PFS between regorafenib + FOLFIRI chemotherapy (ARM A) versus placebo + FOLFIRI (ARM B) in patients failing one prior oxaliplatin-containing regimen for metastatic colorectal cancer. PFS is defined as the time from randomization until metastatic colorectal cancer (mCRC) progression or death as a result of any cause. Radiographic response will be measured by RECIST, Response Evaluation Criteria In Solid Tumors Criteria, indicating if subject experienced a Complete Response (CR), disappearance of all target lesions; Partial Response (PR), >=30% decrease in the sum of the longest diameter of target lesions; Stable Disease (SD), no response or less response than Partial or Progressive; or Progressive Disease (PD), as a 20% increase in the sum of the longest diameter of target lesions, or a measurable increase in a non-target lesion, or the appearance of new lesions.

End point type	Primary
End point timeframe: 5.5 years	

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	120	61		
Units: Months				
median (confidence interval 95%)	6.1 (5.5 to 7.3)	5.3 (4.1 to 6.0)		

Statistical analyses

Statistical analysis title	Improvement in PFS in Arm A vs Arm B

Statistical analysis description:

Unstratified log-rank test was used to test for differences between treatment arms in the time-to-event analyses

Comparison groups	Arm B v Arm A

Number of subjects included in analysis	181
Analysis specification	Pre-specified
Analysis type	superiority
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.73
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.53
upper limit	1.01
Variability estimate	Standard deviation
Dispersion value	1.01

Secondary: Overall Response (OR) Rate

End point title	Overall Response (OR) Rate

End point description:

To compare overall response (OR) rates (OR= CR + PR) between ARM A and ARM B as defined via Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) for target lesions and assessed by MRI: Complete Response (CR), Disappearance of all target lesions; Partial Response (PR), >=30% decrease in the sum of the longest diameter of target lesions; Overall Response (OR) = CR + PR.

End point type	Secondary

End point timeframe:

3 years

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	102[1]	58[2]		
Units: Participants				
number (not applicable)				
Complete Response (CR)	0	0		
Partial Response (PR)	35	12		
Other	67	46		

Notes:

[1] - Only evaluable subjects (those who had RECIST measurements after baseline) were included in analysis

[2] - Only evaluable subjects (those who had RECIST measurements after baseline) were included in analysis

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Control (DC) Rate

End point title	Disease Control (DC) Rate

End point description:

To compare Disease Control (DC) Rate (DC= CR + PR + SD) between ARM A and ARM B as defined via

Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) for target lesions and assessed by MRI: Complete Response (CR), Disappearance of all target lesions; Partial Response (PR), >=30% decrease in the sum of the longest diameter of target lesions and Stable Disease (SD)), no response or less response than Partial or Progressive; or Progressive Disease (PD), as a 20% increase in the sum of the longest diameter of target lesions, or a measurable increase in a non-target lesion, or the appearance of new lesions.

End point type	Secondary

End point timeframe:

3 years

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	102[3]	58[4]		
Units: Participants				
number (not applicable)				
Disease Control Total (CR+PR+SD)	84	43		
Progression	18	15		

Notes:

[3] - Only evaluable subjects (those who had RECIST measurements after baseline)were included in analysis

[4] - Only evaluable subjects (those who had RECIST measurements after baseline)were included in analysis

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

To compare overall survival (OS) between ARM A and ARM B. OS is defined as the time from randomization until death as a result of any cause.

End point type	Secondary

End point timeframe:

5.5 years

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	120	61		
Units: Months				
median (full range (min-max))				
Overall Survival (OS)	13.8 (10.5 to 14.8)	11.7 (9.0 to 15.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Drug Metabolism

End point title	Drug Metabolism

End point description:

To compare the pharmacokinetic (PK) profile of FOLFIRI between a subset of patients receiving regorafenib (ARM A) and patients receiving placebo (Arm B). The Area Under the Curve (AUC) levels of the irinotecan metabolite SN-38 were compared

End point type	Secondary

End point timeframe:

28 days

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11[5]	11[6]		
Units: AUC/dose=(ng/mL*h)/(mg/m^2)				
median (inter-quartile range (Q1-Q3))				
Cycle 1	0.68 (0.49 to 0.89)	0.63 (0.47 to 0.91)		
Cycle 2	0.59 (0.24 to 0.85)	0.72 (0.47 to 0.91)		

Notes:

[5] - This objective was designed to only look at a small subset of participants (11 on each arm)

[6] - This objective was designed to only look at a small subset of participants (11 on each arm)

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Patients with Severe Adverse Events

End point title	Percentage of Patients with Severe Adverse Events

End point description:

Toxicity Assessments were made according to NCI CTCAE v. 4.0 . Severe events (grades 3-4) that occurred in a higher percentage of regorafenib treated participants as compared to placebo are reported below.

End point type	Secondary

End point timeframe:

3 years

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	120	61		
Units: percentage of participants				
number (not applicable)				
neutropenia	41	30		

diarrhea	15	5		
hypophosphatemia	14	0		
hypertension	8	2		
elevated lipase	8	3		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

SAEs must be recorded in the SAE console within Oncore™ for that patient within 24 hours of learning of its occurrence.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups

Reporting group title	Arm A
Reporting group description:	
regorafenib 160 mg + FOLFIRI	
Reporting group title	Arm B
Reporting group description:	
Placebo + FOLFIRI	

Serious adverse events	Arm A	Arm B	
Total subjects affected by serious adverse events			
subjects affected / exposed	60 / 120 (50.00%)	20 / 61 (32.79%)	
number of deaths (all causes)	112	59	
number of deaths resulting from adverse events		0	
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 120 (0.83%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Surgical and medical procedures			
subjects affected / exposed	0 / 120 (0.00%)	1 / 61 (1.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chills			
subjects affected / exposed	0 / 120 (0.00%)	1 / 61 (1.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death NOS			

subjects affected / exposed	2 / 120 (1.67%)	2 / 61 (3.28%)	
occurrences causally related to treatment / all	1 / 2	0 / 2	
deaths causally related to treatment / all	1 / 2	0 / 2	
Fatigue			
subjects affected / exposed	2 / 120 (1.67%)	1 / 61 (1.64%)	
occurrences causally related to treatment / all	1 / 2	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fever			
subjects affected / exposed	9 / 120 (7.50%)	3 / 61 (4.92%)	
occurrences causally related to treatment / all	7 / 11	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Flu like Symptoms			
subjects affected / exposed	1 / 120 (0.83%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperhidrosis			
subjects affected / exposed	1 / 120 (0.83%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	1 / 120 (0.83%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	1 / 120 (0.83%)	1 / 61 (1.64%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pressure in head			
subjects affected / exposed	1 / 120 (0.83%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rigors			

subjects affected / exposed	1 / 120 (0.83%)	0 / 61 (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 / 120 (0.83%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour pain			
subjects affected / exposed	1 / 120 (0.83%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Lung Infection			
subjects affected / exposed	2 / 120 (1.67%)	1 / 61 (1.64%)	
occurrences causally related to treatment / all	3 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Aspiration			
subjects affected / exposed	0 / 120 (0.00%)	1 / 61 (1.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cough			
subjects affected / exposed	1 / 120 (0.83%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnea			
subjects affected / exposed	3 / 120 (2.50%)	1 / 61 (1.64%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 120 (0.83%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pneumonitis			
subjects affected / exposed	0 / 120 (0.00%)	1 / 61 (1.64%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper Respiratory Infection			
subjects affected / exposed	1 / 120 (0.83%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Headache			
subjects affected / exposed	1 / 120 (0.83%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Insomnia			
subjects affected / exposed	1 / 120 (0.83%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psycosis			
subjects affected / exposed	1 / 120 (0.83%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Alkaline Phosphatase Increased			
subjects affected / exposed	1 / 120 (0.83%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asparate aminotransferase increased			
subjects affected / exposed	1 / 120 (0.83%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood bilirubin increased			
subjects affected / exposed	1 / 120 (0.83%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Deteriorating LFTs			
subjects affected / exposed	1 / 120 (0.83%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Elevated INR			
subjects affected / exposed	1 / 120 (0.83%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
GGT Increased			
subjects affected / exposed	1 / 120 (0.83%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelet count decreased			
subjects affected / exposed	22 / 120 (18.33%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary Tract Infection			
subjects affected / exposed	0 / 120 (0.00%)	1 / 61 (1.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Alkaline Aminotransferase Increased			
subjects affected / exposed	1 / 120 (0.83%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infusion related reaction			
subjects affected / exposed	1 / 120 (0.83%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal Stoma Site Bleeding			
subjects affected / exposed	1 / 120 (0.83%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Severely elevated lipase level			
subjects affected / exposed	1 / 120 (0.83%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 120 (0.83%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain- cardiac			
subjects affected / exposed	2 / 120 (1.67%)	1 / 61 (1.64%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left ventricular systolic dysfunction			
subjects affected / exposed	1 / 120 (0.83%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Palpitations			
subjects affected / exposed	1 / 120 (0.83%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus bradicardia			
subjects affected / exposed	1 / 120 (0.83%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular tachycardia			
subjects affected / exposed	1 / 120 (0.83%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 120 (1.67%)	3 / 61 (4.92%)	
occurrences causally related to treatment / all	2 / 2	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	

Esophageal varices hemorrhage			
subjects affected / exposed	0 / 120 (0.00%)	1 / 61 (1.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutrophil count decreased			
subjects affected / exposed	6 / 120 (5.00%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	6 / 6	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomal Ulcer			
subjects affected / exposed	1 / 120 (0.83%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thromboembolic event			
subjects affected / exposed	2 / 120 (1.67%)	2 / 61 (3.28%)	
occurrences causally related to treatment / all	1 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal Pain			
subjects affected / exposed	9 / 120 (7.50%)	2 / 61 (3.28%)	
occurrences causally related to treatment / all	1 / 9	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	0 / 120 (0.00%)	1 / 61 (1.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangitis			
subjects affected / exposed	1 / 120 (0.83%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	3 / 120 (2.50%)	1 / 61 (1.64%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			

subjects affected / exposed	1 / 120 (0.83%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colonic Hemorrhage			
subjects affected / exposed	1 / 120 (0.83%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colonic obstruction			
subjects affected / exposed	1 / 120 (0.83%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colonic perforation			
subjects affected / exposed	1 / 120 (0.83%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	1 / 120 (0.83%)	2 / 61 (3.28%)	
occurrences causally related to treatment / all	0 / 1	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	10 / 120 (8.33%)	1 / 61 (1.64%)	
occurrences causally related to treatment / all	9 / 11	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	1 / 120 (0.83%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	3 / 120 (2.50%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Movements involuntary			

subjects affected / exposed	0 / 120 (0.00%)	1 / 61 (1.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucositis oral			
subjects affected / exposed	3 / 120 (2.50%)	1 / 61 (1.64%)	
occurrences causally related to treatment / all	6 / 6	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	2 / 120 (1.67%)	1 / 61 (1.64%)	
occurrences causally related to treatment / all	1 / 2	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal hemorrhage			
subjects affected / exposed	4 / 120 (3.33%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	2 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal perforation			
subjects affected / exposed	1 / 120 (0.83%)	0 / 61 (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 / 120 (0.00%)	2 / 61 (3.28%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Palmar-plantar erythrodysesthesia syndrome			
subjects affected / exposed	1 / 120 (0.83%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 120 (0.83%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Hepatic Failure			
subjects affected / exposed	1 / 120 (0.83%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obstructive Jaundice			
subjects affected / exposed	1 / 120 (0.83%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	0 / 120 (0.00%)	1 / 61 (1.64%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back Pain			
subjects affected / exposed	1 / 120 (0.83%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Generalized muscle weakness			
subjects affected / exposed	1 / 120 (0.83%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscle weakness lower limb			
subjects affected / exposed	0 / 120 (0.00%)	1 / 61 (1.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic Pain			
subjects affected / exposed	0 / 120 (0.00%)	1 / 61 (1.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Right hip abscess			
subjects affected / exposed	1 / 120 (0.83%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Infections and infestations			
Abdominal infection			
subjects affected / exposed	1 / 120 (0.83%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anorectal Infection			
subjects affected / exposed	0 / 120 (0.00%)	1 / 61 (1.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheter related infection			
subjects affected / exposed	1 / 120 (0.83%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cecal Infection			
subjects affected / exposed	1 / 120 (0.83%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis infectious			
subjects affected / exposed	0 / 120 (0.00%)	1 / 61 (1.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	7 / 120 (5.83%)	3 / 61 (4.92%)	
occurrences causally related to treatment / all	6 / 7	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection of unknown source			
subjects affected / exposed	1 / 120 (0.83%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations - Other, specify			
subjects affected / exposed	0 / 120 (0.00%)	1 / 61 (1.64%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Sepsis			
subjects affected / exposed	2 / 120 (1.67%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin Infection			
subjects affected / exposed	0 / 120 (0.00%)	1 / 61 (1.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Soft Tissue Infection			
subjects affected / exposed	2 / 120 (1.67%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Anorexia			
subjects affected / exposed	3 / 120 (2.50%)	1 / 61 (1.64%)	
occurrences causally related to treatment / all	1 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	5 / 120 (4.17%)	3 / 61 (4.92%)	
occurrences causally related to treatment / all	6 / 8	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoalbuminemia			
subjects affected / exposed	1 / 120 (0.83%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malnutrition			
subjects affected / exposed	1 / 120 (0.83%)	0 / 61 (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	Arm A	Arm B	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	120 / 120 (100.00%)	61 / 61 (100.00%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	23 / 120 (19.17%)	9 / 61 (14.75%)	
occurrences (all)	83	15	
Hypotension			
subjects affected / exposed	10 / 120 (8.33%)	3 / 61 (4.92%)	
occurrences (all)	17	3	
Thromboembolic event			
subjects affected / exposed	10 / 120 (8.33%)	1 / 61 (1.64%)	
occurrences (all)	11	1	
General disorders and administration site conditions			
Edema limbs			
subjects affected / exposed	5 / 120 (4.17%)	4 / 61 (6.56%)	
occurrences (all)	6	4	
Fatigue			
subjects affected / exposed	76 / 120 (63.33%)	33 / 61 (54.10%)	
occurrences (all)	200	47	
Fever			
subjects affected / exposed	18 / 120 (15.00%)	3 / 61 (4.92%)	
occurrences (all)	28	3	
Flu like symptoms			
subjects affected / exposed	7 / 120 (5.83%)	1 / 61 (1.64%)	
occurrences (all)	7	1	
Pain			
subjects affected / exposed	26 / 120 (21.67%)	4 / 61 (6.56%)	
occurrences (all)	48	4	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	15 / 120 (12.50%)	4 / 61 (6.56%)	
occurrences (all)	29	5	
Dyspnea			

subjects affected / exposed	22 / 120 (18.33%)	7 / 61 (11.48%)	
occurrences (all)	33	11	
Epistaxis			
subjects affected / exposed	9 / 120 (7.50%)	2 / 61 (3.28%)	
occurrences (all)	9	3	
Hoarseness			
subjects affected / exposed	15 / 120 (12.50%)	0 / 61 (0.00%)	
occurrences (all)	20	0	
Sore throat			
subjects affected / exposed	11 / 120 (9.17%)	11 / 61 (18.03%)	
occurrences (all)	12	1	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	6 / 120 (5.00%)	1 / 61 (1.64%)	
occurrences (all)	7	2	
Depression			
subjects affected / exposed	9 / 120 (7.50%)	5 / 61 (8.20%)	
occurrences (all)	11	6	
Insomnia			
subjects affected / exposed	13 / 120 (10.83%)	3 / 61 (4.92%)	
occurrences (all)	15	4	
Investigations			
Activated partial thromboplastin time prolonged			
subjects affected / exposed	7 / 120 (5.83%)	3 / 61 (4.92%)	
occurrences (all)	11	5	
Alanine aminotransferase increased			
subjects affected / exposed	30 / 120 (25.00%)	9 / 61 (14.75%)	
occurrences (all)	74	13	
Alkaline phosphatase increased			
subjects affected / exposed	35 / 120 (29.17%)	14 / 61 (22.95%)	
occurrences (all)	59	21	
Aspartate aminotransferase increased			
subjects affected / exposed	28 / 120 (23.33%)	10 / 61 (16.39%)	
occurrences (all)	57	17	
Blood bilirubin increased			

subjects affected / exposed	22 / 120 (18.33%)	4 / 61 (6.56%)	
occurrences (all)	47	5	
Creatinine increased			
subjects affected / exposed	6 / 120 (5.00%)	5 / 61 (8.20%)	
occurrences (all)	24	14	
INR increased			
subjects affected / exposed	6 / 120 (5.00%)	5 / 61 (8.20%)	
occurrences (all)	10	8	
Lipase increased			
subjects affected / exposed	21 / 120 (17.50%)	13 / 61 (21.31%)	
occurrences (all)	45	32	
Lymphocyte count decreased			
subjects affected / exposed	15 / 120 (12.50%)	11 / 61 (18.03%)	
occurrences (all)	48	26	
Neutrophil count decreased			
subjects affected / exposed	69 / 120 (57.50%)	36 / 61 (59.02%)	
occurrences (all)	189	86	
Platelet count decreased			
subjects affected / exposed	34 / 120 (28.33%)	9 / 61 (14.75%)	
occurrences (all)	97	11	
Serum amylase increased			
subjects affected / exposed	16 / 120 (13.33%)	8 / 61 (13.11%)	
occurrences (all)	23	19	
Weight loss			
subjects affected / exposed	27 / 120 (22.50%)	5 / 61 (8.20%)	
occurrences (all)	45	5	
White blood cell decreased			
subjects affected / exposed	35 / 120 (29.17%)	23 / 61 (37.70%)	
occurrences (all)	121	75	
Cardiac disorders			
Sinus tachycardia			
subjects affected / exposed	6 / 120 (5.00%)	2 / 61 (3.28%)	
occurrences (all)	12	2	
Nervous system disorders			
Dizziness			

subjects affected / exposed	9 / 120 (7.50%)	1 / 61 (1.64%)	
occurrences (all)	15	1	
Headache			
subjects affected / exposed	24 / 120 (20.00%)	6 / 61 (9.84%)	
occurrences (all)	27	7	
Peripheral sensory neuropathy			
subjects affected / exposed	28 / 120 (23.33%)	8 / 61 (13.11%)	
occurrences (all)	40	12	
Blood and lymphatic system disorders			
Anemia			
subjects affected / exposed	67 / 120 (55.83%)	38 / 61 (62.30%)	
occurrences (all)	159	86	
Febrile neutropenia			
subjects affected / exposed	7 / 120 (5.83%)	1 / 61 (1.64%)	
occurrences (all)	10	3	
Gastrointestinal disorders			
Abdominal Pain			
subjects affected / exposed	41 / 120 (34.17%)	9 / 61 (14.75%)	
occurrences (all)	77	10	
Constipation			
subjects affected / exposed	41 / 120 (34.17%)	17 / 61 (27.87%)	
occurrences (all)	67	24	
Diarrhoea			
subjects affected / exposed	63 / 120 (52.50%)	28 / 61 (45.90%)	
occurrences (all)	212	51	
Dysgeusia			
subjects affected / exposed	6 / 120 (5.00%)	2 / 61 (3.28%)	
occurrences (all)	8	3	
Dyspepsia			
subjects affected / exposed	9 / 120 (7.50%)	1 / 61 (1.64%)	
occurrences (all)	11	1	
Dysphagia			
subjects affected / exposed	6 / 120 (5.00%)	1 / 61 (1.64%)	
occurrences (all)	6	1	
Hemorrhoids			

subjects affected / exposed	10 / 120 (8.33%)	2 / 61 (3.28%)	
occurrences (all)	14	2	
Mucositis oral			
subjects affected / exposed	65 / 120 (54.17%)	20 / 61 (32.79%)	
occurrences (all)	146	34	
Nausea			
subjects affected / exposed	60 / 120 (50.00%)	34 / 61 (55.74%)	
occurrences (all)	124	53	
Oral pain			
subjects affected / exposed	8 / 120 (6.67%)	0 / 61 (0.00%)	
occurrences (all)	12	0	
Rectal pain			
subjects affected / exposed	10 / 120 (8.33%)	1 / 61 (1.64%)	
occurrences (all)	14	1	
Vomiting			
subjects affected / exposed	40 / 120 (33.33%)	10 / 61 (16.39%)	
occurrences (all)	68	19	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	30 / 120 (25.00%)	15 / 61 (24.59%)	
occurrences (all)	34	17	
Dry skin			
subjects affected / exposed	15 / 120 (12.50%)	5 / 61 (8.20%)	
occurrences (all)	20	6	
Palmar-plantar erythrodysesthesia syndrome			
subjects affected / exposed	35 / 120 (29.17%)	6 / 61 (9.84%)	
occurrences (all)	80	14	
Rash maculo-papular			
subjects affected / exposed	18 / 120 (15.00%)	5 / 61 (8.20%)	
occurrences (all)	28	6	
Rash acneiform			
subjects affected / exposed	12 / 120 (10.00%)	2 / 61 (3.28%)	
occurrences (all)	30	2	
Renal and urinary disorders			

Hematuria			
subjects affected / exposed	9 / 120 (7.50%)	3 / 61 (4.92%)	
occurrences (all)	11	5	
Proteinuria			
subjects affected / exposed	18 / 120 (15.00%)	14 / 61 (22.95%)	
occurrences (all)	51	25	
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	8 / 120 (6.67%)	1 / 61 (1.64%)	
occurrences (all)	9	1	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	12 / 120 (10.00%)	4 / 61 (6.56%)	
occurrences (all)	17	4	
Bone pain			
subjects affected / exposed	6 / 120 (5.00%)	0 / 61 (0.00%)	
occurrences (all)	7	0	
Pain in extremity			
subjects affected / exposed	8 / 120 (6.67%)	3 / 61 (4.92%)	
occurrences (all)	16	4	
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	11 / 120 (9.17%)	3 / 61 (4.92%)	
occurrences (all)	19	3	
Metabolism and nutrition disorders			
Anorexia			
subjects affected / exposed	43 / 120 (35.83%)	7 / 61 (11.48%)	
occurrences (all)	70	7	
Dehydration			
subjects affected / exposed	15 / 120 (12.50%)	5 / 61 (8.20%)	
occurrences (all)	23	5	
Hyperglycemia			
subjects affected / exposed	17 / 120 (14.17%)	16 / 61 (26.23%)	
occurrences (all)	41	44	
Hypertriglyceridemia			

subjects affected / exposed	25 / 120 (20.83%)	19 / 61 (31.15%)	
occurrences (all)	72	42	
Hypoalbuminemia			
subjects affected / exposed	37 / 120 (30.83%)	14 / 61 (22.95%)	
occurrences (all)	93	28	
Hyperuricemia			
subjects affected / exposed	5 / 120 (4.17%)	7 / 61 (11.48%)	
occurrences (all)	10	13	
Hypocalcemia			
subjects affected / exposed	29 / 120 (24.17%)	10 / 61 (16.39%)	
occurrences (all)	57	12	
Hypokalemia			
subjects affected / exposed	40 / 120 (33.33%)	19 / 61 (31.15%)	
occurrences (all)	82	33	
Hypomagnesemia			
subjects affected / exposed	16 / 120 (13.33%)	9 / 61 (14.75%)	
occurrences (all)	28	15	
Hyponatremia			
subjects affected / exposed	20 / 120 (16.67%)	13 / 61 (21.31%)	
occurrences (all)	33	20	
Hypophosphatemia			
subjects affected / exposed	38 / 120 (31.67%)	6 / 61 (9.84%)	
occurrences (all)	109	7	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 April 2012	Protocol V3: First protocol approved in EU. Updates from Protocol Amendment 2 included editorial and admin changes as well as Therapy changes
23 May 2012	Protocol Amendment 4: Protocol Amendment 4 has Updated safety information on regorafenib from Investigator Brochure, Version 7.0 and revised dose modification instructions for changes in liver function tests attributed to Regorafenib and for FOLFIRI toxicities
03 April 2013	Protocol Amendment 5: has updated regorafenib dose modification instructions, monitoring for liver toxicity and potential drug interactions in line with the Sept 2012 prescribing information published for regorafenib which is now licenced in the US under the trade name Stivarga®.
11 September 2013	Protocol Amendment 6: Inclusion criterion 3.1.5 amended from "progression during or within 3 months following administration of a standard regimen…" to "progression during or within 6 months following administration of a standard regimen…" Other updates detailed in cover page of protocol update
29 September 2014	Protocol Amendment 7: The main purpose of this Global protocol amendment is to revise the study to meet MHRA requirements in the UK. LCCC 1029 - ICORG 12-07 Protocol Amendment 7, 10th June 2014 - Clarified in objective 2.2.4 that pharmacokinetic sub-study will be limited to UNC and other selected sites. - Section 3.1.10 requires contraception to be used for 6 months (not 3 months) post chemotherapy, and advice on counseling for sperm preservation added to ensure patients informed. - Added exclusion criteria 3.2.31 (Any chronic inflammatory bowel disease and/or chronic bowl obstruction) and 3.2.32 (Unwilling to avoid vaccinations with live vaccine and concomitant use of attenuated live vaccines) - Section 4.2 (Emergency Unblinding) was revised "Unblinding" to emphasize that the study Investigator may also receive unblinded patient information after disease progression to inform subsequent treatment decisions. - Section 5.1.5: added "Prolonged exposure to sunlight is not advisable because of risk to photosensitivity during the administration of regorafenib" - Each of the generic drugs now as the following statement in the Drug information section (section 5.0) In addition, the SPC (or SmPC) is a Summary of Product Characteristics document for licensed marketed products as licensed in the UK. The Investigators can use whichever generic irinotecan product they choose per local practice for the purposes of this study. - Each of the generic drugs has additional information related to contraception and pregnancy from a representative SmPC (Section 5.0) - Section 7.8.3 (European SAE and SUSAR reporting requirements) was added. - Appendix I (a list of protocol abbreviations) was added to the end of the protocol document.
09 March 2015	Protocol Amendment 8: The main purpose of this Global protocol amendment is to revise the target accrual of this study. This is as a result of a decision by UNC (international sponsor) in consultation with manufacturer of the IMP regorafenib (Bayer) to close study once total accrual of 180 (versus 240) is reached. This will still allow 90% power to detect 60% improvement in median PFS when regorafenib is added to FOLFIRI. As a consequence of this decision the study will no longer be opening at sites in the United Kingdom.

09 June 2016	Protocol Amendment 9: Updates made further to new safety information becoming available. Protocol: • Section 4.6: Concomitant Medications/Treatments: Clarified that regorafenib has no effect on digoxin pharmacokinetics, and can be given with drugs that are p-glycoprotein substrates. • Section 4.6.2: Prohibited Drugs: updated information regarding CYP3A4 inhibitors and inducers. • Section 4.6.3: Drugs to be used with Caution: updated guidance for medications that have a narrow therapeutic index. • Section 11.2: Appendix B List of Prohibited Drugs: updated list with new drugs.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported