Clinical trial results:
A Phase 3, Randomized, Double-Blind Study of Pamrevlumab or Placebo in combination with Gemcitabine Plus Nab-paclitaxel or FOLFIRINOX as Neoadjuvant Treatment in Patients with Locally Advanced, Unresectable Pancreatic Cancer

Summary

EudraCT number	2019-001925-28
Trial protocol	AT ES DE GB FR BE IT
Global end of trial date	11 June 2024

Results information

Result version number	v1 (current)
This version publication date	31 October 2024
First version publication date	31 October 2024

Trial information

Trial identification

Sponsor protocol code	FGCL-3019-087

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03941093
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	FibroGen, Inc.
Sponsor organisation address	409 Illinois Street, San Francisco, United States, CA 94158
Public contact	Clinical Trial Information Desk, FibroGen, Inc., lapis@fibrogen.com
Scientific contact	Clinical Trial Information Desk, FibroGen, Inc., lapis@fibrogen.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	19 July 2024
Is this the analysis of the primary completion data?	Yes
Primary completion date	11 June 2024
Global end of trial reached?	Yes
Global end of trial date	11 June 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this trial is to evaluate the efficacy and safety of neoadjuvant treatment with pamrevlumab in combination with either gemcitabine plus nab-paclitaxel or FOLFIRINOX when compared to treatment with placebo in combination with either gemcitabine plus nab-paclitaxel or FOLFIRINOX in locally advanced, unresectable pancreatic cancer.

Protection of trial subjects:

This trial was conducted according to the International Conference On Harmonization (ICH) Harmonized Tripartite Guideline in compliance with Good Clinical Practices (GCP), including the archiving of essential documents.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	10 May 2019
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 99
Country: Number of subjects enrolled	Canada: 17
Country: Number of subjects enrolled	France: 27
Country: Number of subjects enrolled	Italy: 24
Country: Number of subjects enrolled	Spain: 27
Country: Number of subjects enrolled	Belgium: 8
Country: Number of subjects enrolled	Israel: 4
Country: Number of subjects enrolled	Germany: 10
Country: Number of subjects enrolled	Austria: 4
Country: Number of subjects enrolled	United Kingdom: 11
Country: Number of subjects enrolled	Korea, Democratic People's Republic of: 32
Country: Number of subjects enrolled	China: 21
Worldwide total number of subjects	284
EEA total number of subjects	100

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)	140
From 65 to 84 years	143
85 years and over	1

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Participants were randomized in a 1:1 ratio to one of the 2 study treatment arms: Pamrevlumab with Gemcitabine/Nab-paclitaxel or FOLFIRINOX or Placebo with Gemcitabine/Nab-paclitaxel or FOLFIRINOX.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Pamrevlumab + Gemcitabine/Nab-paclitaxel or FOLFIRINOX

Arm description:

Participants received pamrevlumab in combination with one chemotherapy treatment regimen (gemcitabine plus nab-paclitaxel or FOLFIRINOX) over a 28-day cycle, for up to 6 cycles. Pamrevlumab was administered on Days 1, 8 and 15 of Treatment Cycle 1 and on Day 1 and 15 of each subsequent treatment cycle via intravenous (IV) infusion. Nab-paclitaxel was administered on Days 1, 8 and 15 of each 28-day treatment cycle via IV infusion. Gemcitabine was administered on Days 1, 8 and 15 of each 28-day treatment cycle via IV infusion. FOLFIRINOX was a combination of several agents administered on Days 1 and 15 of each 28-day treatment cycle via IV infusion. The specific agents were oxaliplatin, folinic acid, irinotecan, and fluorouracil.

Arm type	Experimental
Investigational medicinal product name	Pamrevlumab
Investigational medicinal product code	FG-3019
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Pamrevlumab was administered per schedule specified in the arm description.

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

Dosage and administration details:

FOLFIRINOX is a combination of several agents including Oxaliplatin, Folinic Acid, Irinotecan, and Fluorouracil. FOLFIRINOX was administered per schedule specified in the arm description.

Investigational medicinal product name	Gemcitabine plus Nab-paclitaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Gemcitabine plus nab-paclitaxel was administered per schedule specified in the arm description.

Arm title	Placebo + Gemcitabine/Nab-paclitaxel or FOLFIRINOX

Arm description:

Participants received pamrevlumab matched placebo in combination with one chemotherapy treatment regimen (gemcitabine plus nab-paclitaxel or FOLFIRINOX) over a 28-day cycle, for up to 6 cycles. Placebo was administered on Days 1, 8 and 15 of Treatment Cycle 1 and on Day 1 and 15 of each subsequent treatment cycle via IV infusion. Nab-paclitaxel was administered on Days 1, 8 and 15 of each 28-day treatment cycle via IV infusion. Gemcitabine was administered on Days 1, 8 and 15 of each 28-day treatment cycle via IV infusion. FOLFIRINOX was a combination of several agents administered on Days 1 and 15 of each 28-day treatment cycle via IV infusion. The specific agents were oxaliplatin, folinic acid, irinotecan, and fluorouracil.

Arm type	Experimental
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Placebo matched to pamrevlumab was administered per schedule specified in the arm description.

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

Dosage and administration details:

FOLFIRINOX is a combination of several agents including Oxaliplatin, Folinic Acid, Irinotecan, and Fluorouracil. FOLFIRINOX was administered per schedule specified in the arm description.

Investigational medicinal product name	Gemcitabine plus Nab-paclitaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Gemcitabine plus nab-paclitaxel was administered per schedule specified in the arm description.

Number of subjects in period 1	Pamrevlumab + Gemcitabine/Nab-paclitaxel or FOLFIRINOX	Placebo + Gemcitabine/Nab-paclitaxel or FOLFIRINOX
Started	143	141
Received At Least 1 Dose of Study Drug	142	141
Completed	134	134
Not completed	9	7
Consent withdrawn by subject	9	6
Protocol deviation	-	1

Baseline characteristics

Reporting groups

Reporting group title	Pamrevlumab + Gemcitabine/Nab-paclitaxel or FOLFIRINOX

Reporting group description:

Participants received pamrevlumab in combination with one chemotherapy treatment regimen (gemcitabine plus nab-paclitaxel or FOLFIRINOX) over a 28-day cycle, for up to 6 cycles. Pamrevlumab was administered on Days 1, 8 and 15 of Treatment Cycle 1 and on Day 1 and 15 of each subsequent treatment cycle via intravenous (IV) infusion. Nab-paclitaxel was administered on Days 1, 8 and 15 of each 28-day treatment cycle via IV infusion. Gemcitabine was administered on Days 1, 8 and 15 of each 28-day treatment cycle via IV infusion. FOLFIRINOX was a combination of several agents administered on Days 1 and 15 of each 28-day treatment cycle via IV infusion. The specific agents were oxaliplatin, folinic acid, irinotecan, and fluorouracil.

Reporting group title	Placebo + Gemcitabine/Nab-paclitaxel or FOLFIRINOX

Reporting group description:

Participants received pamrevlumab matched placebo in combination with one chemotherapy treatment regimen (gemcitabine plus nab-paclitaxel or FOLFIRINOX) over a 28-day cycle, for up to 6 cycles. Placebo was administered on Days 1, 8 and 15 of Treatment Cycle 1 and on Day 1 and 15 of each subsequent treatment cycle via IV infusion. Nab-paclitaxel was administered on Days 1, 8 and 15 of each 28-day treatment cycle via IV infusion. Gemcitabine was administered on Days 1, 8 and 15 of each 28-day treatment cycle via IV infusion. FOLFIRINOX was a combination of several agents administered on Days 1 and 15 of each 28-day treatment cycle via IV infusion. The specific agents were oxaliplatin, folinic acid, irinotecan, and fluorouracil.

Reporting group values	Pamrevlumab + Gemcitabine/Nab-paclitaxel or FOLFIRINOX	Placebo + Gemcitabine/Nab-paclitaxel or FOLFIRINOX	Total
Number of subjects	143	141	284
Age categorical Units: Subjects			
Age Continuous Units: years			
arithmetic mean	64.5	64.5	
standard deviation	± 9.54	± 9.60	-
Sex: Female, Male Units: participants			
Female	61	72	133
Male	82	69	151
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	2	2
Asian	25	35	60
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	5	5	10
White	96	79	175
More than one race	0	0	0
Unknown or Not Reported	17	20	37
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	10	2	12
Not Hispanic or Latino	122	124	246

Unknown or Not Reported	11	15	26

End points

End points reporting groups

Reporting group title	Pamrevlumab + Gemcitabine/Nab-paclitaxel or FOLFIRINOX

Reporting group description:

Participants received pamrevlumab in combination with one chemotherapy treatment regimen (gemcitabine plus nab-paclitaxel or FOLFIRINOX) over a 28-day cycle, for up to 6 cycles. Pamrevlumab was administered on Days 1, 8 and 15 of Treatment Cycle 1 and on Day 1 and 15 of each subsequent treatment cycle via intravenous (IV) infusion. Nab-paclitaxel was administered on Days 1, 8 and 15 of each 28-day treatment cycle via IV infusion. Gemcitabine was administered on Days 1, 8 and 15 of each 28-day treatment cycle via IV infusion. FOLFIRINOX was a combination of several agents administered on Days 1 and 15 of each 28-day treatment cycle via IV infusion. The specific agents were oxaliplatin, folinic acid, irinotecan, and fluorouracil.

Reporting group title	Placebo + Gemcitabine/Nab-paclitaxel or FOLFIRINOX

Reporting group description:

Participants received pamrevlumab matched placebo in combination with one chemotherapy treatment regimen (gemcitabine plus nab-paclitaxel or FOLFIRINOX) over a 28-day cycle, for up to 6 cycles. Placebo was administered on Days 1, 8 and 15 of Treatment Cycle 1 and on Day 1 and 15 of each subsequent treatment cycle via IV infusion. Nab-paclitaxel was administered on Days 1, 8 and 15 of each 28-day treatment cycle via IV infusion. Gemcitabine was administered on Days 1, 8 and 15 of each 28-day treatment cycle via IV infusion. FOLFIRINOX was a combination of several agents administered on Days 1 and 15 of each 28-day treatment cycle via IV infusion. The specific agents were oxaliplatin, folinic acid, irinotecan, and fluorouracil.

Primary: Overall Survival

End point title	Overall Survival

End point description:

Overall survival was defined as the time from date of randomization to date of death due to any cause. Overall survival was calculated using the Kaplan-Meier method. The intent-to-treat (ITT) population included all randomized participants regardless of whether or not study treatment was received.

End point type	Primary

End point timeframe:

Up to approximately 5 years

End point values	Pamrevlumab + Gemcitabine/Nab-paclitaxel or FOLFIRINOX	Placebo + Gemcitabine/Nab-paclitaxel or FOLFIRINOX		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	143	141		
Units: months				
median (confidence interval 95%)	17.25 (15.47 to 18.89)	17.94 (14.59 to 20.34)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Pamrevlumab + Gemcitabine/Nab-paclitaxel or FOLFIRINOX v

	Placebo + Gemcitabine/Nab-paclitaxel or FOLFIRINOX
Number of subjects included in analysis	284
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.5487
Method	Stratified Log Rank Test
Parameter estimate	Hazard ratio (HR)
Point estimate	1.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.83
upper limit	1.41

Secondary: Progression-free Survival (PFS) as Assessed Using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1

End point title	Progression-free Survival (PFS) as Assessed Using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1

End point description:

The PFS was defined as time from date of randomization until disease progression or death due to any cause, whichever occurred first. PFS was calculated using the Kaplan-Meier method. Progression was defined as at least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study. In addition to the relative increase of 20%, the sum must also have demonstrated an absolute increase of at least 5 millimeters (mm). Unequivocal progression of existing non-target lesions and the appearance of one or more new lesions was also considered progression. The ITT population included all randomized participants regardless of whether or not study treatment was received.

End point type	Secondary

End point timeframe:

Up to approximately 5 years

End point values	Pamrevlumab + Gemcitabine/Nab-paclitaxel or FOLFIRINOX	Placebo + Gemcitabine/Nab-paclitaxel or FOLFIRINOX		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	143	141		
Units: months				
median (confidence interval 95%)	9.36 (7.75 to 11.79)	9.40 (7.69 to 10.84)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Best Overall Objective Response as Assessed Using RECIST v1.1

End point title	Number of Participants With Best Overall Objective Response as Assessed Using RECIST v1.1

End point description:

Best overall objective response was defined as a complete response (CR) or partial response (PR). CR was defined as disappearance of all target or non-target lesions and normalization of tumor marker level (for non-target lesions), any pathological lymph nodes (whether target or non-target) must have reduced in short axis to <10 mm. PR was defined as at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters. The ITT population included all randomized participants regardless of whether or not study treatment was received.

End point type	Secondary

End point timeframe:

Up to approximately 5 years

End point values	Pamrevlumab + Gemcitabine/Nab-paclitaxel or FOLFIRINOX	Placebo + Gemcitabine/Nab-paclitaxel or FOLFIRINOX		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	143	141		
Units: participants	43	64		

Statistical analyses

No statistical analyses for this end point

Secondary: Event-free Survival (EFS)

End point title	Event-free Survival (EFS)

End point description:

The EFS endpoint was a composite time-to-event endpoint. The event being analyzed (‘treatment failure’) was defined as the earliest occurrence of: a) failure to achieve disease-free status locally after completion of neoadjuvant treatment and/or after surgery (that is, resection failure or progression that precludes surgery); b) local or distant recurrence, or c) death. The EFS was calculated using the Kaplan-Meier method. The ITT population included all randomized participants regardless of whether or not study treatment was received.

End point type	Secondary

End point timeframe:

Up to approximately 5 years

End point values	Pamrevlumab + Gemcitabine/Nab-paclitaxel or FOLFIRINOX	Placebo + Gemcitabine/Nab-paclitaxel or FOLFIRINOX		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	143	141		
Units: months				
median (confidence interval 95%)	5.72 (5.59 to 6.01)	5.78 (5.62 to 6.37)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to approximately 5 years

Adverse event reporting additional description:

Per planned analysis all-cause mortality data were collected and reported for all randomized participants. Adverse events (serious and other) were collected and reported for all randomized participants who received study drug.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	26.0

Reporting groups

Reporting group title	Placebo + Gemcitabine/Nab-paclitaxel or FOLFIRINOX

Reporting group description:

Participants received pamrevlumab matched placebo in combination with one chemotherapy treatment regimen (gemcitabine plus nab-paclitaxel or FOLFIRINOX) over a 28-day cycle, for up to 6 cycles. Placebo was administered on Days 1, 8 and 15 of Treatment Cycle 1 and on Day 1 and 15 of each subsequent treatment cycle via IV infusion. Nab-paclitaxel was administered on Days 1, 8 and 15 of each 28-day treatment cycle via IV infusion. Gemcitabine was administered on Days 1, 8 and 15 of each 28-day treatment cycle via IV infusion. FOLFIRINOX was a combination of several agents administered on Days 1 and 15 of each 28-day treatment cycle via IV infusion. The specific agents were oxaliplatin, folinic acid, irinotecan, and fluorouracil.

Reporting group title	Pamrevlumab + Gemcitabine/Nab-paclitaxel or FOLFIRINOX

Reporting group description:

Participants received pamrevlumab in combination with one chemotherapy treatment regimen (gemcitabine plus nab-paclitaxel or FOLFIRINOX) over a 28-day cycle, for up to 6 cycles. Pamrevlumab was administered on Days 1, 8 and 15 of Treatment Cycle 1 and on Day 1 and 15 of each subsequent treatment cycle via IV infusion. Nab-paclitaxel was administered on Days 1, 8 and 15 of each 28-day treatment cycle via IV infusion. Gemcitabine was administered on Days 1, 8 and 15 of each 28-day treatment cycle via IV infusion. FOLFIRINOX was a combination of several agents administered on Days 1 and 15 of each 28-day treatment cycle via IV infusion. The specific agents were oxaliplatin, folinic acid, irinotecan, and fluorouracil.

Serious adverse events	Placebo + Gemcitabine/Nab-paclitaxel or FOLFIRINOX	Pamrevlumab + Gemcitabine/Nab-paclitaxel or FOLFIRINOX	
Total subjects affected by serious adverse events			
subjects affected / exposed	62 / 141 (43.97%)	75 / 142 (52.82%)	
number of deaths (all causes)	112	118	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant neoplasm progression			
subjects affected / exposed	2 / 141 (1.42%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cancer pain			

subjects affected / exposed	0 / 141 (0.00%)	2 / 142 (1.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 141 (0.00%)	1 / 142 (0.70%)	
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	2 / 141 (1.42%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	2 / 141 (1.42%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shock haemorrhagic			
subjects affected / exposed	1 / 141 (0.71%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous thrombosis limb			
subjects affected / exposed	1 / 141 (0.71%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	1 / 141 (0.71%)	1 / 142 (0.70%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypothermia			
subjects affected / exposed	0 / 141 (0.00%)	1 / 142 (0.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Death			
subjects affected / exposed	0 / 141 (0.00%)	1 / 142 (0.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthenia			
subjects affected / exposed	0 / 141 (0.00%)	3 / 142 (2.11%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	6 / 141 (4.26%)	5 / 142 (3.52%)	
occurrences causally related to treatment / all	2 / 6	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	1 / 141 (0.71%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pneumonitis			
subjects affected / exposed	1 / 141 (0.71%)	3 / 142 (2.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspiration			
subjects affected / exposed	0 / 141 (0.00%)	2 / 142 (1.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory distress syndrome			
subjects affected / exposed	0 / 141 (0.00%)	1 / 142 (0.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory failure			
subjects affected / exposed	0 / 141 (0.00%)	1 / 142 (0.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pulmonary oedema			
subjects affected / exposed	1 / 141 (0.71%)	1 / 142 (0.70%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	0 / 141 (0.00%)	1 / 142 (0.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	2 / 141 (1.42%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung disorder			
subjects affected / exposed	1 / 141 (0.71%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 141 (0.71%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	1 / 141 (0.71%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Anxiety disorder			
subjects affected / exposed	1 / 141 (0.71%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Device occlusion			
subjects affected / exposed	2 / 141 (1.42%)	1 / 142 (0.70%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Investigations			
Neutrophil count decreased			
subjects affected / exposed	2 / 141 (1.42%)	1 / 142 (0.70%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelet count decreased			
subjects affected / exposed	1 / 141 (0.71%)	1 / 142 (0.70%)	
occurrences causally related to treatment / all	2 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood bilirubin increased			
subjects affected / exposed	1 / 141 (0.71%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 141 (0.00%)	1 / 142 (0.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	0 / 141 (0.00%)	1 / 142 (0.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haemorrhage			
subjects affected / exposed	1 / 141 (0.71%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural fistula			
subjects affected / exposed	1 / 141 (0.71%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural fever			
subjects affected / exposed	1 / 141 (0.71%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Anastomotic complication			
subjects affected / exposed	1 / 141 (0.71%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint dislocation			
subjects affected / exposed	0 / 141 (0.00%)	1 / 142 (0.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	1 / 141 (0.71%)	1 / 142 (0.70%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal compression fracture			
subjects affected / exposed	1 / 141 (0.71%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Hydrocele			
subjects affected / exposed	0 / 141 (0.00%)	1 / 142 (0.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 141 (0.00%)	1 / 142 (0.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	0 / 141 (0.00%)	1 / 142 (0.70%)	
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	0 / 141 (0.00%)	1 / 142 (0.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Cardiac failure			
subjects affected / exposed	1 / 141 (0.71%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Syncope			
subjects affected / exposed	0 / 141 (0.00%)	1 / 142 (0.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalopathy			
subjects affected / exposed	0 / 141 (0.00%)	1 / 142 (0.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	0 / 141 (0.00%)	1 / 142 (0.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	0 / 141 (0.00%)	1 / 142 (0.70%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuropathy peripheral			
subjects affected / exposed	1 / 141 (0.71%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	2 / 141 (1.42%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	1 / 141 (0.71%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Haemolytic uraemic syndrome			
subjects affected / exposed	0 / 141 (0.00%)	1 / 142 (0.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	2 / 141 (1.42%)	4 / 142 (2.82%)	
occurrences causally related to treatment / all	1 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			
subjects affected / exposed	0 / 141 (0.00%)	2 / 142 (1.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Colitis			
subjects affected / exposed	0 / 141 (0.00%)	4 / 142 (2.82%)	
occurrences causally related to treatment / all	0 / 0	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	3 / 141 (2.13%)	4 / 142 (2.82%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	0 / 141 (0.00%)	1 / 142 (0.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			
subjects affected / exposed	0 / 141 (0.00%)	1 / 142 (0.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal ischaemia			
subjects affected / exposed	0 / 141 (0.00%)	1 / 142 (0.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jejunal perforation			

subjects affected / exposed	0 / 141 (0.00%)	1 / 142 (0.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obstruction gastric			
subjects affected / exposed	0 / 141 (0.00%)	1 / 142 (0.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Varices oesophageal			
subjects affected / exposed	0 / 141 (0.00%)	1 / 142 (0.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorder			
subjects affected / exposed	0 / 141 (0.00%)	1 / 142 (0.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis			
subjects affected / exposed	2 / 141 (1.42%)	1 / 142 (0.70%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	0 / 141 (0.00%)	1 / 142 (0.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer			
subjects affected / exposed	0 / 141 (0.00%)	1 / 142 (0.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal obstruction			
subjects affected / exposed	0 / 141 (0.00%)	1 / 142 (0.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			

subjects affected / exposed	0 / 141 (0.00%)	1 / 142 (0.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	1 / 141 (0.71%)	1 / 142 (0.70%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal adhesions			
subjects affected / exposed	1 / 141 (0.71%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	4 / 141 (2.84%)	2 / 142 (1.41%)	
occurrences causally related to treatment / all	1 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	6 / 141 (4.26%)	3 / 142 (2.11%)	
occurrences causally related to treatment / all	2 / 6	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	3 / 141 (2.13%)	4 / 142 (2.82%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 141 (0.00%)	2 / 142 (1.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 141 (0.71%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal distension			

subjects affected / exposed	1 / 141 (0.71%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematemesis			
subjects affected / exposed	1 / 141 (0.71%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal haemorrhage			
subjects affected / exposed	1 / 141 (0.71%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	2 / 141 (1.42%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatic fistula			
subjects affected / exposed	1 / 141 (0.71%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	0 / 141 (0.00%)	1 / 142 (0.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaundice cholestatic			
subjects affected / exposed	1 / 141 (0.71%)	2 / 142 (1.41%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gallbladder rupture			
subjects affected / exposed	0 / 141 (0.00%)	2 / 142 (1.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			

subjects affected / exposed	0 / 141 (0.00%)	2 / 142 (1.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biliary obstruction			
subjects affected / exposed	5 / 141 (3.55%)	3 / 142 (2.11%)	
occurrences causally related to treatment / all	0 / 5	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangitis			
subjects affected / exposed	8 / 141 (5.67%)	7 / 142 (4.93%)	
occurrences causally related to treatment / all	0 / 8	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperbilirubinaemia			
subjects affected / exposed	1 / 141 (0.71%)	1 / 142 (0.70%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver injury			
subjects affected / exposed	1 / 141 (0.71%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic cytolysis			
subjects affected / exposed	1 / 141 (0.71%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangitis acute			
subjects affected / exposed	1 / 141 (0.71%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant biliary obstruction			
subjects affected / exposed	0 / 141 (0.00%)	1 / 142 (0.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Erythema			

subjects affected / exposed	0 / 141 (0.00%)	1 / 142 (0.70%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash			
subjects affected / exposed	0 / 141 (0.00%)	1 / 142 (0.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash maculo-papular			
subjects affected / exposed	0 / 141 (0.00%)	1 / 142 (0.70%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pseudocellulitis			
subjects affected / exposed	1 / 141 (0.71%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Urinary retention			
subjects affected / exposed	1 / 141 (0.71%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
subjects affected / exposed	1 / 141 (0.71%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal injury			
subjects affected / exposed	0 / 141 (0.00%)	1 / 142 (0.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute kidney injury			
subjects affected / exposed	2 / 141 (1.42%)	4 / 142 (2.82%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			

Spinal osteoarthritis			
subjects affected / exposed	0 / 141 (0.00%)	1 / 142 (0.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular weakness			
subjects affected / exposed	0 / 141 (0.00%)	1 / 142 (0.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	0 / 141 (0.00%)	1 / 142 (0.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Enterocolitis infectious			
subjects affected / exposed	0 / 141 (0.00%)	1 / 142 (0.70%)	
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	0 / 141 (0.00%)	1 / 142 (0.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis infective			
subjects affected / exposed	3 / 141 (2.13%)	1 / 142 (0.70%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangitis infective			
subjects affected / exposed	0 / 141 (0.00%)	1 / 142 (0.70%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheter site infection			
subjects affected / exposed	0 / 141 (0.00%)	1 / 142 (0.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biliary tract infection			

subjects affected / exposed	0 / 141 (0.00%)	1 / 142 (0.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			
subjects affected / exposed	0 / 141 (0.00%)	1 / 142 (0.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumocystis jirovecii pneumonia			
subjects affected / exposed	0 / 141 (0.00%)	2 / 142 (1.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver abscess			
subjects affected / exposed	3 / 141 (2.13%)	2 / 142 (1.41%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	4 / 141 (2.84%)	5 / 142 (3.52%)	
occurrences causally related to treatment / all	0 / 4	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 141 (0.71%)	7 / 142 (4.93%)	
occurrences causally related to treatment / all	0 / 1	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia sepsis			
subjects affected / exposed	1 / 141 (0.71%)	1 / 142 (0.70%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	0 / 141 (0.00%)	1 / 142 (0.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic sepsis			

subjects affected / exposed	0 / 141 (0.00%)	1 / 142 (0.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parainfluenzae virus infection			
subjects affected / exposed	0 / 141 (0.00%)	1 / 142 (0.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural infection			
subjects affected / exposed	1 / 141 (0.71%)	1 / 142 (0.70%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	1 / 141 (0.71%)	1 / 142 (0.70%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tongue fungal infection			
subjects affected / exposed	0 / 141 (0.00%)	1 / 142 (0.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 141 (0.71%)	1 / 142 (0.70%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19			
subjects affected / exposed	1 / 141 (0.71%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	1 / 141 (0.71%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			

subjects affected / exposed	1 / 141 (0.71%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	1 / 141 (0.71%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal sepsis			
subjects affected / exposed	1 / 141 (0.71%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Streptococcal bacteraemia			
subjects affected / exposed	1 / 141 (0.71%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	1 / 141 (0.71%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hypophosphataemia			
subjects affected / exposed	1 / 141 (0.71%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	0 / 141 (0.00%)	3 / 142 (2.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	1 / 141 (0.71%)	2 / 142 (1.41%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Decreased appetite			

subjects affected / exposed	0 / 141 (0.00%)	1 / 142 (0.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malnutrition			
subjects affected / exposed	1 / 141 (0.71%)	1 / 142 (0.70%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperlipidaemia			
subjects affected / exposed	1 / 141 (0.71%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	2 / 141 (1.42%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypomagnesaemia			
subjects affected / exposed	1 / 141 (0.71%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo + Gemcitabine/Nab-paclitaxel or FOLFIRINOX	Pamrevlumab + Gemcitabine/Nab-paclitaxel or FOLFIRINOX	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	140 / 141 (99.29%)	139 / 142 (97.89%)	
Vascular disorders			
Hypotension			
subjects affected / exposed	13 / 141 (9.22%)	16 / 142 (11.27%)	
occurrences (all)	15	17	
Hypertension			
subjects affected / exposed	8 / 141 (5.67%)	5 / 142 (3.52%)	
occurrences (all)	8	12	
General disorders and administration site conditions			

Fatigue			
subjects affected / exposed	76 / 141 (53.90%)	84 / 142 (59.15%)	
occurrences (all)	164	178	
Oedema peripheral			
subjects affected / exposed	52 / 141 (36.88%)	44 / 142 (30.99%)	
occurrences (all)	75	59	
Asthenia			
subjects affected / exposed	27 / 141 (19.15%)	27 / 142 (19.01%)	
occurrences (all)	45	68	
Pyrexia			
subjects affected / exposed	30 / 141 (21.28%)	30 / 142 (21.13%)	
occurrences (all)	64	60	
Chills			
subjects affected / exposed	11 / 141 (7.80%)	10 / 142 (7.04%)	
occurrences (all)	17	15	
Influenza like illness			
subjects affected / exposed	8 / 141 (5.67%)	4 / 142 (2.82%)	
occurrences (all)	19	5	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	18 / 141 (12.77%)	17 / 142 (11.97%)	
occurrences (all)	31	28	
Pulmonary embolism			
subjects affected / exposed	5 / 141 (3.55%)	8 / 142 (5.63%)	
occurrences (all)	5	8	
Epistaxis			
subjects affected / exposed	14 / 141 (9.93%)	12 / 142 (8.45%)	
occurrences (all)	18	19	
Cough			
subjects affected / exposed	21 / 141 (14.89%)	10 / 142 (7.04%)	
occurrences (all)	25	12	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	20 / 141 (14.18%)	16 / 142 (11.27%)	
occurrences (all)	25	16	
Anxiety			

subjects affected / exposed	10 / 141 (7.09%)	6 / 142 (4.23%)	
occurrences (all)	11	6	
Depression			
subjects affected / exposed	8 / 141 (5.67%)	4 / 142 (2.82%)	
occurrences (all)	10	5	
Investigations			
Neutrophil count decreased			
subjects affected / exposed	56 / 141 (39.72%)	51 / 142 (35.92%)	
occurrences (all)	170	128	
White blood cell count decreased			
subjects affected / exposed	28 / 141 (19.86%)	24 / 142 (16.90%)	
occurrences (all)	130	64	
Alanine aminotransferase increased			
subjects affected / exposed	19 / 141 (13.48%)	19 / 142 (13.38%)	
occurrences (all)	25	31	
Weight decreased			
subjects affected / exposed	18 / 141 (12.77%)	19 / 142 (13.38%)	
occurrences (all)	26	29	
Aspartate aminotransferase increased			
subjects affected / exposed	12 / 141 (8.51%)	17 / 142 (11.97%)	
occurrences (all)	24	29	
Platelet count decreased			
subjects affected / exposed	43 / 141 (30.50%)	36 / 142 (25.35%)	
occurrences (all)	131	125	
Blood alkaline phosphatase increased			
subjects affected / exposed	9 / 141 (6.38%)	8 / 142 (5.63%)	
occurrences (all)	15	18	
Blood creatinine increased			
subjects affected / exposed	4 / 141 (2.84%)	9 / 142 (6.34%)	
occurrences (all)	5	14	
Lymphocyte count decreased			
subjects affected / exposed	18 / 141 (12.77%)	5 / 142 (3.52%)	
occurrences (all)	106	23	
Injury, poisoning and procedural complications			

Fall			
subjects affected / exposed	7 / 141 (4.96%)	10 / 142 (7.04%)	
occurrences (all)	9	13	
Nervous system disorders			
Dysgeusia			
subjects affected / exposed	26 / 141 (18.44%)	23 / 142 (16.20%)	
occurrences (all)	34	30	
Peripheral sensory neuropathy			
subjects affected / exposed	29 / 141 (20.57%)	23 / 142 (16.20%)	
occurrences (all)	53	31	
Paraesthesia			
subjects affected / exposed	18 / 141 (12.77%)	17 / 142 (11.97%)	
occurrences (all)	30	38	
Neuropathy peripheral			
subjects affected / exposed	26 / 141 (18.44%)	30 / 142 (21.13%)	
occurrences (all)	41	59	
Headache			
subjects affected / exposed	18 / 141 (12.77%)	15 / 142 (10.56%)	
occurrences (all)	29	22	
Dizziness			
subjects affected / exposed	22 / 141 (15.60%)	9 / 142 (6.34%)	
occurrences (all)	29	10	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	67 / 141 (47.52%)	54 / 142 (38.03%)	
occurrences (all)	260	159	
Thrombocytopenia			
subjects affected / exposed	23 / 141 (16.31%)	18 / 142 (12.68%)	
occurrences (all)	51	52	
Neutropenia			
subjects affected / exposed	30 / 141 (21.28%)	31 / 142 (21.83%)	
occurrences (all)	73	62	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	73 / 141 (51.77%)	68 / 142 (47.89%)	
occurrences (all)	138	130	
Diarrhoea			

subjects affected / exposed	90 / 141 (63.83%)	81 / 142 (57.04%)	
occurrences (all)	214	177	
Stomatitis			
subjects affected / exposed	25 / 141 (17.73%)	25 / 142 (17.61%)	
occurrences (all)	37	34	
Abdominal pain upper			
subjects affected / exposed	15 / 141 (10.64%)	16 / 142 (11.27%)	
occurrences (all)	16	20	
Abdominal pain			
subjects affected / exposed	36 / 141 (25.53%)	34 / 142 (23.94%)	
occurrences (all)	68	55	
Vomiting			
subjects affected / exposed	40 / 141 (28.37%)	38 / 142 (26.76%)	
occurrences (all)	67	58	
Constipation			
subjects affected / exposed	39 / 141 (27.66%)	38 / 142 (26.76%)	
occurrences (all)	60	56	
Haemorrhoids			
subjects affected / exposed	10 / 141 (7.09%)	7 / 142 (4.93%)	
occurrences (all)	12	9	
Gastrooesophageal reflux disease			
subjects affected / exposed	4 / 141 (2.84%)	9 / 142 (6.34%)	
occurrences (all)	6	9	
Abdominal distension			
subjects affected / exposed	10 / 141 (7.09%)	13 / 142 (9.15%)	
occurrences (all)	10	15	
Dyspepsia			
subjects affected / exposed	6 / 141 (4.26%)	11 / 142 (7.75%)	
occurrences (all)	8	12	
Dry mouth			
subjects affected / exposed	6 / 141 (4.26%)	10 / 142 (7.04%)	
occurrences (all)	8	11	
Flatulence			
subjects affected / exposed	6 / 141 (4.26%)	9 / 142 (6.34%)	
occurrences (all)	6	9	
Skin and subcutaneous tissue disorders			

Alopecia			
subjects affected / exposed	57 / 141 (40.43%)	53 / 142 (37.32%)	
occurrences (all)	69	62	
Rash			
subjects affected / exposed	11 / 141 (7.80%)	18 / 142 (12.68%)	
occurrences (all)	12	22	
Dry skin			
subjects affected / exposed	6 / 141 (4.26%)	8 / 142 (5.63%)	
occurrences (all)	11	8	
Pruritus			
subjects affected / exposed	17 / 141 (12.06%)	14 / 142 (9.86%)	
occurrences (all)	21	25	
Rash maculo-papular			
subjects affected / exposed	12 / 141 (8.51%)	12 / 142 (8.45%)	
occurrences (all)	20	17	
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	10 / 141 (7.09%)	3 / 142 (2.11%)	
occurrences (all)	10	4	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	18 / 141 (12.77%)	14 / 142 (9.86%)	
occurrences (all)	20	18	
Back pain			
subjects affected / exposed	17 / 141 (12.06%)	13 / 142 (9.15%)	
occurrences (all)	21	14	
Pain in extremity			
subjects affected / exposed	14 / 141 (9.93%)	6 / 142 (4.23%)	
occurrences (all)	17	8	
Muscular weakness			
subjects affected / exposed	16 / 141 (11.35%)	6 / 142 (4.23%)	
occurrences (all)	23	6	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	48 / 141 (34.04%)	50 / 142 (35.21%)	
occurrences (all)	73	93	

Hypokalaemia			
subjects affected / exposed	33 / 141 (23.40%)	18 / 142 (12.68%)	
occurrences (all)	64	33	
Hypoalbuminaemia			
subjects affected / exposed	14 / 141 (9.93%)	7 / 142 (4.93%)	
occurrences (all)	36	10	
Hyperglycaemia			
subjects affected / exposed	9 / 141 (6.38%)	9 / 142 (6.34%)	
occurrences (all)	15	14	
Hypomagnesaemia			
subjects affected / exposed	6 / 141 (4.26%)	14 / 142 (9.86%)	
occurrences (all)	12	23	
Dehydration			
subjects affected / exposed	8 / 141 (5.67%)	9 / 142 (6.34%)	
occurrences (all)	10	10	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 October 2021	It included following key changes: - Updated Secondary Objective to evaluate the effect of neoadjuvant treatment with pamrevlumab in combination with gemcitabineplus nab-paclitaxel or FOLFIRINOX on EFS. - Updated endpoint for Accelerated Approval; replacing resection rate with EFS and specified details of evaluation during interim analysis. - Re-ordering of Secondary Endpoints; positioning PFS as key secondary endpoint with quality of life (QOL) endpoints next in hierarchical testing order. - Included infusion 'windows' for FOLFIRINOX dosing regimen. - Updated language to clarify use of cytochrome P (CYP) inhibitors and inducers in participants receiving nab-paclitaxel. - Added language to clarify documentation of protocol deviations due to COVID-19.
16 May 2022	It included following key changes: - Per Protocol (PP) Population was added. - Objective Response Rate (ORR) was added as a secondary endpoint and the ordering of secondary endpoints was clarified. - Revised exclusion criteria and Prohibited Concomitant Medications section. - Updated statistical methods.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported