Clinical trial results:
A randomised, open-label, Phase II, dose/schedule optimisation study of NUC-3373/leucovorin/irinotecan plus bevacizumab (NUFIRI-bev) versus 5-FU/leucovorin/irinotecan plus bevacizumab (FOLFIRI-bev) for the treatment of patients with previously treated unresectable metastatic colorectal cancer

Summary

EudraCT number	2022-001459-17
Trial protocol	ES DE IT FR
Global end of trial date	29 August 2024

Results information

Result version number	v1 (current)
This version publication date	23 August 2025
First version publication date	23 August 2025

Trial information

Trial identification

Sponsor protocol code	NuTide:323

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT05678257
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	NuCana plc
Sponsor organisation address	3 Lochside Way, Edinburgh, United Kingdom, EH12 9DT
Public contact	NuCana Clinical Study Information, NuCana plc, 0044 13165711110, NuTide323@nucana.com
Scientific contact	NuCana Clinical Study Information, NuCana plc, 0044 13165711110, NuTide323@nucana.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	29 August 2024
Is this the analysis of the primary completion data?	Yes
Primary completion date	29 August 2024
Global end of trial reached?	Yes
Global end of trial date	29 August 2024
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

• To compare progression-free survival (PFS) of NUC-3373 in combination with leucovorin (LV), irinotecan and bevacizumab (NUFIRI-bev) with 5-fluorouracil (5-FU) in combination with LV, irinotecan and bevacizumab (FOLFIRI-bev)
• To determine the optimal NUFIRI-bev dosing schedule

Protection of trial subjects:

The Chief Investigator (CI) ensured that the study was conducted in full conformity with the principles of the 1964 Declaration of Helsinki and any subsequent revisions and in accordance with the guidelines laid down by the International Conference on Harmonisation for Good Clinical Practice (ICH GCP E6 guidelines). Precautions were taken to ensure that patient confidentiality was preserved at all times. The Informed Consent Form identified those individuals who required access to patient data and identifiable details and obtained appropriate permission from the consenting patient.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	18 April 2023
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 72
Country: Number of subjects enrolled	France: 19
Country: Number of subjects enrolled	Germany: 9
Country: Number of subjects enrolled	Italy: 34
Country: Number of subjects enrolled	United Kingdom: 28
Country: Number of subjects enrolled	United States: 18
Worldwide total number of subjects	180
EEA total number of subjects	134

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)	89
From 65 to 84 years	90
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

Patients were recruited across 59 centres in the UK, USA, Germany, France, Italy, and Spain.

Pre-assignment

Screening details:

Patients with histologically or cytologically confirmed unresectable colorectal adenocarcinoma that is metastatic and measurable were eligible. Patients must have received a prior fluoropyrimidine and oxaliplatin-containing regimen.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm A

Arm description:

NUFIRI-bev Q1W

Arm type	Experimental
Investigational medicinal product name	Fosifloxuridine nafalbenamide
Investigational medicinal product code	NUC-3373
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

1500 mg/m2 NUC-3373 on Days 1, 8, 15, and 22 of 28-day cycles

Investigational medicinal product name	Calcium folinate
Investigational medicinal product code	LV
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

400 mg/m2 LV on Days 1, 8, 15, and 22 of 28-day cycles

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

Dosage and administration details:

180 mg/m2 irinotecan on Days 1 and 15 of 28-day cycles

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

Dosage and administration details:

5 mg/kg bevacizumab on Days 1 and 15 of 28-day cycles

Arm title	Arm B
Arm description: NUFIRI-bev Q2W	
Arm type	Experimental
Investigational medicinal product name	Fosifloxuridine nafalbenamide
Investigational medicinal product code	NUC-3373
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use
Dosage and administration details: 1500 mg/m2 NUC-3373 on Days 1 and 15 of 28-day cycles	
Investigational medicinal product name	Calcium folinate
Investigational medicinal product code	LV
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use
Dosage and administration details: 400 mg/m2 LV on on Days 1 and 15 of 28-day cycles	
Investigational medicinal product name	Irinotecan
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use
Dosage and administration details: 180 mg/m2 irinotecan on Days 1 and 15 of 28-day cycles	
Investigational medicinal product name	Bevacizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use
Dosage and administration details: 5 mg/kg bevacizumab on Days 1 and 15 of 28-day cycles	
Arm title	Arm C
Arm description: FOLFIRI-bev	
Arm type	Active comparator
Investigational medicinal product name	5-fluorouracil
Investigational medicinal product code	5-FU
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use
Dosage and administration details: 400 mg/m2 bolus followed by 2400 mg/m2 infusion over 46 hours on Days 1 and 15 of 28-day cycles	
Investigational medicinal product name	Calcium folinate
Investigational medicinal product code	LV
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use
Dosage and administration details: 400 mg/m2 LV on Days 1 and 15 of 28-day cycles	

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

Dosage and administration details:

180 mg/m2 irinotecan on Days 1 and 15 of 28-day cycles

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

Dosage and administration details:

5 mg/kg bevacizumab on Days 1 and 15 of 28-day cycles

Number of subjects in period 1	Arm A	Arm B	Arm C
Started	57	65	58
Completed	35	34	32
Not completed	22	31	26
Consent withdrawn by subject	2	-	5
Physician decision	1	-	1
Adverse event, non-fatal	1	3	1
Progressive Disease	11	18	7
No longer clinically benefitting	2	1	-
Sponsor request	5	9	8
Patient non-compliance	-	-	3
Protocol deviation	-	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Arm A
Reporting group description: NUFIRI-bev Q1W	
Reporting group title	Arm B
Reporting group description: NUFIRI-bev Q2W	
Reporting group title	Arm C
Reporting group description: FOLFIRI-bev	

Reporting group values	Arm A	Arm B	Arm C
Number of subjects	57	65	58
Age categorical Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous Units: years			
median	64.0	64.0	65.0
full range (min-max)	38 to 78	37 to 79	27 to 85
Gender categorical Units: Subjects			
Female	21	27	24
Male	36	38	34
Race Units: Subjects			
Asian	2	2	0
Black or African American	4	3	4
White	42	44	42
Not reported	8	14	11
Unknown	1	2	1
ECOG performance status Units: Subjects			
Zero	31	36	38
One	25	28	18
Not reported	1	1	2
Stage at initial diagnosis			

Units: Subjects			
Stage I (A-C)	0	0	2
Stage II (A-C)	3	1	3
Stage IIIA	2	3	1
Stage IIIB	4	13	9
Stage IIIC	2	2	6
Stage IV	30	28	24
Stage IVA	11	8	9
Stage IVB	3	4	4
Stage IVC	1	3	0
Not reported	1	3	0
Primary tumour location Units: Subjects			
Colon - right side	15	26	15
Colon - left side	20	23	21
Colon - unknown	6	5	8
Rectum	16	11	14
Liver metastases Units: Subjects			
Yes	46	45	35
No	11	20	23
Number of metastatic sites Units: Subjects			
One	1	2	3
Two	9	10	7
Three	19	16	20
≥four	28	36	28
Not reported	0	1	0

Reporting group values	Total		
Number of subjects	180		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	0		
Adolescents (12-17 years)	0		
Adults (18-64 years)	0		
From 65-84 years	0		
85 years and over	0		
Age continuous Units: years			
median			
full range (min-max)	-		
Gender categorical Units: Subjects			
Female	72		
Male	108		

Race Units: Subjects			
Asian	4		
Black or African American	11		
White	128		
Not reported	33		
Unknown	4		
ECOG performance status Units: Subjects			
Zero	105		
One	71		
Not reported	4		
Stage at initial diagnosis Units: Subjects			
Stage I (A-C)	2		
Stage II (A-C)	7		
Stage IIIA	6		
Stage IIIB	26		
Stage IIIC	10		
Stage IV	82		
Stage IVA	28		
Stage IVB	11		
Stage IVC	4		
Not reported	4		
Primary tumour location Units: Subjects			
Colon - right side	56		
Colon - left side	64		
Colon - unknown	19		
Rectum	41		
Liver metastases Units: Subjects			
Yes	126		
No	54		
Number of metastatic sites Units: Subjects			
One	6		
Two	26		
Three	55		
≥four	92		
Not reported	1		

End points

End points reporting groups

Reporting group title	Arm A
Reporting group description: NUFIRI-bev Q1W	
Reporting group title	Arm B
Reporting group description: NUFIRI-bev Q2W	
Reporting group title	Arm C
Reporting group description: FOLFIRI-bev	

Primary: Progression-Free Survival

End point title	Progression-Free Survival[1]

End point description:

PFS was defined as the time from randomisation to the first observation of objective tumour progression or death from any cause. Patients who had not experienced disease progression or death at the time of final analysis were censored at the time of the latest date of assessment from their last evaluable RECIST v1.1 assessment.

End point type	Primary

End point timeframe:

Assessed every 8 weeks from Day 1 until the end of study (up to 16 months)

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The study was stopped early for futility; therefore, the analyses performed should only be viewed descriptively.

End point values	Arm A	Arm B	Arm C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	57	65	58	
Units: Months				
median (full range (min-max))	5.68 (0.03 to 11.17)	5.52 (0.03 to 10.84)	9.03 (0.03 to 15.01)	

Statistical analyses

No statistical analyses for this end point

Secondary: Objective Response Rate

End point title	Objective Response Rate

End point description:

ORR was defined as the number of patients achieving a BOR of CR or PR. BOR was the best response recorded during the study period up to the earliest of disease progression, initiation of subsequent anti-cancer therapy or death.

End point type	Secondary

End point timeframe:

Assessed every 8 weeks from Day 1 to the end of study (up to 16 months)

End point values	Arm A	Arm B	Arm C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	57	65	58	
Units: Percentage	7	19	21	

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Control Rate

End point title	Disease Control Rate

End point description:

The DCR was defined as the number of patients achieving a response (CR or PR) or SD as BOR.

End point type	Secondary

End point timeframe:

Assessed every 8 weeks from Day 1 until the end of study (up to 16 months)

End point values	Arm A	Arm B	Arm C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	57	65	58	
Units: Percentage	61	65	79	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Each patient was assessed for adverse events from the date of consent until 30 days after the last dose of study treatment.	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	27.0

Reporting groups	
Reporting group title	Arm A
Reporting group description: NUFIRI-bev Q1W	
Reporting group title	Arm B
Reporting group description: NUFIRI-bev Q2W	
Reporting group title	Arm C
Reporting group description: FOLFIRI-bev	

Serious adverse events	Arm A	Arm B	Arm C
Total subjects affected by serious adverse events			
subjects affected / exposed	11 / 56 (19.64%)	13 / 64 (20.31%)	17 / 57 (29.82%)
number of deaths (all causes)	18	14	6
number of deaths resulting from adverse events	1	0	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Hepatobiliary cancer			
subjects affected / exposed	0 / 56 (0.00%)	1 / 64 (1.56%)	0 / 57 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 56 (1.79%)	0 / 64 (0.00%)	0 / 57 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Asthenia			

subjects affected / exposed	0 / 56 (0.00%)	0 / 64 (0.00%)	3 / 57 (5.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	1 / 56 (1.79%)	0 / 64 (0.00%)	1 / 57 (1.75%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Catheter site extravasation			
subjects affected / exposed	0 / 56 (0.00%)	1 / 64 (1.56%)	0 / 57 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Complication associated with device			
subjects affected / exposed	0 / 56 (0.00%)	0 / 64 (0.00%)	1 / 57 (1.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Inadequate analgesia			
subjects affected / exposed	1 / 56 (1.79%)	0 / 64 (0.00%)	0 / 57 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	0 / 56 (0.00%)	1 / 64 (1.56%)	0 / 57 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypersensitivity			
subjects affected / exposed	0 / 56 (0.00%)	1 / 64 (1.56%)	0 / 57 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	0 / 56 (0.00%)	0 / 64 (0.00%)	3 / 57 (5.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Epistaxis			
subjects affected / exposed	0 / 56 (0.00%)	1 / 64 (1.56%)	1 / 57 (1.75%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed	0 / 56 (0.00%)	0 / 64 (0.00%)	1 / 57 (1.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Infusion-related reaction			
subjects affected / exposed	0 / 56 (0.00%)	1 / 64 (1.56%)	0 / 57 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Procedural pneumothorax			
subjects affected / exposed	0 / 56 (0.00%)	0 / 64 (0.00%)	1 / 57 (1.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Stress cardiomyopathy			
subjects affected / exposed	1 / 56 (1.79%)	0 / 64 (0.00%)	0 / 57 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Epilepsy			
subjects affected / exposed	0 / 56 (0.00%)	0 / 64 (0.00%)	1 / 57 (1.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	0 / 56 (0.00%)	1 / 64 (1.56%)	1 / 57 (1.75%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			

subjects affected / exposed	0 / 56 (0.00%)	0 / 64 (0.00%)	1 / 57 (1.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Intestinal obstruction			
subjects affected / exposed	2 / 56 (3.57%)	1 / 64 (1.56%)	2 / 57 (3.51%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	2 / 56 (3.57%)	2 / 64 (3.13%)	0 / 57 (0.00%)
occurrences causally related to treatment / all	2 / 2	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower gastrointestinal haemorrhage			
subjects affected / exposed	1 / 56 (1.79%)	0 / 64 (0.00%)	1 / 57 (1.75%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	0 / 56 (0.00%)	2 / 64 (3.13%)	0 / 57 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 56 (0.00%)	2 / 64 (3.13%)	0 / 57 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain			
subjects affected / exposed	0 / 56 (0.00%)	0 / 64 (0.00%)	1 / 57 (1.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	0 / 56 (0.00%)	0 / 64 (0.00%)	1 / 57 (1.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enteritis			

subjects affected / exposed	0 / 56 (0.00%)	0 / 64 (0.00%)	1 / 57 (1.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			
subjects affected / exposed	0 / 56 (0.00%)	1 / 64 (1.56%)	0 / 57 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal haemorrhage			
subjects affected / exposed	0 / 56 (0.00%)	1 / 64 (1.56%)	0 / 57 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction			
subjects affected / exposed	0 / 56 (0.00%)	0 / 64 (0.00%)	1 / 57 (1.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Hyperbilirubinaemia			
subjects affected / exposed	2 / 56 (3.57%)	0 / 64 (0.00%)	0 / 57 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intrahepatic portal hepatic venous fistula			
subjects affected / exposed	0 / 56 (0.00%)	1 / 64 (1.56%)	0 / 57 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Urinary tract obstruction			
subjects affected / exposed	0 / 56 (0.00%)	1 / 64 (1.56%)	1 / 57 (1.75%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure			
subjects affected / exposed	0 / 56 (0.00%)	1 / 64 (1.56%)	0 / 57 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Infections and infestations			
Pneumonia			
subjects affected / exposed	0 / 56 (0.00%)	1 / 64 (1.56%)	1 / 57 (1.75%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal sepsis			
subjects affected / exposed	0 / 56 (0.00%)	0 / 64 (0.00%)	1 / 57 (1.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Biliary tract infection			
subjects affected / exposed	1 / 56 (1.79%)	0 / 64 (0.00%)	0 / 57 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Liver abscess			
subjects affected / exposed	0 / 56 (0.00%)	1 / 64 (1.56%)	0 / 57 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Perihepatic abscess			
subjects affected / exposed	0 / 56 (0.00%)	1 / 64 (1.56%)	0 / 57 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal abscess			
subjects affected / exposed	1 / 56 (1.79%)	0 / 64 (0.00%)	0 / 57 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection			
subjects affected / exposed	0 / 56 (0.00%)	1 / 64 (1.56%)	0 / 57 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 56 (0.00%)	0 / 64 (0.00%)	1 / 57 (1.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			

subjects affected / exposed	1 / 56 (1.79%)	0 / 64 (0.00%)	0 / 57 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 56 (1.79%)	0 / 64 (0.00%)	1 / 57 (1.75%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemia			
subjects affected / exposed	0 / 56 (0.00%)	0 / 64 (0.00%)	1 / 57 (1.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalaemia			
subjects affected / exposed	0 / 56 (0.00%)	1 / 64 (1.56%)	0 / 57 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Arm A	Arm B	Arm C
Total subjects affected by non-serious adverse events			
subjects affected / exposed	55 / 56 (98.21%)	62 / 64 (96.88%)	57 / 57 (100.00%)
Vascular disorders			
Hypertension			
subjects affected / exposed	5 / 56 (8.93%)	11 / 64 (17.19%)	8 / 57 (14.04%)
occurrences (all)	12	13	12
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	25 / 56 (44.64%)	23 / 64 (35.94%)	26 / 57 (45.61%)
occurrences (all)	45	56	60
Fatigue			
subjects affected / exposed	10 / 56 (17.86%)	14 / 64 (21.88%)	11 / 57 (19.30%)
occurrences (all)	14	23	18
Pyrexia			

subjects affected / exposed	9 / 56 (16.07%)	9 / 64 (14.06%)	5 / 57 (8.77%)
occurrences (all)	12	10	5
Mucosal inflammation			
subjects affected / exposed	5 / 56 (8.93%)	3 / 64 (4.69%)	9 / 57 (15.79%)
occurrences (all)	8	3	13
Influenza-like illness			
subjects affected / exposed	1 / 56 (1.79%)	1 / 64 (1.56%)	5 / 57 (8.77%)
occurrences (all)	2	1	6
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	3 / 56 (5.36%)	7 / 64 (10.94%)	7 / 57 (12.28%)
occurrences (all)	4	8	7
Cough			
subjects affected / exposed	7 / 56 (12.50%)	6 / 64 (9.38%)	3 / 57 (5.26%)
occurrences (all)	7	6	5
Dyspnoea			
subjects affected / exposed	2 / 56 (3.57%)	6 / 64 (9.38%)	6 / 57 (10.53%)
occurrences (all)	2	6	6
Dysphonia			
subjects affected / exposed	6 / 56 (10.71%)	3 / 64 (4.69%)	4 / 57 (7.02%)
occurrences (all)	7	3	6
Rhinorrhoea			
subjects affected / exposed	3 / 56 (5.36%)	3 / 64 (4.69%)	1 / 57 (1.75%)
occurrences (all)	3	3	1
Psychiatric disorders			
Insomnia			
subjects affected / exposed	3 / 56 (5.36%)	5 / 64 (7.81%)	7 / 57 (12.28%)
occurrences (all)	6	5	8
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	14 / 56 (25.00%)	4 / 64 (6.25%)	4 / 57 (7.02%)
occurrences (all)	46	4	4
Aspartate aminotransferase increased			
subjects affected / exposed	10 / 56 (17.86%)	4 / 64 (6.25%)	5 / 57 (8.77%)
occurrences (all)	32	5	5
Blood alkaline phosphatase increased			

subjects affected / exposed	1 / 56 (1.79%)	7 / 64 (10.94%)	5 / 57 (8.77%)
occurrences (all)	1	7	6
Neutrophil count decreased			
subjects affected / exposed	1 / 56 (1.79%)	0 / 64 (0.00%)	11 / 57 (19.30%)
occurrences (all)	1	0	18
Weight decreased			
subjects affected / exposed	4 / 56 (7.14%)	1 / 64 (1.56%)	5 / 57 (8.77%)
occurrences (all)	6	1	6
Blood bilirubin increased			
subjects affected / exposed	4 / 56 (7.14%)	2 / 64 (3.13%)	0 / 57 (0.00%)
occurrences (all)	4	2	0
Platelet count decreased			
subjects affected / exposed	1 / 56 (1.79%)	2 / 64 (3.13%)	3 / 57 (5.26%)
occurrences (all)	1	5	3
Blood lactate dehydrogenase increased			
subjects affected / exposed	3 / 56 (5.36%)	1 / 64 (1.56%)	1 / 57 (1.75%)
occurrences (all)	3	1	1
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 56 (1.79%)	0 / 64 (0.00%)	3 / 57 (5.26%)
occurrences (all)	1	0	5
Injury, poisoning and procedural complications			
Infusion-related reaction			
subjects affected / exposed	4 / 56 (7.14%)	3 / 64 (4.69%)	0 / 57 (0.00%)
occurrences (all)	4	4	0
Nervous system disorders			
Headache			
subjects affected / exposed	13 / 56 (23.21%)	6 / 64 (9.38%)	2 / 57 (3.51%)
occurrences (all)	25	6	2
Dysgeusia			
subjects affected / exposed	2 / 56 (3.57%)	2 / 64 (3.13%)	6 / 57 (10.53%)
occurrences (all)	3	3	6
Neuropathy peripheral			
subjects affected / exposed	4 / 56 (7.14%)	4 / 64 (6.25%)	2 / 57 (3.51%)
occurrences (all)	4	5	3
Dizziness			

subjects affected / exposed	2 / 56 (3.57%)	4 / 64 (6.25%)	2 / 57 (3.51%)
occurrences (all)	5	8	2
Neurotoxicity			
subjects affected / exposed	0 / 56 (0.00%)	0 / 64 (0.00%)	3 / 57 (5.26%)
occurrences (all)	0	0	4
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	4 / 56 (7.14%)	4 / 64 (6.25%)	16 / 57 (28.07%)
occurrences (all)	7	6	28
Anaemia			
subjects affected / exposed	7 / 56 (12.50%)	9 / 64 (14.06%)	5 / 57 (8.77%)
occurrences (all)	8	16	10
Thrombocytopenia			
subjects affected / exposed	5 / 56 (8.93%)	3 / 64 (4.69%)	0 / 57 (0.00%)
occurrences (all)	7	7	0
Leukopenia			
subjects affected / exposed	1 / 56 (1.79%)	3 / 64 (4.69%)	3 / 57 (5.26%)
occurrences (all)	1	4	4
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	35 / 56 (62.50%)	33 / 64 (51.56%)	28 / 57 (49.12%)
occurrences (all)	113	79	76
Nausea			
subjects affected / exposed	29 / 56 (51.79%)	37 / 64 (57.81%)	22 / 57 (38.60%)
occurrences (all)	81	80	51
Vomiting			
subjects affected / exposed	22 / 56 (39.29%)	18 / 64 (28.13%)	9 / 57 (15.79%)
occurrences (all)	40	41	30
Abdominal pain			
subjects affected / exposed	18 / 56 (32.14%)	13 / 64 (20.31%)	8 / 57 (14.04%)
occurrences (all)	30	22	8
Constipation			
subjects affected / exposed	13 / 56 (23.21%)	7 / 64 (10.94%)	13 / 57 (22.81%)
occurrences (all)	21	14	19
Stomatitis			

subjects affected / exposed	7 / 56 (12.50%)	6 / 64 (9.38%)	12 / 57 (21.05%)
occurrences (all)	8	10	23
Abdominal pain upper			
subjects affected / exposed	5 / 56 (8.93%)	5 / 64 (7.81%)	4 / 57 (7.02%)
occurrences (all)	5	7	4
Dyspepsia			
subjects affected / exposed	4 / 56 (7.14%)	5 / 64 (7.81%)	4 / 57 (7.02%)
occurrences (all)	11	5	4
Gastrooesophageal reflux disease			
subjects affected / exposed	3 / 56 (5.36%)	2 / 64 (3.13%)	3 / 57 (5.26%)
occurrences (all)	4	2	3
Haemorrhoids			
subjects affected / exposed	1 / 56 (1.79%)	4 / 64 (6.25%)	3 / 57 (5.26%)
occurrences (all)	1	4	6
Rectal haemorrhage			
subjects affected / exposed	4 / 56 (7.14%)	0 / 64 (0.00%)	3 / 57 (5.26%)
occurrences (all)	4	0	3
Flatulence			
subjects affected / exposed	3 / 56 (5.36%)	2 / 64 (3.13%)	1 / 57 (1.75%)
occurrences (all)	4	3	1
Salivary hypersecretion			
subjects affected / exposed	3 / 56 (5.36%)	3 / 64 (4.69%)	0 / 57 (0.00%)
occurrences (all)	5	3	0
Odynophagia			
subjects affected / exposed	3 / 56 (5.36%)	2 / 64 (3.13%)	0 / 57 (0.00%)
occurrences (all)	6	2	0
Hepatobiliary disorders			
Hypertransaminasaemia			
subjects affected / exposed	4 / 56 (7.14%)	2 / 64 (3.13%)	0 / 57 (0.00%)
occurrences (all)	11	3	0
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	3 / 56 (5.36%)	0 / 64 (0.00%)	14 / 57 (24.56%)
occurrences (all)	3	0	16
Palmar-plantar erythrodysaesthesia syndrome			

subjects affected / exposed	3 / 56 (5.36%)	2 / 64 (3.13%)	2 / 57 (3.51%)
occurrences (all)	3	2	2
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	11 / 56 (19.64%)	4 / 64 (6.25%)	4 / 57 (7.02%)
occurrences (all)	12	5	4
Myalgia			
subjects affected / exposed	4 / 56 (7.14%)	2 / 64 (3.13%)	1 / 57 (1.75%)
occurrences (all)	9	2	1
Arthralgia			
subjects affected / exposed	1 / 56 (1.79%)	0 / 64 (0.00%)	4 / 57 (7.02%)
occurrences (all)	1	0	6
Pain in extremity			
subjects affected / exposed	1 / 56 (1.79%)	1 / 64 (1.56%)	3 / 57 (5.26%)
occurrences (all)	5	1	3
Infections and infestations			
COVID-19			
subjects affected / exposed	4 / 56 (7.14%)	1 / 64 (1.56%)	1 / 57 (1.75%)
occurrences (all)	4	1	1
Influenza			
subjects affected / exposed	3 / 56 (5.36%)	1 / 64 (1.56%)	0 / 57 (0.00%)
occurrences (all)	3	1	0
Upper respiratory tract infection			
subjects affected / exposed	3 / 56 (5.36%)	1 / 64 (1.56%)	0 / 57 (0.00%)
occurrences (all)	5	2	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	13 / 56 (23.21%)	11 / 64 (17.19%)	16 / 57 (28.07%)
occurrences (all)	18	20	22
Hypokalaemia			
subjects affected / exposed	3 / 56 (5.36%)	4 / 64 (6.25%)	3 / 57 (5.26%)
occurrences (all)	5	5	4
Hypophosphataemia			
subjects affected / exposed	4 / 56 (7.14%)	1 / 64 (1.56%)	1 / 57 (1.75%)
occurrences (all)	5	2	3

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 September 2023	All country-specific updates were consolidated into the v2.0 protocol. In addition, the following key updates were made: • Analytes to be measured as part of PK endpoint updated. • Eligibility criteria updated to: o Be more representative of the 2nd-line patient population. o Allow patients who have relapsed on prior neoadjuvant therapy. o Ensure that patients who can no longer receive oxaliplatin due to toxicity or allergy are eligible regardless of duration of prior therapy. o Ensure that patients with benign neutropenia who are otherwise eligible are not excluded. o Allow patients who tolerated prior treatment with 5-FU but at a reduced dose level to participate and to receive 5-FU at the same reduced dose. o Clarify that dosing of prednisolone ≥10 mg is not permitted during study participation. o Allow patients with skin reactions that are due to recent anti-cancer treatment. o Allow Investigators to initially withhold bevacizumab (for a maximum of 1 cycle) to allow wound healing. o Exclude concomitant use of sorivudine or analogues. • Text added to ensure that 5-FU dose adjustments in patients with partial DPD deficiency are in accordance with standard practices on a country-by-country basis. • Text added to allow Investigators to perform an initial dose reduction of irinotecan for patients with a known mutation that may affect their ability to metabolise irinotecan. • Text added to allow patients who have previously tolerated bevacizumab infusions well to receive all infusions over 30 minutes, rather than receiving the first and second infusions over 90 and 60 minutes, respectively. • The use of levo-LV was removed. • Time that live vaccines are prohibited extended to 3 months after the last dose of study treatment. • SAE reporting requirements updated to align with latest guidelines.
06 February 2024	The following key updates were made: • Inclusion criterion 12 updated to clarify that patients with Gilbert's syndrome do not need to meet the threshold for bilirubin levels. • It was clarified that Investigators can perform DPD status testing by either genotyping or phenotyping as per their local standard practices.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

Due to the early closure of the study, many patients were censored for the efficacy endpoints and the data should therefore be interpreted with caution.

Notes: