Clinical trial results:
An Open-Label Exploratory Phase 2/3 Study of Nivolumab with Standard of Care Therapy vs Standard of Care Therapy for First-Line Treatment of Metastatic Colorectal Cancer (CheckMate 9X8: CHECKpoint pathway and nivoluMab clinical Trial Evaluation 9X8)

Summary

EudraCT number	2017-003662-27
Trial protocol	ES
Global end of trial date	28 December 2022

Results information

Result version number	v1 (current)
This version publication date	12 November 2023
First version publication date	12 November 2023

Trial information

Trial identification

Sponsor protocol code	CA209-9X8

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Bristol-Myers Squibb
Sponsor organisation address	Chaussee de la Hulpe 185, Brussels, Belgium, 1170
Public contact	EU Study Start-Up Unit, Bristol-Myers Squibb International Corporation, Clinical.Trials@bms.com
Scientific contact	Bristol-Myers Squibb Study Director, Bristol-Myers Squibb, Clinical.Trials@bms.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	14 February 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	28 December 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the efficacy of nivolumab plus standard of care (SOC) chemotherapy with bevacizumab (Nivo + SOC) with SOC chemotherapy with bevacizumab in participants with mCRC

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization Good Clinical Practice Guidelines. All the local regulatory requirements pertinent to safety of trial participants were followed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	20 February 2018
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	Canada: 19
Country: Number of subjects enrolled	Japan: 17
Country: Number of subjects enrolled	Spain: 15
Country: Number of subjects enrolled	United States: 144
Worldwide total number of subjects	195
EEA total number of subjects	15

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)	136
From 65 to 84 years	57

85 years and over	2

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

195 participants randomized and 185 participants treated

Period 1

Period 1 title	Pre-Treatment
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm A: NIV+mFOLFOX+BEV

Arm description:

Nivolumab 240 mg + Standard of Care (SOC) mFOLFOX6/bevacizuma every 2 weeks

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

Dosage and administration details:

240 mg IV every 2 weeks

Investigational medicinal product name	Bevacizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

5 mg/kg IV every 2 weeks

Investigational medicinal product name	Fluorouracil
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

400 mg/m2 IV every 2 weeks

Investigational medicinal product name	Fluorouracil
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

1200 mg/m2 continuous infusion every 2 weeks

Investigational medicinal product name	Fluorouracil
Investigational medicinal product code	
Other name	

Pharmaceutical forms	Infusion
Routes of administration	Intravenous use
Dosage and administration details: 400 mg/m2 IV every 2 weeks	
Investigational medicinal product name	Leucovorin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use
Dosage and administration details: 400 mg/m2 IV every 2 weeks	
Investigational medicinal product name	Leucovorin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use
Dosage and administration details: 350 mg/m2 IV every 2 weeks	
Investigational medicinal product name	Oxaliplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use
Dosage and administration details: 85 mg/m2 IV every 2 weeks	
Investigational medicinal product name	Fluorouracil
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use
Dosage and administration details: 2400 mg/m2 continuous infusion every 2 weeks	
Arm title	Arm B: mFOLFOX+BEV
Arm description: mFOLFOX6/bevacizumab (SOC) every 2 weeks	
Arm type	Experimental
Investigational medicinal product name	Bevacizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use
Dosage and administration details: 5 mg/kg IV every 2 weeks	
Investigational medicinal product name	Fluorouracil
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use
Dosage and administration details: 400 mg/m2 IV every 2 weeks	

Investigational medicinal product name	Fluorouracil
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:
1200 mg/m2 continuous infusion every 2 weeks

Investigational medicinal product name	Oxaliplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:
85 mg/m2 IV every 2 weeks

Investigational medicinal product name	Leucovorin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:
400 mg/m2 IV every 2 weeks

Investigational medicinal product name	Leucovorin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:
350 mg/m2 IV every 2 weeks

Investigational medicinal product name	Fluorouracil
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:
2400 mg/m2 continuous infusion every 2 weeks

Number of subjects in period 1	Arm A: NIV+mFOLFOX+BEV	Arm B: mFOLFOX+BEV
Started	127	68
Completed	123	62
Not completed	4	6
Participant withdrew consent	1	3
Participant no longer meets study criteria	2	3
Other reasons	1	-

Period 2

Period 2 title	Treatment
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm A: NIV+mFOLFOX+BEV

Arm description:

Nivolumab 240 mg + Standard of Care (SOC) mFOLFOX6/bevacizuma every 2 weeks

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

Dosage and administration details:

240 mg IV every 2 weeks

Investigational medicinal product name	Bevacizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

5 mg/kg IV every 2 weeks

Investigational medicinal product name	Fluorouracil
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

400 mg/m2 IV every 2 weeks

Investigational medicinal product name	Fluorouracil
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

2400 mg/m2 IV every 2 weeks

Investigational medicinal product name	Leucovorin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

350 mg/m2 IV every 2 weeks

Investigational medicinal product name	Oxaliplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use
Dosage and administration details: 85 mg/m2 IV every 2 weeks	
Investigational medicinal product name	Fluorouracil
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use
Dosage and administration details: 1200 mg/m2 IV every 2 weeks	
Investigational medicinal product name	Leucovorin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use
Dosage and administration details: 400 mg/m2 IV every 2 weeks	
Arm title	Arm B: mFOLFOX+BEV
Arm description: mFOLFOX6/bevacizumab (SOC) every 2 weeks	
Arm type	Experimental
Investigational medicinal product name	Bevacizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use
Dosage and administration details: 5 mg/kg IV every 2 weeks	
Investigational medicinal product name	Fluorouracil
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use
Dosage and administration details: 400 mg/m2 IV every 2 weeks	
Investigational medicinal product name	Fluorouracil
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use
Dosage and administration details: 1200 mg/m2 IV every 2 weeks	
Investigational medicinal product name	Oxaliplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details: 85 mg/m2 IV every 2 weeks	
Investigational medicinal product name	Leucovorin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use
Dosage and administration details: 400 mg/m2 IV every 2 weeks	
Investigational medicinal product name	Leucovorin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use
Dosage and administration details: 350 mg/m2 IV every 2 weeks	
Investigational medicinal product name	Fluorouracil
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use
Dosage and administration details: 2400 mg/m2 IV every 2 weeks	

Number of subjects in period 2	Arm A: NIV+mFOLFOX+BEV	Arm B: mFOLFOX+BEV
Started	123	62
Completed	9	0
Not completed	114	62
Adverse event, serious fatal	-	1
Participant withdrew consent	4	3
Not reported	1	-
Maximum clinical benefit	5	9
Adverse Event Unrelated to Study Drug	5	2
Other reasons	3	2
Study Drug Toxicity	10	5
Lost to follow-up	-	1
Poor/non-compliance	2	-
Administrative reasons by sponsor	1	-
Disease Progression	75	29
Participant request to discontinue study treatment	8	10

Baseline characteristics

Reporting groups	
Reporting group title	Arm A: NIV+mFOLFOX+BEV
Reporting group description: Nivolumab 240 mg + Standard of Care (SOC) mFOLFOX6/bevacizuma every 2 weeks	
Reporting group title	Arm B: mFOLFOX+BEV
Reporting group description: mFOLFOX6/bevacizumab (SOC) every 2 weeks	

Reporting group values	Arm A: NIV+mFOLFOX+BEV	Arm B: mFOLFOX+BEV	Total
Number of subjects	127	68	195
Age categorical Units: Subjects			
Adults (18-64 years)	89	47	136
From 65-84 years	28	18	46
85 years and over	10	3	13
Age Continuous Units: Years			
arithmetic mean	56.8	57.2	
standard deviation	± 13.3	± 11.4	-
Sex: Female, Male Units: Participants			
Female	57	19	76
Male	70	49	119
Race/Ethnicity, Customized Units: Subjects			
White	96	57	153
Black or African American	8	2	10
Asian	15	5	20
Other	6	3	9
Not Reported	2	1	3
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	7	9	16
Not Hispanic or Latino	108	53	161
Unknown or Not Reported	12	6	18

End points

End points reporting groups

Reporting group title	Arm A: NIV+mFOLFOX+BEV
Reporting group description: Nivolumab 240 mg + Standard of Care (SOC) mFOLFOX6/bevacizuma every 2 weeks	
Reporting group title	Arm B: mFOLFOX+BEV
Reporting group description: mFOLFOX6/bevacizumab (SOC) every 2 weeks	
Reporting group title	Arm A: NIV+mFOLFOX+BEV
Reporting group description: Nivolumab 240 mg + Standard of Care (SOC) mFOLFOX6/bevacizuma every 2 weeks	
Reporting group title	Arm B: mFOLFOX+BEV
Reporting group description: mFOLFOX6/bevacizumab (SOC) every 2 weeks	

Primary: Progression Free Survival (PFS) per Blinded Independent Central Review (BICR)

End point title	Progression Free Survival (PFS) per Blinded Independent Central Review (BICR)

End point description:

Progression Free Survival (PFS) is defined as the time from randomization to the date of the first documented progression, as determined by BICR (per RECIST 1.1), or death due to any cause, whichever occurs first. Baseline tumor assessment is defined as tumor scans prior to or on randomization date. Participants who did not have documented progression per BICR and who did not die or participants who started any subsequent anti-cancer therapy without a prior reported progression per BICR will be censored at the date of the last tumor assessment on or prior to initiation of the subsequent anticancer therapy, if any. Participants who die without a reported prior progression per BICR will be considered to have progressed on the date of death. Participants who did not have any baseline or post baseline tumor assessments and did not die (or died after initiation of the subsequent anti-cancer therapy) will be censored at the randomization date.

End point type	Primary

End point timeframe:

From randomization to up to the date of the first documented progression (up to 16 months)

End point values	Arm A: NIV+mFOLFOX +BEV	Arm B: mFOLFOX+BEV		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	127	68		
Units: Months				
median (confidence interval 95%)	11.86 (8.94 to 15.70)	11.93 (10.09 to 12.19)		

Statistical analyses

Statistical analysis title	PFS
Statistical analysis description:	
Hazard Ratio is Arm A: NIV+mFOLFOX+BEV over Arm B: mFOLFOX+BEV	
Comparison groups	Arm A: NIV+mFOLFOX+BEV v Arm B: mFOLFOX+BEV
Number of subjects included in analysis	195
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.3022 [1]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.81
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.53
upper limit	1.23

Notes:

[1] - Stratified regular log-rank test

Statistical analysis title	PFS
Statistical analysis description:	
Hazard Ratio is Arm A: NIV+mFOLFOX+BEV over Arm B: mFOLFOX+BEV	
Comparison groups	Arm A: NIV+mFOLFOX+BEV v Arm B: mFOLFOX+BEV
Number of subjects included in analysis	195
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.3022 [2]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.81
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	0.61
upper limit	1.07

Notes:

[2] - Stratified regular log-rank test

Secondary: Objective Response Rate (ORR) per Blinded Independent Central Review (BICR)

End point title	Objective Response Rate (ORR) per Blinded Independent Central Review (BICR)

End point description:

ORR is defined as the percentage of participants with a best overall response (BOR) of complete response (CR) or partial response (PR). BOR is defined as the best response designation as determined by BICR per RECIST 1.1, recorded between the date of randomization and the date of objectively documented progression per RECIST 1.1 or the date of subsequent anticancer therapy (including tumor-directed radiotherapy and tumor-directed surgery), whichever occurs first. PR is defined as at least a 30% decrease in the sum of diameters of target lesions. CR is defined as the disappearance of all target lesions and the reduction of any pathological lymph nodes to <10 mm.

End point type	Secondary

End point timeframe:

From the date of randomization up to the date of objectively documented progression or the date of subsequent anticancer therapy, whichever occurs first (up to approximately 44 months)

End point values	Arm A: NIV+mFOLFOX +BEV	Arm B: mFOLFOX+BEV		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	127	68		
Units: Percentage of Participants				
number (confidence interval 95%)	60.6 (51.6 to 69.2)	45.6 (33.5 to 58.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Objective Response Rate (ORR) per Investigator Assessment

End point title	Objective Response Rate (ORR) per Investigator Assessment

End point description:

ORR is defined as the percentage of participants with a best overall response (BOR) of complete response (CR) or partial response (PR). BOR is defined as the best response designation as determined by tumor assessments by the Investigator per RECIST 1.1, recorded between the date of randomization and the date of objectively documented progression per RECIST 1.1 or the date of subsequent anticancer therapy (including tumor-directed radiotherapy and tumor-directed surgery), whichever occurs first. PR is defined as at least a 30% decrease in the sum of diameters of target lesions. CR is defined as the disappearance of all target lesions and the reduction of any pathological lymph nodes to <10 mm.

End point type	Secondary

End point timeframe:

From the date of randomization up to the date of objectively documented progression or the date of subsequent anticancer therapy, whichever occurs first (up to approximately 44 months)

End point values	Arm A: NIV+mFOLFOX +BEV	Arm B: mFOLFOX+BEV		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	127	68		
Units: Percentage of participants				
number (confidence interval 95%)	60.6 (51.6 to 69.2)	52.9 (40.4 to 65.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Objective Response per Investigator Assessment

End point title	Time to Objective Response per Investigator Assessment

End point description:

TTR is defined as the time from the randomization date to the date of the first confirmed complete response (CR) or partial response (PR) as assessed by investigator. PR is defined as at least a 30% decrease in the sum of diameters of target lesions. CR is defined as the disappearance of all target lesions and the reduction of any pathological lymph nodes to <10 mm. TTR is derived for responders only.

End point type	Secondary

End point timeframe:

From the randomization date up to the date of the first confirmed CR or PR (up to 44 months)

End point values	Arm A: NIV+mFOLFOX +BEV	Arm B: mFOLFOX+BEV		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	77	36		
Units: Months				
median (standard deviation)	2.83 (± 2.51)	2.83 (± 1.34)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Objective Response per Blinded Independent Central Review (BICR)

End point title	Time to Objective Response per Blinded Independent Central Review (BICR)

End point description:

Time to objective response (TTR) is defined as the time from the randomization date to the date of the first confirmed complete response (CR) or partial response (PR) as assessed by BICR. PR is defined as at least a 30% decrease in the sum of diameters of target lesions. CR is defined as the disappearance of all target lesions and the reduction of any pathological lymph nodes to <10 mm. TTR is derived for responders only.

End point type	Secondary

End point timeframe:

From the randomization date up to the date of the first confirmed CR or PR (up to approximately 44 months)

End point values	Arm A: NIV+mFOLFOX +BEV	Arm B: mFOLFOX+BEV		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	77	31		
Units: Months				
median (standard deviation)	2.83 (± 1.51)	2.83 (± 1.45)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DoR) per Blinded Independent Central Review (BICR)

End point title	Duration of Response (DoR) per Blinded Independent Central Review (BICR)

End point description:

Duration of objective response (DoR) is defined as the time between the date of first confirmed complete response (CR) or partial response (PR) to the date of the first documented tumor progression as assessed by the BICR based on RECIST 1.1 criteria or death due to any cause, whichever occurs first. PR is defined as at least a 30% decrease in the sum of diameters of target lesions. CR is defined as the disappearance of all target lesions and the reduction of any pathological lymph nodes to <10 mm.

End point type	Secondary

End point timeframe:

From randomization up to the date of the first documented progression (per RECIST 1.1) or death due to any cause, whichever occurs first (up to 44 months)

End point values	Arm A: NIV+mFOLFOX +BEV	Arm B: mFOLFOX+BEV		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	77	31		
Units: Months				
median (confidence interval 95%)	12.88 (9.00 to 14.72)	9.26 (7.49 to 11.30)		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival (PFS) per Investigator Assessment

End point title	Progression Free Survival (PFS) per Investigator Assessment

End point description:

Progression Free Survival (PFS) is defined as the time from randomization to the date of the first documented progression, as determined by Investigator Assessment, or death due to any cause, whichever occurs first. Baseline tumor assessment is defined as tumor scans prior to or on randomization date. Participants who did not have documented progression per Investigator Assessment and who did not die or participants who started any subsequent anti-cancer therapy without a prior reported progression will be censored at the date of the last tumor assessment on or prior to initiation of the subsequent anticancer therapy, if any. Participants who die without a reported prior progression per Investigator Assessment will be considered to have progressed on the date of death. Participants who did not have any baseline or post baseline tumor assessments and did not die (or died after initiation of the subsequent anti-cancer therapy) will be censored at the randomization date.

End point type	Secondary

End point timeframe:

From randomization up to the date of the first documented progression (up to approximately 44 months)

End point values	Arm A: NIV+mFOLFOX +BEV	Arm B: mFOLFOX+BEV		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	127	68		
Units: Months				
median (confidence interval 95%)	13.77 (11.53 to 15.70)	12.19 (10.25 to 14.06)		

Statistical analyses

Statistical analysis title	PFS

Statistical analysis description:

Hazard Ratio is Arm A: NIV+mFOLFOX+BEV over Arm B: mFOLFOX+BEV

Comparison groups	Arm A: NIV+mFOLFOX+BEV v Arm B: mFOLFOX+BEV
Number of subjects included in analysis	195
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.54
upper limit	1.19

Secondary: Number of Participants With Adverse Events (AEs)

End point title	Number of Participants With Adverse Events (AEs)

End point description:

An Adverse Event (AE) is defined as any new untoward medical occurrence or worsening of a pre-existing medical condition in a clinical investigation participant administered study treatment and that does not necessarily have a causal relationship with this treatment. Adverse events are graded on a scale from 1 to 5, with Grade 1 being mild and asymptomatic; Grade 2 is moderate requiring minimal, local or noninvasive intervention; Grade 3 is severe or medically significant but not immediately life-threatening; Grade 4 events are usually severe enough to require hospitalization; Grade 5 events are fatal.

End point type	Secondary

End point timeframe:

From first dose to 30 days post last dose (up to 45 months)

End point values	Arm A: NIV+mFOLFOX +BEV	Arm B: mFOLFOX+BEV		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	123	62		
Units: Participants				
Any Grade	122	61		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Serious Adverse Events (SAEs)

End point title	Number of Participants With Serious Adverse Events (SAEs)

End point description:

Number of participants with any grade of serious adverse events (SAEs) graded by Common Terminology Criteria for Adverse Events (CTCAE v4.0) to determine safety and tolerability. SAE is defined as any untoward medical occurrence that, at any dose results in death, is life-threatening (defined as an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe), requires inpatient hospitalization or causes prolongation of existing hospitalization.

End point type	Secondary

End point timeframe:

From first dose to 30 days post last dose (up to 45 months)

End point values	Arm A: NIV+mFOLFOX +BEV	Arm B: mFOLFOX+BEV		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	123	62		
Units: Participants	57	20		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DoR) per Investigator Assessment

End point title	Duration of Response (DoR) per Investigator Assessment

End point description:

Duration of objective response (DoR) is defined as the time between the date of first confirmed complete response (CR) or partial response (PR) to the date of the first documented tumor progression as assessed by the investigator based on RECIST 1.1 criteria or death due to any cause, whichever occurs first. PR is defined as at least a 30% decrease in the sum of diameters of target lesions. CR is defined as the disappearance of all target lesions and the reduction of any pathological lymph nodes to

<10 mm.

End point type	Secondary

End point timeframe:

From randomization up to the date of the first documented progression (per RECIST 1.1) or death due to any cause, whichever occurs first (up to 44 months)

End point values	Arm A: NIV+mFOLFOX +BEV	Arm B: mFOLFOX+BEV		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	77	36		
Units: Months				
median (confidence interval 95%)	12.48 (8.87 to 16.72)	11.07 (9.43 to 17.31)		

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Control Rate (DCR) per Blinded Independent Central Review (BICR)

End point title	Disease Control Rate (DCR) per Blinded Independent Central Review (BICR)

End point description:

Disease Control Rate (DCR) is defined as the percentage of participants whose Best Overall Response (BOR) is complete response (CR) or partial response (PR) or stable disease (SD). CR is defined as the disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm. PR is defined as at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters. SD is defined as neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease, taking as reference the smallest sum diameters while on study.

End point type	Secondary

End point timeframe:

From the date of randomization up to the date of objectively documented progression or the date of subsequent anticancer therapy, whichever occurs first (up to approximately 44 months)

End point values	Arm A: NIV+mFOLFOX +BEV	Arm B: mFOLFOX+BEV		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	127	68		
Units: Percentage of participants				
number (confidence interval 95%)	91.3 (85.0 to 95.6)	83.8 (72.9 to 91.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Control Rate (DCR) per Investigator

End point title	Disease Control Rate (DCR) per Investigator

End point description:

Disease Control Rate (DCR) is defined as the percentage of participants whose Best Overall Response (BOR) is complete response (CR) or partial response (PR) or stable disease (SD). CR is defined as the disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm. PR is defined as at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters. SD is defined as neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease, taking as reference the smallest sum diameters while on study.

End point type	Secondary

End point timeframe:

From the date of randomization up to the date of objectively documented progression or the date of subsequent anticancer therapy, whichever occurs first (up to approximately 44 months)

End point values	Arm A: NIV+mFOLFOX +BEV	Arm B: mFOLFOX+BEV		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	127	68		
Units: Percentage of participants				
number (confidence interval 95%)	85.8 (85.0 to 95.6)	77.9 (66.2 to 87.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

Overall Survival (OS) is defined as the time between the date of randomization and the date of death. For those without documentation of death, OS will be censored on the last date the participant was known to be alive.

End point type	Secondary

End point timeframe:

From the date of randomization up to the date of death (up to 44 months)

End point values	Arm A: NIV+mFOLFOX +BEV	Arm B: mFOLFOX+BEV		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	127	68		
Units: Months				
median (confidence interval 95%)	30.52 (25.20 to 39.39)	31.77 (24.38 to 38.70)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Experiencing Death

End point title	Number of Participants Experiencing Death

End point description:

The number of participants who died during the treatment period

End point type	Secondary

End point timeframe:

From first dose up to 6 weeks post last dose (up to 46 months)

End point values	Arm A: NIV+mFOLFOX +BEV	Arm B: mFOLFOX+BEV		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	123	62		
Units: Participants	87	42		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Laboratory Abnormalities in Specific Liver Tests

End point title	Number of Participants with Laboratory Abnormalities in Specific Liver Tests

End point description:

The number of participants with laboratory abnormalities in specific liver tests based on SI conventional units. ALT = Alanine Aminotransferase AST = Aspartate Aminotransferase ULN = Upper Limit of Normal

End point type	Secondary

End point timeframe:

From first dose up to 30 days post last dose (up to 45 months)

End point values	Arm A: NIV+mFOLFOX +BEV	Arm B: mFOLFOX+BEV		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	123	62		
Units: Participants				
ALT OR AST > 3XULN	16	6		
ALT OR AST > 5XULN	7	2		
ALT OR AST > 10XULN	2	0		
ALT OR AST > 20XULN	0	0		
TOTAL BILIRUBIN > 2XULN	0	1		
ALP > 1.5XULN	39	20		
ALT/AST ELEV.>3XULN & TOT. BILIRUBIN>1.5XULN 1 DAY	2	1		
ALT/AST ELEV>3XULN &TOT. BILIRUBIN>1.5XULN 30 DAYS	2	1		
ALT/AST ELEV.>3XULN & TOT. BILIRUBIN>2XULN 1 DAY	0	1		
ALT/AST ELEV.>3XULN & TOT. BILIRUBIN>2XULN 30 DAYS	0	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Laboratory Abnormalities in Specific Thyroid Tests

End point title	Number of Participants with Laboratory Abnormalities in Specific Thyroid Tests

End point description:

The number of participants with laboratory abnormalities in specific thyroid tests based on SI conventional units. TSH = Thyroid Stimulating Hormone LLN = Lower Limit of Normal ULN = Upper Limit of Normal

End point type	Secondary

End point timeframe:

From first dose up to 30 days post last dose (up to 45 months)

End point values	Arm A: NIV+mFOLFOX +BEV	Arm B: mFOLFOX+BEV		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	123	60		
Units: Participants				
TSH > ULN	45	23		
TSH > ULN WITH TSH <= ULN AT BASELINE	37	16		
TSH > ULN WITH AT LEAST 1 FT3/FT4 TEST VALUE<LLN	20	2		
TSH > ULN WITH ALL OTHER FT3/FT4 TEST VALUES>=LLN	11	9		

TSH > ULN WITH FT3/FT4 TEST MISSING	14	12		
TSH < LLN	25	3		
TSH < LLN WITH TSH >= LLN AT BASELINE	22	3		
TSH < LLN WITH AT LEAST 1 FT3/FT4 TEST VALUE>ULN	13	0		
TSH < LLN WITH ALL OTHER FT3/FT4 TEST VALUES<=ULN	8	2		
TSH < LLN WITH FT3/FT4 TEST MISSING	4	1		

Statistical analyses

No statistical analyses for this end point

Post-hoc: Progression Free Survival (PFS) per Blinded Independent Central Review (BICR) - Extended Collection

End point title	Progression Free Survival (PFS) per Blinded Independent Central Review (BICR) - Extended Collection

End point description:

PFS is the time from randomization to the date of first documented progression, as determined by BICR, or death due to any cause, whichever occurs first. Baseline tumor assessment is defined as tumor scans prior to or on randomization date. Participants who did not have documented progression and did not die or participants who started any subsequent anti-cancer therapy without a prior reported progression were censored on date of last tumor assessment on or prior to initiation of the subsequent anticancer therapy, if any. Participants who died without prior progression were considered to have progressed on the date of death. Participants who did not have any baseline assessments and did not die (or died after initiation of the subsequent anti-cancer therapy) were censored at the randomization date. Note: This outcome measure represents an updated version of the primary endpoint to include additional data collection that has occurred after the primary completion date.

End point type	Post-hoc

End point timeframe:

From randomization to up to the date of the first documented progression (up to 44 months)

End point values	Arm A: NIV+mFOLFOX+BEV	Arm B: mFOLFOX+BEV		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	127	68		
Units: Months				
median (confidence interval 95%)	11.99 (9.99 to 15.74)	12.02 (10.25 to 13.37)		

Statistical analyses

Statistical analysis title	PFS

Statistical analysis description:

Hazard Ratio is Arm A: NIV+mFOLFOX+BEV over Arm B: mFOLFOX+BEV

Comparison groups	Arm A: NIV+mFOLFOX+BEV v Arm B: mFOLFOX+BEV

Number of subjects included in analysis	195
Analysis specification	Post-hoc
Analysis type	
P-value	= 0.5041 [3]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.88
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	0.67
upper limit	1.15

Notes:

[3] - Stratified regular log-rank test

Statistical analysis title	PFS

Statistical analysis description:

Hazard Ratio is Arm A: NIV+mFOLFOX+BEV over Arm B: mFOLFOX+BEV

Comparison groups	Arm A: NIV+mFOLFOX+BEV v Arm B: mFOLFOX+BEV
Number of subjects included in analysis	195
Analysis specification	Post-hoc
Analysis type	
P-value	= 0.5041 [4]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.88
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.58
upper limit	1.32

Notes:

[4] - Stratified regular log-rank test

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Participants were assessed for all-cause mortality from their randomization to study completion, (up to approximately 58 months). SAEs and Other AEs were assessed from first dose to 100 days following last dose (up to approximately 45 months)

Adverse event reporting additional description:

The number at Risk for All-Cause Mortality represents all Randomized Participants. The number at Risk for Serious Adverse Events and Other (Not Including Serious) Adverse Events represents all participants that received at least 1 dose of study medication

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25.1

Reporting groups

Reporting group title	mFOLFOX+BEV

Reporting group description:

mFOLFOX6/bevacizumab (SOC) every 2 weeks

Reporting group title	NIV+mFOLFOX+BEV

Reporting group description:

Nivolumab 240 mg + Standard of Care (SOC) mFOLFOX6/bevacizuma every 2 weeks

Serious adverse events	mFOLFOX+BEV	NIV+mFOLFOX+BEV	
Total subjects affected by serious adverse events			
subjects affected / exposed	25 / 62 (40.32%)	67 / 123 (54.47%)	
number of deaths (all causes)	42	87	
number of deaths resulting from adverse events	8	13	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Metastases to liver			
subjects affected / exposed	1 / 62 (1.61%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon cancer metastatic			
subjects affected / exposed	1 / 62 (1.61%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant neoplasm progression			

subjects affected / exposed	1 / 62 (1.61%)	6 / 123 (4.88%)	
occurrences causally related to treatment / all	0 / 1	0 / 6	
deaths causally related to treatment / all	0 / 1	0 / 6	
Metastases to ovary			
subjects affected / exposed	0 / 62 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to lung			
subjects affected / exposed	1 / 62 (1.61%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Orthostatic hypotension			
subjects affected / exposed	0 / 62 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	0 / 62 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	1 / 62 (1.61%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolism			
subjects affected / exposed	0 / 62 (0.00%)	1 / 123 (0.81%)	
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			
Asthenia			
subjects affected / exposed	0 / 62 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Death			
subjects affected / exposed	2 / 62 (3.23%)	2 / 123 (1.63%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 2	0 / 2	
Infusion site extravasation			
subjects affected / exposed	0 / 62 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	1 / 62 (1.61%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	0 / 62 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	1 / 62 (1.61%)	3 / 123 (2.44%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	0 / 62 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 62 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	1 / 62 (1.61%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pleural effusion			
subjects affected / exposed	0 / 62 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	0 / 62 (0.00%)	2 / 123 (1.63%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Pneumothorax			
subjects affected / exposed	0 / 62 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	2 / 62 (3.23%)	6 / 123 (4.88%)	
occurrences causally related to treatment / all	1 / 2	5 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			
subjects affected / exposed	1 / 62 (1.61%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 62 (1.61%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 62 (0.00%)	1 / 123 (0.81%)	
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 / 62 (1.61%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Blood potassium increased			
subjects affected / exposed	0 / 62 (0.00%)	1 / 123 (0.81%)	
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	1 / 62 (1.61%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelet count decreased			
subjects affected / exposed	0 / 62 (0.00%)	1 / 123 (0.81%)	
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			
Fall			
subjects affected / exposed	1 / 62 (1.61%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal anastomotic leak			
subjects affected / exposed	0 / 62 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incisional hernia			
subjects affected / exposed	1 / 62 (1.61%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thoracic vertebral fracture			
subjects affected / exposed	0 / 62 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Forearm fracture			
subjects affected / exposed	1 / 62 (1.61%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Stoma prolapse			
subjects affected / exposed	0 / 62 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Myocarditis			
subjects affected / exposed	0 / 62 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Myocardial infarction			
subjects affected / exposed	0 / 62 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intracardiac thrombus			
subjects affected / exposed	0 / 62 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	1 / 62 (1.61%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	1 / 1	0 / 1	
Tachycardia			
subjects affected / exposed	0 / 62 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Depressed level of consciousness			
subjects affected / exposed	1 / 62 (1.61%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Syncope			
subjects affected / exposed	0 / 62 (0.00%)	1 / 123 (0.81%)	
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	1 / 62 (1.61%)	6 / 123 (4.88%)	
occurrences causally related to treatment / all	1 / 1	5 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Autoimmune haemolytic anaemia			
subjects affected / exposed	0 / 62 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 62 (0.00%)	3 / 123 (2.44%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer			
subjects affected / exposed	0 / 62 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	0 / 62 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	0 / 62 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune-mediated enterocolitis			
subjects affected / exposed	0 / 62 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	1 / 62 (1.61%)	3 / 123 (2.44%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	

Intestinal perforation			
subjects affected / exposed	2 / 62 (3.23%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	1 / 2	1 / 1	
deaths causally related to treatment / all	1 / 2	0 / 0	
Large intestinal obstruction			
subjects affected / exposed	1 / 62 (1.61%)	2 / 123 (1.63%)	
occurrences causally related to treatment / all	1 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	1 / 62 (1.61%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	0 / 62 (0.00%)	9 / 123 (7.32%)	
occurrences causally related to treatment / all	0 / 0	11 / 12	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	0 / 62 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	1 / 62 (1.61%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	3 / 62 (4.84%)	5 / 123 (4.07%)	
occurrences causally related to treatment / all	1 / 3	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine perforation			
subjects affected / exposed	0 / 62 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mesenteric vein thrombosis			

subjects affected / exposed	1 / 62 (1.61%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower gastrointestinal haemorrhage			
subjects affected / exposed	0 / 62 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	0 / 62 (0.00%)	3 / 123 (2.44%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	0 / 62 (0.00%)	2 / 123 (1.63%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Proctalgia			
subjects affected / exposed	1 / 62 (1.61%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			
subjects affected / exposed	0 / 62 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal perforation			
subjects affected / exposed	0 / 62 (0.00%)	2 / 123 (1.63%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	0 / 62 (0.00%)	3 / 123 (2.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 1	
Upper gastrointestinal haemorrhage			

subjects affected / exposed	0 / 62 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 62 (0.00%)	3 / 123 (2.44%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	0 / 62 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal obstruction			
subjects affected / exposed	0 / 62 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatic lesion			
subjects affected / exposed	0 / 62 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangitis			
subjects affected / exposed	0 / 62 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Autoimmune hepatitis			
subjects affected / exposed	0 / 62 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 62 (0.00%)	1 / 123 (0.81%)	
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			
Back pain			
subjects affected / exposed	0 / 62 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abdominal abscess			
subjects affected / exposed	1 / 62 (1.61%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal infection			
subjects affected / exposed	1 / 62 (1.61%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess neck			
subjects affected / exposed	0 / 62 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile infection			
subjects affected / exposed	1 / 62 (1.61%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea infectious			
subjects affected / exposed	0 / 62 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	0 / 62 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocarditis bacterial			
subjects affected / exposed	0 / 62 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Gastroenteritis			
subjects affected / exposed	1 / 62 (1.61%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	1 / 62 (1.61%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal candidiasis			
subjects affected / exposed	0 / 62 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Perirectal abscess			
subjects affected / exposed	1 / 62 (1.61%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 62 (0.00%)	4 / 123 (3.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pneumonia pseudomonal			
subjects affected / exposed	0 / 62 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal abscess			
subjects affected / exposed	0 / 62 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 62 (1.61%)	6 / 123 (4.88%)	
occurrences causally related to treatment / all	0 / 1	3 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular device infection			

subjects affected / exposed	0 / 62 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 62 (1.61%)	0 / 123 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spontaneous bacterial peritonitis			
subjects affected / exposed	0 / 62 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Norovirus infection			
subjects affected / exposed	0 / 62 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 62 (0.00%)	1 / 123 (0.81%)	
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	0 / 62 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Failure to thrive			
subjects affected / exposed	0 / 62 (0.00%)	2 / 123 (1.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	0 / 62 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolic acidosis			

subjects affected / exposed	0 / 62 (0.00%)	1 / 123 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	mFOLFOX+BEV	NIV+mFOLFOX+BEV	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	61 / 62 (98.39%)	122 / 123 (99.19%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	12 / 62 (19.35%)	40 / 123 (32.52%)	
occurrences (all)	17	55	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	6 / 62 (9.68%)	22 / 123 (17.89%)	
occurrences (all)	11	34	
Chills			
subjects affected / exposed	1 / 62 (1.61%)	17 / 123 (13.82%)	
occurrences (all)	1	21	
Fatigue			
subjects affected / exposed	38 / 62 (61.29%)	73 / 123 (59.35%)	
occurrences (all)	47	99	
Influenza like illness			
subjects affected / exposed	1 / 62 (1.61%)	10 / 123 (8.13%)	
occurrences (all)	2	10	
Malaise			
subjects affected / exposed	3 / 62 (4.84%)	7 / 123 (5.69%)	
occurrences (all)	3	7	
Mucosal inflammation			
subjects affected / exposed	12 / 62 (19.35%)	15 / 123 (12.20%)	
occurrences (all)	14	20	
Non-cardiac chest pain			
subjects affected / exposed	4 / 62 (6.45%)	5 / 123 (4.07%)	
occurrences (all)	5	5	
Oedema peripheral			

subjects affected / exposed	2 / 62 (3.23%)	12 / 123 (9.76%)	
occurrences (all)	2	14	
Pain			
subjects affected / exposed	3 / 62 (4.84%)	8 / 123 (6.50%)	
occurrences (all)	3	11	
Pyrexia			
subjects affected / exposed	10 / 62 (16.13%)	35 / 123 (28.46%)	
occurrences (all)	13	53	
Temperature intolerance			
subjects affected / exposed	14 / 62 (22.58%)	32 / 123 (26.02%)	
occurrences (all)	16	35	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	2 / 62 (3.23%)	10 / 123 (8.13%)	
occurrences (all)	4	12	
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	4 / 62 (6.45%)	7 / 123 (5.69%)	
occurrences (all)	5	7	
Nasal congestion			
subjects affected / exposed	3 / 62 (4.84%)	8 / 123 (6.50%)	
occurrences (all)	5	14	
Hiccups			
subjects affected / exposed	6 / 62 (9.68%)	5 / 123 (4.07%)	
occurrences (all)	7	6	
Epistaxis			
subjects affected / exposed	13 / 62 (20.97%)	39 / 123 (31.71%)	
occurrences (all)	15	43	
Dyspnoea			
subjects affected / exposed	3 / 62 (4.84%)	26 / 123 (21.14%)	
occurrences (all)	3	32	
Dysphonia			
subjects affected / exposed	6 / 62 (9.68%)	16 / 123 (13.01%)	
occurrences (all)	6	17	
Cough			

subjects affected / exposed	10 / 62 (16.13%)	29 / 123 (23.58%)	
occurrences (all)	12	33	
Rhinorrhoea			
subjects affected / exposed	5 / 62 (8.06%)	9 / 123 (7.32%)	
occurrences (all)	6	10	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	10 / 62 (16.13%)	33 / 123 (26.83%)	
occurrences (all)	10	37	
Depression			
subjects affected / exposed	3 / 62 (4.84%)	13 / 123 (10.57%)	
occurrences (all)	3	14	
Anxiety			
subjects affected / exposed	2 / 62 (3.23%)	13 / 123 (10.57%)	
occurrences (all)	2	14	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	11 / 62 (17.74%)	19 / 123 (15.45%)	
occurrences (all)	12	32	
Aspartate aminotransferase increased			
subjects affected / exposed	10 / 62 (16.13%)	27 / 123 (21.95%)	
occurrences (all)	13	43	
Blood alkaline phosphatase increased			
subjects affected / exposed	5 / 62 (8.06%)	15 / 123 (12.20%)	
occurrences (all)	5	23	
Blood creatinine increased			
subjects affected / exposed	2 / 62 (3.23%)	11 / 123 (8.94%)	
occurrences (all)	3	19	
Neutrophil count decreased			
subjects affected / exposed	12 / 62 (19.35%)	39 / 123 (31.71%)	
occurrences (all)	46	86	
Platelet count decreased			
subjects affected / exposed	10 / 62 (16.13%)	25 / 123 (20.33%)	
occurrences (all)	20	52	
Weight decreased			

subjects affected / exposed	12 / 62 (19.35%)	18 / 123 (14.63%)	
occurrences (all)	14	19	
White blood cell count decreased			
subjects affected / exposed	5 / 62 (8.06%)	15 / 123 (12.20%)	
occurrences (all)	32	38	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 62 (1.61%)	11 / 123 (8.94%)	
occurrences (all)	1	11	
Infusion related reaction			
subjects affected / exposed	5 / 62 (8.06%)	27 / 123 (21.95%)	
occurrences (all)	6	41	
Cardiac disorders			
Tachycardia			
subjects affected / exposed	1 / 62 (1.61%)	7 / 123 (5.69%)	
occurrences (all)	1	8	
Nervous system disorders			
Taste disorder			
subjects affected / exposed	2 / 62 (3.23%)	8 / 123 (6.50%)	
occurrences (all)	3	8	
Peripheral sensory neuropathy			
subjects affected / exposed	28 / 62 (45.16%)	45 / 123 (36.59%)	
occurrences (all)	29	49	
Paraesthesia			
subjects affected / exposed	5 / 62 (8.06%)	11 / 123 (8.94%)	
occurrences (all)	5	13	
Neurotoxicity			
subjects affected / exposed	2 / 62 (3.23%)	12 / 123 (9.76%)	
occurrences (all)	5	16	
Neuropathy peripheral			
subjects affected / exposed	21 / 62 (33.87%)	54 / 123 (43.90%)	
occurrences (all)	25	76	
Hypoaesthesia			
subjects affected / exposed	6 / 62 (9.68%)	4 / 123 (3.25%)	
occurrences (all)	6	4	
Headache			

subjects affected / exposed	6 / 62 (9.68%)	25 / 123 (20.33%)	
occurrences (all)	6	40	
Dysgeusia			
subjects affected / exposed	12 / 62 (19.35%)	25 / 123 (20.33%)	
occurrences (all)	12	26	
Dizziness			
subjects affected / exposed	9 / 62 (14.52%)	22 / 123 (17.89%)	
occurrences (all)	9	25	
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	7 / 62 (11.29%)	26 / 123 (21.14%)	
occurrences (all)	10	33	
Neutropenia			
subjects affected / exposed	14 / 62 (22.58%)	45 / 123 (36.59%)	
occurrences (all)	18	81	
Anaemia			
subjects affected / exposed	12 / 62 (19.35%)	32 / 123 (26.02%)	
occurrences (all)	29	46	
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	3 / 62 (4.84%)	12 / 123 (9.76%)	
occurrences (all)	3	13	
Abdominal pain			
subjects affected / exposed	19 / 62 (30.65%)	40 / 123 (32.52%)	
occurrences (all)	26	51	
Abdominal distension			
subjects affected / exposed	2 / 62 (3.23%)	7 / 123 (5.69%)	
occurrences (all)	2	10	
Colitis			
subjects affected / exposed	1 / 62 (1.61%)	7 / 123 (5.69%)	
occurrences (all)	1	12	
Vomiting			
subjects affected / exposed	13 / 62 (20.97%)	49 / 123 (39.84%)	
occurrences (all)	14	87	
Toothache			

subjects affected / exposed	4 / 62 (6.45%)	5 / 123 (4.07%)	
occurrences (all)	4	8	
Stomatitis			
subjects affected / exposed	18 / 62 (29.03%)	28 / 123 (22.76%)	
occurrences (all)	19	40	
Proctalgia			
subjects affected / exposed	2 / 62 (3.23%)	12 / 123 (9.76%)	
occurrences (all)	2	18	
Nausea			
subjects affected / exposed	35 / 62 (56.45%)	83 / 123 (67.48%)	
occurrences (all)	51	152	
Haemorrhoids			
subjects affected / exposed	4 / 62 (6.45%)	6 / 123 (4.88%)	
occurrences (all)	5	7	
Gastrooesophageal reflux disease			
subjects affected / exposed	5 / 62 (8.06%)	7 / 123 (5.69%)	
occurrences (all)	5	7	
Dyspepsia			
subjects affected / exposed	6 / 62 (9.68%)	15 / 123 (12.20%)	
occurrences (all)	7	15	
Diarrhoea			
subjects affected / exposed	20 / 62 (32.26%)	74 / 123 (60.16%)	
occurrences (all)	32	149	
Constipation			
subjects affected / exposed	21 / 62 (33.87%)	52 / 123 (42.28%)	
occurrences (all)	29	80	
Dry mouth			
subjects affected / exposed	3 / 62 (4.84%)	15 / 123 (12.20%)	
occurrences (all)	3	18	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	6 / 62 (9.68%)	10 / 123 (8.13%)	
occurrences (all)	6	10	
Skin hyperpigmentation			
subjects affected / exposed	4 / 62 (6.45%)	9 / 123 (7.32%)	
occurrences (all)	4	10	

Rash maculo-papular			
subjects affected / exposed	0 / 62 (0.00%)	11 / 123 (8.94%)	
occurrences (all)	0	14	
Rash			
subjects affected / exposed	4 / 62 (6.45%)	14 / 123 (11.38%)	
occurrences (all)	5	17	
Pruritus			
subjects affected / exposed	2 / 62 (3.23%)	13 / 123 (10.57%)	
occurrences (all)	3	16	
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	8 / 62 (12.90%)	14 / 123 (11.38%)	
occurrences (all)	8	16	
Dry skin			
subjects affected / exposed	6 / 62 (9.68%)	17 / 123 (13.82%)	
occurrences (all)	6	17	
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	9 / 62 (14.52%)	18 / 123 (14.63%)	
occurrences (all)	21	33	
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	1 / 62 (1.61%)	7 / 123 (5.69%)	
occurrences (all)	1	7	
Hypothyroidism			
subjects affected / exposed	1 / 62 (1.61%)	21 / 123 (17.07%)	
occurrences (all)	1	22	
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	3 / 62 (4.84%)	21 / 123 (17.07%)	
occurrences (all)	3	21	
Myalgia			
subjects affected / exposed	3 / 62 (4.84%)	10 / 123 (8.13%)	
occurrences (all)	4	10	
Arthralgia			
subjects affected / exposed	9 / 62 (14.52%)	37 / 123 (30.08%)	
occurrences (all)	12	46	

Back pain			
subjects affected / exposed	9 / 62 (14.52%)	24 / 123 (19.51%)	
occurrences (all)	12	29	
Bone pain			
subjects affected / exposed	4 / 62 (6.45%)	5 / 123 (4.07%)	
occurrences (all)	4	5	
Muscle spasms			
subjects affected / exposed	0 / 62 (0.00%)	10 / 123 (8.13%)	
occurrences (all)	0	13	
Muscular weakness			
subjects affected / exposed	3 / 62 (4.84%)	11 / 123 (8.94%)	
occurrences (all)	3	12	
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	6 / 62 (9.68%)	17 / 123 (13.82%)	
occurrences (all)	7	23	
Urinary tract infection			
subjects affected / exposed	7 / 62 (11.29%)	14 / 123 (11.38%)	
occurrences (all)	8	23	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	16 / 62 (25.81%)	47 / 123 (38.21%)	
occurrences (all)	18	68	
Dehydration			
subjects affected / exposed	5 / 62 (8.06%)	26 / 123 (21.14%)	
occurrences (all)	5	37	
Hyperglycaemia			
subjects affected / exposed	2 / 62 (3.23%)	14 / 123 (11.38%)	
occurrences (all)	2	22	
Hypokalaemia			
subjects affected / exposed	5 / 62 (8.06%)	33 / 123 (26.83%)	
occurrences (all)	10	49	
Hyponatraemia			
subjects affected / exposed	1 / 62 (1.61%)	9 / 123 (7.32%)	
occurrences (all)	1	11	
Hypophosphataemia			

subjects affected / exposed occurrences (all)	6 / 62 (9.68%) 11	8 / 123 (6.50%) 11	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 February 2018	Updated Medical Monitor and added Study Director. Revisions to laboratory tests exclusion criteria, revisions to dose modification criteria, urinalysis and biomarker sample collection requirements. Deletion of iRECIST response assessment exploratory endpoint. Addition of a definition of DILI for participants with elevated liver function tests at baseline. Updated rationale for the 2-year treatment duration, in addition of a number of other minor changes and corrections.
06 August 2018	Updated Medical Monitor information. Revises prohibited and/or restricted treatments; laboratory tests, assessments, and other analyses; dose modification criteria; urinalysis; and biomarker sample collection requirements. Adds additional exploratory endpoint and clarifies eligibility criteria. Updates rationale to include additional mandated biopsies. Minor changes and corrections including revisions to reflect the most recent language for BMS studies.
13 September 2018	Adding Appendix 11 back into the document; reinstates exclusion criteria 2j
07 December 2018	Clarifies the infusion days for fluorouracil, updates Appendix 3, and aligns Appendix 4 with contraceptive guidance for nivolumab and other components of study treatment.
19 December 2019	This revised protocol removes Interim Analysis 2 (IA2).
02 June 2020	Major change: Clarifies study treatment duration for standard of care (SOC). SOC may continue, after the maximum treatment duration of 24 months for nivolumab, until progression, unacceptable toxicity, withdrawal of consent, or the end of the study, whichever comes first.
13 November 2020	Incorporates Administrative Letter 05 and allows the last patient last visit for the progression-free survival (PFS) final analysis to be triggered when at least 114 PFS events by blinded independent central review are observed or at approximately 20 months minimum follow-up, whichever occurs first.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported