Clinical trial results:
PRESERVE 1: A Phase 3 Randomized, Double-blind Trial of Trilaciclib versus Placebo in Patients Receiving FOLFOXIRI/Bevacizumab for Metastatic Colorectal Cancer

Summary

EudraCT number	2019-003826-25
Trial protocol	GB SK PL HU IT
Global end of trial date	31 March 2023

Results information

Result version number	v1 (current)
This version publication date	22 May 2024
First version publication date	22 May 2024

Trial information

Trial identification

Sponsor protocol code	G1T28-207

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04607668
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	G1 Therapeutics, Inc.
Sponsor organisation address	700 Park Offices Drive, Suite 200, Research Triangle Park, United States, 27709
Public contact	Clinical Trial Info, G1 Therapeutics, Inc., +1 919 213 9835, clinicalinfo@g1therapeutics.com
Scientific contact	Clinical Trial Info, G1 Therapeutics, Inc., +1 919 213 9835, clinicalinfo@g1therapeutics.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	31 March 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	31 March 2023
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To assess the effects of trilaciclib on the neutrophil lineage compared with placebo in participants receiving FOLFOXIRI/bevacizumab for proficient mismatch repair/microsatellite stable (pMMR/MSS) metastatic colorectal cancer (mCRC).

Protection of trial subjects:

This study was conducted in full conformance with the ethical principles of the Declaration of Helsinki (as amended in Tokyo, Venice, Hong Kong, and South Africa) or with the laws and regulations of the country in which the research was conducted, whichever afforded the greater protection to the individual. A Data Safety Monitoring Committee (DMC) reviewed safety of trilaciclib for all participants enrolled. The DMC monitored accumulating safety and disposition data approximately every 4 months. The committee consisted of individuals with extensive multicenter clinical study experience drawn from the fields of clinical oncology (specifically, CRC) and biostatistics. These individuals were entirely independent of the conduct of the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	16 October 2020
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	25 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 19
Country: Number of subjects enrolled	Spain: 41
Country: Number of subjects enrolled	United Kingdom: 13
Country: Number of subjects enrolled	Hungary: 20
Country: Number of subjects enrolled	Italy: 11
Country: Number of subjects enrolled	China: 53
Country: Number of subjects enrolled	Ukraine: 44
Country: Number of subjects enrolled	United States: 125
Worldwide total number of subjects	326
EEA total number of subjects	91

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)	244
From 65 to 84 years	82
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 82 sites enrolled participants in China, Hungary, Italy, Poland, Spain, Ukraine, United Kingdom and United States. The first participant was enrolled on 16 October 2020, and the last participant completed on 31 March 2023.

Pre-assignment

Screening details:

A total of 458 participants were screened in this study of which 132 were reported as screen failures. Thus, 326 participants were randomized in the study.

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Trilaciclib + FOLFOXIRI/Bevacizumab

Arm description:

Participants received trilaciclib 240 milligram per meter square (mg/m^2) on Days 1 and 2 administered intravenously (IV) prior to FOLFOXIRI (fluorouracil [5FU {infusional}], leucovorin, oxaliplatin, and irinotecan)/bevacizumab in 14-day cycles for up to 12 cycles (induction). Following completion of induction, participants continued in maintenance, where they received trilaciclib per randomization allocation at study entry. Trilaciclib was administered prior to infusional-5FU/leucovorin/bevacizumab at the same dose and schedule used during induction. Participants continued to receive treatment until disease progression, unacceptable toxicity, withdrawal of consent, discontinuation by Investigator, or the end of the trial, whichever occurred first.

Arm type	Experimental
Investigational medicinal product name	Trilaciclib
Investigational medicinal product code	
Other name	G1T28
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Trilaciclib 240 mg/m^2 was provided as a single-use, sterile powder to be reconstituted then diluted with 250 milliliter (mL) of dextrose 5% in water or normal saline (NaCl 0.9%).

Investigational medicinal product name	FOLFOXIRI
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Fluorouracil 2400 to 3200 mg/m^2, Leucovorin 400 mg/m^2 (LEVO leucovorin 200 mg/m^2 was an acceptable alternative), Oxaliplatin 85 mg/m^2 and Irinotecan 165 mg/m^2 was administered as Standard of Care (SOC) therapy.

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

Dosage and administration details:

Bevacizumab 5 mg/kilogram (kg) was administered as SOC therapy.

Arm title	Placebo + FOLFOXIRI/Bevacizumab

Arm description:

Participants received placebo on Days 1 and 2 administered IV prior to FOLFOXIRI/bevacizumab in 14-day cycles for up to 12 cycles (induction). Following completion of induction, participants continued in maintenance, where they received placebo per randomization allocation at study entry. Placebo was administered prior to infusional-5FU/leucovorin/bevacizumab at the same dose and schedule used during induction. Participants continued to receive treatment until disease progression, unacceptable toxicity, withdrawal of consent, discontinuation by Investigator, or the end of the trial, whichever occurred first.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Placebo was provided as 250 mL of dextrose 5% in water or normal saline (NaCl 0.9%).

Investigational medicinal product name	FOLFOXIRI
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Fluorouracil 2400 to 3200 mg/m^2, Leucovorin 400 mg/m^2 (LEVO leucovorin 200 mg/m^2 was an acceptable alternative), Oxaliplatin 85 mg/m^2 and Irinotecan 165 mg/m^2 was administered as SOC therapy.

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

Dosage and administration details:

Bevacizumab 5 mg/kilogram (kg) was administered as SOC therapy.

Number of subjects in period 1	Trilaciclib + FOLFOXIRI/Bevacizumab	Placebo + FOLFOXIRI/Bevacizumab
Started	164	162
Completed	0	0
Not completed	164	162
Consent withdrawn by subject	12	11
Study terminated by Sponsor	92	114
Death	49	26
Unspecified	8	7

Lost to follow-up	3	4

Baseline characteristics

Reporting groups	
Reporting group title	Trilaciclib + FOLFOXIRI/Bevacizumab

Reporting group description:

Participants received trilaciclib 240 milligram per meter square (mg/m^2) on Days 1 and 2 administered intravenously (IV) prior to FOLFOXIRI (fluorouracil [5FU {infusional}], leucovorin, oxaliplatin, and irinotecan)/bevacizumab in 14-day cycles for up to 12 cycles (induction). Following completion of induction, participants continued in maintenance, where they received trilaciclib per randomization allocation at study entry. Trilaciclib was administered prior to infusional-5FU/leucovorin/bevacizumab at the same dose and schedule used during induction. Participants continued to receive treatment until disease progression, unacceptable toxicity, withdrawal of consent, discontinuation by Investigator, or the end of the trial, whichever occurred first.

Reporting group title	Placebo + FOLFOXIRI/Bevacizumab

Reporting group description:

Participants received placebo on Days 1 and 2 administered IV prior to FOLFOXIRI/bevacizumab in 14-day cycles for up to 12 cycles (induction). Following completion of induction, participants continued in maintenance, where they received placebo per randomization allocation at study entry. Placebo was administered prior to infusional-5FU/leucovorin/bevacizumab at the same dose and schedule used during induction. Participants continued to receive treatment until disease progression, unacceptable toxicity, withdrawal of consent, discontinuation by Investigator, or the end of the trial, whichever occurred first.

Reporting group values	Trilaciclib + FOLFOXIRI/Bevacizumab	Placebo + FOLFOXIRI/Bevacizumab	Total
Number of subjects	164	162	326
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	120	124	244
From 65-84 years	44	38	82
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	56.2	55.5	
standard deviation	± 11.80	± 10.60	-
Gender categorical Units: Subjects			
Female	58	61	119
Male	106	101	207
Race Units: Subjects			
White	119	112	231
Black or African American	4	9	13
Asian	32	33	65
Other	3	0	3

Not Reported	3	3	6
Unknown	3	5	8

End points

End points reporting groups

Reporting group title	Trilaciclib + FOLFOXIRI/Bevacizumab

Reporting group description:

Participants received trilaciclib 240 milligram per meter square (mg/m^2) on Days 1 and 2 administered intravenously (IV) prior to FOLFOXIRI (fluorouracil [5FU {infusional}], leucovorin, oxaliplatin, and irinotecan)/bevacizumab in 14-day cycles for up to 12 cycles (induction). Following completion of induction, participants continued in maintenance, where they received trilaciclib per randomization allocation at study entry. Trilaciclib was administered prior to infusional-5FU/leucovorin/bevacizumab at the same dose and schedule used during induction. Participants continued to receive treatment until disease progression, unacceptable toxicity, withdrawal of consent, discontinuation by Investigator, or the end of the trial, whichever occurred first.

Reporting group title	Placebo + FOLFOXIRI/Bevacizumab

Reporting group description:

Participants received placebo on Days 1 and 2 administered IV prior to FOLFOXIRI/bevacizumab in 14-day cycles for up to 12 cycles (induction). Following completion of induction, participants continued in maintenance, where they received placebo per randomization allocation at study entry. Placebo was administered prior to infusional-5FU/leucovorin/bevacizumab at the same dose and schedule used during induction. Participants continued to receive treatment until disease progression, unacceptable toxicity, withdrawal of consent, discontinuation by Investigator, or the end of the trial, whichever occurred first.

Subject analysis set title	Trilaciclib + FOLFOXIRI/Bevacizumab
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

Participants received trilaciclib 240 mg/m^2 on Days 1 and 2 administered IV prior to FOLFOXIRI/bevacizumab in 14-day cycles for up to 12 cycles (induction). Following completion of induction, participants continued in maintenance, where they received trilaciclib per randomization allocation at study entry. Trilaciclib was administered prior to infusional-5FU/leucovorin/bevacizumab at the same dose and schedule used during induction. Participants continued to receive treatment until disease progression, unacceptable toxicity, withdrawal of consent, discontinuation by Investigator, or the end of the trial, whichever occurred first.

Subject analysis set title	Placebo + FOLFOXIRI/Bevacizumab
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

Participants received placebo on Days 1 and 2 administered IV prior to FOLFOXIRI/bevacizumab in 14-day cycles for up to 12 cycles (induction). Following completion of induction, participants continued in maintenance, where they received placebo per randomization allocation at study entry. Placebo was administered prior to infusional-5FU/leucovorin/bevacizumab at the same dose and schedule used during induction. Participants continued to receive treatment until disease progression, unacceptable toxicity, withdrawal of consent, discontinuation by Investigator, or the end of the trial, whichever occurred first.

Primary: Duration Of Severe Neutropenia (DSN) (Grade 4) in Cycle 1 to Cycle 4

End point title	Duration Of Severe Neutropenia (DSN) (Grade 4) in Cycle 1 to Cycle 4

End point description:

Severe Neutropenia was defined as Absolute neutrophil count(ANC) value<0.5 ×10^9/Liter(L)(Grade 4 neutropenia per National Cancer Institute[NCI] Common Terminology Criteria for Adverse Events[CTCAE] criteria,version 5.0).DSN in Cycle 1-4 defined as number of days of first SN event that occurred in first 4 cycles of Induction.For participants with at least 1 SN event in Induction in Cycle 1,2,3 or 4,DSN was calculated for first occurrence of event following rules:For participants whose SN was resolved,DSN was derived as number of days from date of first SN occurrence to date of SN resolution;for participants who withdraw from study with unresolved neutropenia,DSN was derived as number of days from date of first SN occurrence to date of withdrawal.Modified intent-to-treat(mITT) analysis set:included all participants randomized in countries other than Ukraine and all participants in Ukraine who were randomized prior to 09-Sep-21,and who completed or completed Induction prior to

End point type	Primary

End point timeframe:

Cycle 1: Days 1, 2, 4, 6, 8, 10 and 12 and Cycles 2, 3, 4: Days 1 and 8 (each cycle is 14 days)

End point values	Trilaciclib + FOLFOXIRI/Bevacizumab	Placebo + FOLFOXIRI/Bevacizumab		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	149	147		
Units: Days				
arithmetic mean (standard deviation)	0.1 (± 0.84)	1.3 (± 3.14)		

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Trilaciclib + FOLFOXIRI/Bevacizumab v Placebo + FOLFOXIRI/Bevacizumab
Number of subjects included in analysis	296
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001 [1]
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-1.2
Confidence interval	
level	Other: 96 %
sides	2-sided
lower limit	-1.7
upper limit	-0.6
Variability estimate	Standard error of the mean
Dispersion value	0.27

Notes:

[1] - Two-sided p-value for treatment effect was generated from a nonparametric ANCOVA controlling for stratification factors of Region and Prior chemotherapy with study baseline ANC value as a covariate.

Primary: Number Of Participants With Occurrence Of SN During Induction

End point title	Number Of Participants With Occurrence Of SN During Induction

End point description:

Severe neutropenia was defined as an ANC value <0.5 × 10^9/L (Grade 4 neutropenia per NCI CTCAE criteria, version 5.0). Occurrence of SN during Induction for a participant was defined as having as least one ANC value < 0.5 × 10^9/L among all ANC measurements during Induction regardless of scheduled or unscheduled visits. Analysis was performed on the mITT analysis set which included all participants randomized in countries other than Ukraine and all participants in Ukraine who were randomized prior to 09-Sep-21, and who completed or completed Induction prior to 24-Feb-22.

End point type	Primary

End point timeframe:

Cycle 1: Days 1, 2, 4, 6, 8, 10 and 12 and Cycles 2, 3, 4: Days 1 and 8 (each cycle is 14 days)

End point values	Trilaciclib + FOLFOXIRI/Bevacizumab	Placebo + FOLFOXIRI/Bevacizumab		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	149	147		
Units: Participants	2	29		

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Trilaciclib + FOLFOXIRI/Bevacizumab v Placebo + FOLFOXIRI/Bevacizumab
Number of subjects included in analysis	296
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001 [2]
Method	Modified Poisson model
Parameter estimate	Adjusted relative risk
Point estimate	0.07
Confidence interval	
level	Other: 96 %
sides	2-sided
lower limit	0.02
upper limit	0.31
Variability estimate	Standard error of the mean
Dispersion value	0.051

Notes:

[2] - The aRR, its 96% CI, p-value were generated from modified Poisson model controlling for stratification factors of Region and Prior chemotherapy with baseline ANC value as a covariate. The log-transformed number of cycles was used as offset in model.

Secondary: Overall survival (OS)

End point title	Overall survival (OS)

End point description:

OS was defined as the time (months) from the date of randomization to the date of death for participants who died in the study regardless of cause, or to the last contact date known to be alive for those who survived as of the date for final database lock (censored cases). 99999 indicates that median and upper limit of confidence interval (CI) was not estimable due to insufficient number of participants with events at study closure. mITT analysis set which included all participants randomized in countries other than Ukraine and all participants in Ukraine who were randomized prior to 09-Sep-21, and who completed or completed Induction prior to 24-Feb-22

End point type	Secondary

End point timeframe:

Up to 26 months

End point values	Trilaciclib + FOLFOXIRI/Bevacizumab	Placebo + FOLFOXIRI/Bevacizumab		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	149	147		
Units: Months				
median (confidence interval 95%)	99999 (99999 to 99999)	99999 (99999 to 99999)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From Day 1 (day of first dose of any study drug) until 30 days after the last dose of study drug, approximately up to 115 weeks

Adverse event reporting additional description:

Analysis was performed on the Safety analysis set which included all randomized participants who received at least one dose of any study drug.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.1

Reporting groups

Reporting group title	Trilaciclib + FOLFOXIRI/Bevacizumab

Reporting group description:

Participants received trilaciclib 240 mg/m^2 on Days 1 and 2 administered IV prior to FOLFOXIRI/bevacizumab in 14-day cycles for up to 12 cycles (induction). Following completion of induction, participants continued in maintenance, where they received trilaciclib per randomization allocation at study entry. Trilaciclib was administered prior to infusional-5FU/leucovorin/bevacizumab at the same dose and schedule used during induction. Participants continued to receive treatment until disease progression, unacceptable toxicity, withdrawal of consent, discontinuation by Investigator, or the end of the trial, whichever occurred first.

Reporting group title	Placebo + FOLFOXIRI/Bevacizumab

Reporting group description:

Participants received placebo on Days 1 and 2 administered IV prior to FOLFOXIRI/bevacizumab in 14-day cycles for up to 12 cycles (induction). Following completion of induction, participants continued in maintenance, where they received placebo per randomization allocation at study entry. Placebo was administered prior to infusional-5FU/leucovorin/bevacizumab at the same dose and schedule used during induction. Participants continued to receive treatment until disease progression, unacceptable toxicity, withdrawal of consent, discontinuation by Investigator, or the end of the trial, whichever occurred first.

Serious adverse events	Trilaciclib + FOLFOXIRI/Bevacizumab	Placebo + FOLFOXIRI/Bevacizumab	
Total subjects affected by serious adverse events			
subjects affected / exposed	47 / 159 (29.56%)	47 / 160 (29.38%)	
number of deaths (all causes)	8	3	
number of deaths resulting from adverse events	1	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Gastrointestinal carcinoma			
subjects affected / exposed	1 / 159 (0.63%)	0 / 160 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypertension			

subjects affected / exposed	1 / 159 (0.63%)	1 / 160 (0.63%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous thrombosis			
subjects affected / exposed	0 / 159 (0.00%)	2 / 160 (1.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic embolus			
subjects affected / exposed	1 / 159 (0.63%)	0 / 160 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolism			
subjects affected / exposed	0 / 159 (0.00%)	1 / 160 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jugular vein thrombosis			
subjects affected / exposed	0 / 159 (0.00%)	1 / 160 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Superior vena cava syndrome			
subjects affected / exposed	0 / 159 (0.00%)	1 / 160 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombosis			
subjects affected / exposed	0 / 159 (0.00%)	1 / 160 (0.63%)	
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			
Pyrexia			
subjects affected / exposed	1 / 159 (0.63%)	3 / 160 (1.88%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			

subjects affected / exposed	1 / 159 (0.63%)	0 / 160 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Device related thrombosis			
subjects affected / exposed	1 / 159 (0.63%)	0 / 160 (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 / 159 (0.63%)	0 / 160 (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			
Drug hypersensitivity			
subjects affected / exposed	1 / 159 (0.63%)	0 / 160 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Vaginal haemorrhage			
subjects affected / exposed	0 / 159 (0.00%)	1 / 160 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	4 / 159 (2.52%)	4 / 160 (2.50%)	
occurrences causally related to treatment / all	0 / 5	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory failure			
subjects affected / exposed	1 / 159 (0.63%)	2 / 160 (1.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 1	
Respiratory failure			

subjects affected / exposed	2 / 159 (1.26%)	0 / 160 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Dyspnoea			
subjects affected / exposed	1 / 159 (0.63%)	0 / 160 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary thrombosis			
subjects affected / exposed	1 / 159 (0.63%)	0 / 160 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 159 (0.00%)	1 / 160 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Completed suicide			
subjects affected / exposed	1 / 159 (0.63%)	0 / 160 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 159 (0.63%)	2 / 160 (1.25%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 159 (0.00%)	1 / 160 (0.63%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood bilirubin increased			
subjects affected / exposed	1 / 159 (0.63%)	0 / 160 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 159 (0.00%)	1 / 160 (0.63%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Drain site complication			
subjects affected / exposed	0 / 159 (0.00%)	1 / 160 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 159 (0.63%)	0 / 160 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure acute			
subjects affected / exposed	1 / 159 (0.63%)	0 / 160 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left ventricular dysfunction			
subjects affected / exposed	0 / 159 (0.00%)	1 / 160 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial injury			
subjects affected / exposed	1 / 159 (0.63%)	0 / 160 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular tachycardia			
subjects affected / exposed	0 / 159 (0.00%)	1 / 160 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Syncope			

subjects affected / exposed	1 / 159 (0.63%)	1 / 160 (0.63%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	1 / 159 (0.63%)	0 / 160 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	1 / 159 (0.63%)	0 / 160 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar radiculopathy			
subjects affected / exposed	1 / 159 (0.63%)	0 / 160 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myoclonic epilepsy			
subjects affected / exposed	1 / 159 (0.63%)	0 / 160 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	0 / 159 (0.00%)	1 / 160 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	0 / 159 (0.00%)	5 / 160 (3.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	0 / 159 (0.00%)	5 / 160 (3.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			

subjects affected / exposed	0 / 159 (0.00%)	2 / 160 (1.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			
subjects affected / exposed	0 / 159 (0.00%)	1 / 160 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	1 / 159 (0.63%)	0 / 160 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Intestinal obstruction			
subjects affected / exposed	4 / 159 (2.52%)	3 / 160 (1.88%)	
occurrences causally related to treatment / all	0 / 5	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	2 / 159 (1.26%)	3 / 160 (1.88%)	
occurrences causally related to treatment / all	0 / 2	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	3 / 159 (1.89%)	2 / 160 (1.25%)	
occurrences causally related to treatment / all	3 / 4	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	1 / 159 (0.63%)	3 / 160 (1.88%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	2 / 159 (1.26%)	1 / 160 (0.63%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal obstruction			

subjects affected / exposed	1 / 159 (0.63%)	1 / 160 (0.63%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Intestinal perforation			
subjects affected / exposed	1 / 159 (0.63%)	1 / 160 (0.63%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	1 / 159 (0.63%)	1 / 160 (0.63%)	
occurrences causally related to treatment / all	2 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			
subjects affected / exposed	2 / 159 (1.26%)	0 / 160 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal adhesions			
subjects affected / exposed	0 / 159 (0.00%)	1 / 160 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal fistula			
subjects affected / exposed	1 / 159 (0.63%)	0 / 160 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	0 / 159 (0.00%)	1 / 160 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	1 / 159 (0.63%)	0 / 160 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocutaneous fistula			

subjects affected / exposed	1 / 159 (0.63%)	0 / 160 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoidal haemorrhage			
subjects affected / exposed	1 / 159 (0.63%)	0 / 160 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus paralytic			
subjects affected / exposed	1 / 159 (0.63%)	0 / 160 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestinal obstruction			
subjects affected / exposed	0 / 159 (0.00%)	1 / 160 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine perforation			
subjects affected / exposed	0 / 159 (0.00%)	1 / 160 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower gastrointestinal haemorrhage			
subjects affected / exposed	1 / 159 (0.63%)	0 / 160 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal rupture			
subjects affected / exposed	1 / 159 (0.63%)	0 / 160 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal perforation			
subjects affected / exposed	1 / 159 (0.63%)	0 / 160 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			

subjects affected / exposed	1 / 159 (0.63%)	0 / 160 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subileus			
subjects affected / exposed	1 / 159 (0.63%)	0 / 160 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	0 / 159 (0.00%)	1 / 160 (0.63%)	
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	0 / 159 (0.00%)	1 / 160 (0.63%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	0 / 159 (0.00%)	1 / 160 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 159 (0.63%)	0 / 160 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myopathy			
subjects affected / exposed	1 / 159 (0.63%)	0 / 160 (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			
Pneumonia			

subjects affected / exposed	3 / 159 (1.89%)	1 / 160 (0.63%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 159 (0.63%)	3 / 160 (1.88%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19			
subjects affected / exposed	1 / 159 (0.63%)	1 / 160 (0.63%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cellulitis			
subjects affected / exposed	0 / 159 (0.00%)	2 / 160 (1.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal abscess			
subjects affected / exposed	1 / 159 (0.63%)	0 / 160 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess limb			
subjects affected / exposed	0 / 159 (0.00%)	1 / 160 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal abscess			
subjects affected / exposed	0 / 159 (0.00%)	1 / 160 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anorectal infection			
subjects affected / exposed	1 / 159 (0.63%)	0 / 160 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			

subjects affected / exposed	0 / 159 (0.00%)	1 / 160 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19 pneumonia			
subjects affected / exposed	0 / 159 (0.00%)	1 / 160 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	0 / 159 (0.00%)	1 / 160 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infectious pleural effusion			
subjects affected / exposed	1 / 159 (0.63%)	0 / 160 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal sepsis			
subjects affected / exposed	1 / 159 (0.63%)	0 / 160 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Neutropenic sepsis			
subjects affected / exposed	0 / 159 (0.00%)	1 / 160 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic abscess			
subjects affected / exposed	1 / 159 (0.63%)	0 / 160 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	1 / 159 (0.63%)	0 / 160 (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			
Hypokalaemia			

subjects affected / exposed	1 / 159 (0.63%)	1 / 160 (0.63%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	0 / 159 (0.00%)	1 / 160 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic ketoacidosis			
subjects affected / exposed	1 / 159 (0.63%)	0 / 160 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	1 / 159 (0.63%)	0 / 160 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypocalcaemia			
subjects affected / exposed	1 / 159 (0.63%)	0 / 160 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypomagnesaemia			
subjects affected / exposed	1 / 159 (0.63%)	0 / 160 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypophosphataemia			
subjects affected / exposed	0 / 159 (0.00%)	1 / 160 (0.63%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Trilaciclib + FOLFOXIRI/Bevacizumab	Placebo + FOLFOXIRI/Bevacizumab	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	155 / 159 (97.48%)	159 / 160 (99.38%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	34 / 159 (21.38%)	35 / 160 (21.88%)	
occurrences (all)	82	86	
Hypotension			
subjects affected / exposed	5 / 159 (3.14%)	8 / 160 (5.00%)	
occurrences (all)	8	8	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	53 / 159 (33.33%)	52 / 160 (32.50%)	
occurrences (all)	136	136	
Asthenia			
subjects affected / exposed	28 / 159 (17.61%)	28 / 160 (17.50%)	
occurrences (all)	58	91	
Pyrexia			
subjects affected / exposed	17 / 159 (10.69%)	22 / 160 (13.75%)	
occurrences (all)	27	30	
Mucosal inflammation			
subjects affected / exposed	17 / 159 (10.69%)	18 / 160 (11.25%)	
occurrences (all)	20	31	
Temperature intolerance			
subjects affected / exposed	10 / 159 (6.29%)	5 / 160 (3.13%)	
occurrences (all)	14	6	
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	7 / 159 (4.40%)	28 / 160 (17.50%)	
occurrences (all)	12	43	
Cough			
subjects affected / exposed	13 / 159 (8.18%)	12 / 160 (7.50%)	
occurrences (all)	16	17	
Hiccups			

subjects affected / exposed	14 / 159 (8.81%)	9 / 160 (5.63%)	
occurrences (all)	17	12	
Dyspnoea			
subjects affected / exposed	11 / 159 (6.92%)	8 / 160 (5.00%)	
occurrences (all)	18	10	
Nasal congestion			
subjects affected / exposed	10 / 159 (6.29%)	6 / 160 (3.75%)	
occurrences (all)	10	6	
Rhinorrhoea			
subjects affected / exposed	4 / 159 (2.52%)	10 / 160 (6.25%)	
occurrences (all)	5	14	
Oropharyngeal pain			
subjects affected / exposed	5 / 159 (3.14%)	8 / 160 (5.00%)	
occurrences (all)	6	8	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	15 / 159 (9.43%)	15 / 160 (9.38%)	
occurrences (all)	18	18	
Anxiety			
subjects affected / exposed	13 / 159 (8.18%)	12 / 160 (7.50%)	
occurrences (all)	16	13	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	20 / 159 (12.58%)	24 / 160 (15.00%)	
occurrences (all)	32	40	
Aspartate aminotransferase increased			
subjects affected / exposed	20 / 159 (12.58%)	24 / 160 (15.00%)	
occurrences (all)	42	41	
Neutrophil count decreased			
subjects affected / exposed	12 / 159 (7.55%)	15 / 160 (9.38%)	
occurrences (all)	31	32	
Blood alkaline phosphatase increased			
subjects affected / exposed	13 / 159 (8.18%)	11 / 160 (6.88%)	
occurrences (all)	19	18	
White blood cell count decreased			

subjects affected / exposed	8 / 159 (5.03%)	12 / 160 (7.50%)	
occurrences (all)	20	36	
Gamma-glutamyltransferase increased			
subjects affected / exposed	9 / 159 (5.66%)	9 / 160 (5.63%)	
occurrences (all)	16	22	
Platelet count decreased			
subjects affected / exposed	9 / 159 (5.66%)	7 / 160 (4.38%)	
occurrences (all)	22	11	
Weight decreased			
subjects affected / exposed	20 / 159 (12.58%)	29 / 160 (18.13%)	
occurrences (all)	27	42	
Nervous system disorders			
Peripheral sensory neuropathy			
subjects affected / exposed	37 / 159 (23.27%)	34 / 160 (21.25%)	
occurrences (all)	67	53	
Neuropathy peripheral			
subjects affected / exposed	36 / 159 (22.64%)	26 / 160 (16.25%)	
occurrences (all)	81	89	
Headache			
subjects affected / exposed	32 / 159 (20.13%)	26 / 160 (16.25%)	
occurrences (all)	52	55	
Paraesthesia			
subjects affected / exposed	20 / 159 (12.58%)	15 / 160 (9.38%)	
occurrences (all)	29	22	
Dizziness			
subjects affected / exposed	13 / 159 (8.18%)	19 / 160 (11.88%)	
occurrences (all)	17	24	
Neurotoxicity			
subjects affected / exposed	10 / 159 (6.29%)	13 / 160 (8.13%)	
occurrences (all)	21	36	
Dysgeusia			
subjects affected / exposed	12 / 159 (7.55%)	10 / 160 (6.25%)	
occurrences (all)	17	11	
Tremor			

subjects affected / exposed	8 / 159 (5.03%)	1 / 160 (0.63%)	
occurrences (all)	9	1	
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	61 / 159 (38.36%)	92 / 160 (57.50%)	
occurrences (all)	212	293	
Anaemia			
subjects affected / exposed	57 / 159 (35.85%)	61 / 160 (38.13%)	
occurrences (all)	164	222	
Thrombocytopenia			
subjects affected / exposed	34 / 159 (21.38%)	36 / 160 (22.50%)	
occurrences (all)	106	85	
Leukopenia			
subjects affected / exposed	27 / 159 (16.98%)	35 / 160 (21.88%)	
occurrences (all)	109	129	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	83 / 159 (52.20%)	118 / 160 (73.75%)	
occurrences (all)	212	306	
Nausea			
subjects affected / exposed	85 / 159 (53.46%)	101 / 160 (63.13%)	
occurrences (all)	260	253	
Vomiting			
subjects affected / exposed	54 / 159 (33.96%)	64 / 160 (40.00%)	
occurrences (all)	118	139	
Abdominal pain			
subjects affected / exposed	34 / 159 (21.38%)	36 / 160 (22.50%)	
occurrences (all)	45	61	
Constipation			
subjects affected / exposed	38 / 159 (23.90%)	29 / 160 (18.13%)	
occurrences (all)	53	45	
Stomatitis			
subjects affected / exposed	25 / 159 (15.72%)	42 / 160 (26.25%)	
occurrences (all)	36	69	
Dyspepsia			

subjects affected / exposed	11 / 159 (6.92%)	10 / 160 (6.25%)	
occurrences (all)	14	10	
Abdominal pain upper			
subjects affected / exposed	9 / 159 (5.66%)	8 / 160 (5.00%)	
occurrences (all)	10	9	
Gastrooesophageal reflux disease			
subjects affected / exposed	10 / 159 (6.29%)	6 / 160 (3.75%)	
occurrences (all)	18	8	
Haemorrhoids			
subjects affected / exposed	5 / 159 (3.14%)	11 / 160 (6.88%)	
occurrences (all)	5	14	
Rectal haemorrhage			
subjects affected / exposed	7 / 159 (4.40%)	9 / 160 (5.63%)	
occurrences (all)	7	10	
Abdominal distension			
subjects affected / exposed	9 / 159 (5.66%)	6 / 160 (3.75%)	
occurrences (all)	10	8	
Oral dysaesthesia			
subjects affected / exposed	5 / 159 (3.14%)	8 / 160 (5.00%)	
occurrences (all)	10	18	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	23 / 159 (14.47%)	25 / 160 (15.63%)	
occurrences (all)	25	29	
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	4 / 159 (2.52%)	8 / 160 (5.00%)	
occurrences (all)	11	23	
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	19 / 159 (11.95%)	25 / 160 (15.63%)	
occurrences (all)	47	49	
Musculoskeletal and connective tissue disorders			
Muscle spasms			
subjects affected / exposed	20 / 159 (12.58%)	9 / 160 (5.63%)	
occurrences (all)	31	12	
Arthralgia			

subjects affected / exposed	9 / 159 (5.66%)	13 / 160 (8.13%)	
occurrences (all)	11	23	
Back pain			
subjects affected / exposed	9 / 159 (5.66%)	11 / 160 (6.88%)	
occurrences (all)	12	19	
Pain in extremity			
subjects affected / exposed	8 / 159 (5.03%)	6 / 160 (3.75%)	
occurrences (all)	9	9	
Infections and infestations			
COVID-19			
subjects affected / exposed	18 / 159 (11.32%)	22 / 160 (13.75%)	
occurrences (all)	18	24	
Urinary tract infection			
subjects affected / exposed	11 / 159 (6.92%)	10 / 160 (6.25%)	
occurrences (all)	20	11	
Upper respiratory tract infection			
subjects affected / exposed	7 / 159 (4.40%)	12 / 160 (7.50%)	
occurrences (all)	8	13	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	36 / 159 (22.64%)	39 / 160 (24.38%)	
occurrences (all)	44	71	
Hypokalaemia			
subjects affected / exposed	21 / 159 (13.21%)	21 / 160 (13.13%)	
occurrences (all)	44	33	
Dehydration			
subjects affected / exposed	12 / 159 (7.55%)	11 / 160 (6.88%)	
occurrences (all)	12	18	
Hyperglycaemia			
subjects affected / exposed	11 / 159 (6.92%)	8 / 160 (5.00%)	
occurrences (all)	15	14	
Hypophosphataemia			
subjects affected / exposed	6 / 159 (3.77%)	12 / 160 (7.50%)	
occurrences (all)	9	21	
Hypoalbuminaemia			

subjects affected / exposed	6 / 159 (3.77%)	11 / 160 (6.88%)	
occurrences (all)	13	18	
Hypomagnesaemia			
subjects affected / exposed	9 / 159 (5.66%)	3 / 160 (1.88%)	
occurrences (all)	12	4	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 January 2021	China was added to the study and to the list of countries for stratification. Regions include Unites States, Eastern Europe, Western Europe, and China. An exclusion criterion (#15) was added to exclude those with chronic inflammatory bowel disease and/or intestinal obstruction. It was noted that participants should not be treated until the obstruction has resolved. An exclusion criterion (#19) was added to specify that participants requiring ongoing or anticipated treatment with potent CYP450 3A4 inhibitors or inducers should not be included. An exclusion criterion (#20) was added to prohibit the inclusion of participants with ongoing or anticipated treatment with sorivudine or brivudine. Exclusion criterion # 28 was added to specify any contraindications to the administration of FOLFOXIRI and bevacizumab at the discretion of the investigator. Language was added to clarify that the strata information entered in Interactive web response system (IWRS) at the time of randomization would be used for all stratified statistical analyses.
07 July 2021	Text was added to the criteria for starting Cycle 2 in Section 9.4 to clarify the guidance for initiating subsequent treatment cycles. In addition, the dose modification guidelines for Grade 2 peripheral sensory neuropathy were updated in Table 9 to accommodate differences in clinical practice.
30 August 2022	The sample size was adjusted from 296 to 326 to mitigate the impact of the Russian-Ukraine war on data integrity and to ensure that the objectives of PRESERVE-1 would not be comprised. An additional 30 participants were randomized from outside Ukraine. To account for data integrity issues resulting from the war in Ukraine, a modified intent-to-treat (mITT) population would be utilized as the primary analysis population for all efficacy evaluations. The criteria for the mITT were included in the protocol. The primary myelosuppression endpoint was updated to duration of severe neutropenia (DSN) from Cycles 1 to 4. Measuring DSN during the timeframe of occurrence of the majority of severe neutropenia events, ie, Cycles 1 through 4 allowed an assessment of the risk of febrile neutropenia during the time of greatest clinical risk to participants.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported