Clinical trial results:
A randomized, multicenter, double-blind, placebo-controlled, Phase 3 study of the Bruton`s Tyrosine Kinase inhibitor ibrutinib in combination with nab-paclitaxel and gemcitabine versus placebo in combination with nab-paclitaxel and gemcitabine, in the first line treatment of patients with metastatic pancreatic adenocarcinoma

Summary

EudraCT number	2015-000905-38
Trial protocol	DE ES BE FR IT
Global end of trial date	25 April 2019

Results information

Result version number	v1 (current)
This version publication date	02 July 2020
First version publication date	02 July 2020

Trial information

Trial identification

Sponsor protocol code	PCYC-1137-CA

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01744691
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Pharmacyclics LLC
Sponsor organisation address	995 East Arques Avenue, Sunnyvale, California, United States, 94085
Public contact	Clinical Trial information, Pharmacyclics LLC, 001 408-774-0330, info@pcyc.com
Scientific contact	Clinical Trial information, Pharmacyclics LLC, 001 408-774-0330, info@pcyc.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	30 April 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	25 April 2019
Global end of trial reached?	Yes
Global end of trial date	25 April 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to evaluate the efficacy of ibrutinib in combination with nab-paclitaxel and gemcitabine versus placebo in combination with nab-paclitaxel and gemcitabine, based on investigator assessment of progression-free survival (PFS) and overall survival (OS), for the first line treatment of patients with metastatic pancreatic adenocarcinoma.

Protection of trial subjects:

The study was conducted in accordance with the Declaration of Helsinki and ICH GCP.

Background therapy:

nab-paclitaxel and gemcitabine as approved for 1st line treatment of patients with pancreatic adenocarcinoma.

Evidence for comparator: -

Actual start date of recruitment	08 May 2015
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	Belgium: 32
Country: Number of subjects enrolled	France: 47
Country: Number of subjects enrolled	Germany: 17
Country: Number of subjects enrolled	Italy: 62
Country: Number of subjects enrolled	Korea, Republic of: 105
Country: Number of subjects enrolled	Spain: 64
Country: Number of subjects enrolled	United Kingdom: 27
Country: Number of subjects enrolled	United States: 70
Worldwide total number of subjects	424
EEA total number of subjects	249

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)	237
From 65 to 84 years	186
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

Adult subjects with histologically or cytologically confirmed diagnosis of pancreatic carcinoma Stage IV newly diagnosed within 6 weeks of randomization suitable for treatment with nab-paclitaxel and gemcitabine.

Pre-assignment

Screening details:

Four hundred twenty-four subjects were randomized (ITT population), and 420 subjects received at least 1 dose of ibrutinib and constituted the all treated population and the safety analysis set.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Ibrutinib+Nab-paclitaxel+Gemcitabine

Arm description:

Ibrutinib (560 mg daily) + Nab-paclitaxel (125 mg/m^2) and Gemcitabine (1000 mg/m^2)

Arm type	Experimental
Investigational medicinal product name	Ibrutinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Ibrutinib 560 mg (4 x 140-mg capsules) once daily until disease progression or unacceptable toxicity.

Arm title	Placebo+Nab-paclitaxel+Gemcitabine

Arm description:

Ibrutinib Placebo + Nab-paclitaxel (125 mg/m^2) and Gemcitabine (1000 mg/m^2)

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

Dosage and administration details:

Ibrutinib placebo (4 capsules) once daily until disease progression or unacceptable toxicity.

Number of subjects in period 1	Ibrutinib+Nab-paclitaxel+Gemcitabine	Placebo+Nab-paclitaxel+Gemcitabine
Started	211	213
Completed	193	191
Not completed	18	22
Consent withdrawn by subject	18	21
Lost to follow-up	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Ibrutinib+Nab-paclitaxel+Gemcitabine
Reporting group description:	
Ibrutinib (560 mg daily) + Nab-paclitaxel (125 mg/m^2) and Gemcitabine (1000 mg/m^2)	
Reporting group title	Placebo+Nab-paclitaxel+Gemcitabine
Reporting group description:	
Ibrutinib Placebo + Nab-paclitaxel (125 mg/m^2) and Gemcitabine (1000 mg/m^2)	

Reporting group values	Ibrutinib+Nab-paclitaxel+Gemcitabine	Placebo+Nab-paclitaxel+Gemcitabine	Total
Number of subjects	211	213	424
Age categorical			
Count of Participants			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	108	110	218
From 65-84 years	103	102	205
85 years and over	0	1	1
Age continuous			
Units: years			
arithmetic mean	63.1	62.9	
standard deviation	± 10.37	± 9.33	-
Gender categorical			
Units: Subjects			
Female	97	92	189
Male	114	121	235

End points

End points reporting groups	
Reporting group title	Ibrutinib+Nab-paclitaxel+Gemcitabine
Reporting group description:	
Ibrutinib (560 mg daily) + Nab-paclitaxel (125 mg/m^2) and Gemcitabine (1000 mg/m^2)	
Reporting group title	Placebo+Nab-paclitaxel+Gemcitabine
Reporting group description:	
Ibrutinib Placebo + Nab-paclitaxel (125 mg/m^2) and Gemcitabine (1000 mg/m^2)	

Primary: Overall Survival	
End point title	Overall Survival
End point description:	
OS was defined as the time from the date of randomization to the date of death due to any cause.	
End point type	Primary
End point timeframe:	
The median time on study was 24.3 months for subjects in the Ibr+n-P/G arm and 25.3 months for subjects in the Pbo+n-P/G arm. The median time on treatment was 3.9 months for subjects in the Ibr+n-P/G arm and 5.5 months for subjects in the Pbo+n-P/G arm.	

End point values	Ibrutinib+Nab-paclitaxel+Gemcitabine	Placebo+Nab-paclitaxel+Gemcitabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	211	213		
Units: months				
number (confidence interval 95%)	9.69 (8.57 to 10.41)	10.78 (8.94 to 11.66)		

Statistical analyses

Statistical analysis title	median OS
Statistical analysis description:	
Median overall survival estimated by the Kaplan-Meier method.	
Comparison groups	Ibrutinib+Nab-paclitaxel+Gemcitabine v Placebo+Nab-paclitaxel+Gemcitabine
Number of subjects included in analysis	424
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3225 [1]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.109

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.903
upper limit	1.363

Notes:

[1] - p-value is based on log-rank test stratified by the 3 randomization stratification factors

Primary: Progression Free Survival

End point title	Progression Free Survival

End point description:

PFS assessed by Investigator was defined as the time from the date of randomization to the date of the first documented disease progression per RECIST 1.1 or death due to any cause, whichever occurred first, regardless of the use of subsequent anticancer therapy prior to documented PD or death.

End point type	Primary

End point timeframe:

The median time on study was 24.3 months for subjects in the Ibr+n-P/G arm and 25.3 months for subjects in the Pbo+n-P/G arm. The median time on treatment was 3.9 months for subjects in the Ibr+n-P/G arm and 5.5 months for subjects in the Pbo+n-P/G arm.

End point values	Ibrutinib+Nab-paclitaxel+Gemcitabine	Placebo+Nab-paclitaxel+Gemcitabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	211	213		
Units: months				
number (confidence interval 95%)	5.32 (3.75 to 5.49)	6.01 (5.45 to 7.16)		

Statistical analyses

Statistical analysis title	median PFS

Statistical analysis description:

mPFS was estimated by the Kaplan-Meier method

Comparison groups	Ibrutinib+Nab-paclitaxel+Gemcitabine v Placebo+Nab-paclitaxel+Gemcitabine
Number of subjects included in analysis	424
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [2]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.525
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.241
upper limit	1.873

Notes:

[2] - p-value is from log-rank test stratified by the 3 randomization factors

Secondary: Overall Response Rate

End point title	Overall Response Rate

End point description:

Overall Response Rate was defined as the proportion of subjects achieving a best overall response of CR or PR per investigator assessment per RECIST 1.1.

End point type	Secondary

End point timeframe:

The median time on study was 24.3 months for subjects in the Ibr+n-P/G arm and 25.3 months for subjects in the Pbo+n-P/G arm. The median time on treatment was 3.9 months for subjects in the Ibr+n-P/G arm and 5.5 months for subjects in the Pbo+n-P/G arm.

End point values	Ibrutinib+Nab-paclitaxel+Gemcitabine	Placebo+Nab-paclitaxel+Gemcitabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	211	213		
Units: percent				
number (confidence interval 95%)	29.4 (23.3 to 36.0)	42.3 (35.5 to 49.2)		

Statistical analyses

Statistical analysis title	ORR

Statistical analysis description:

The overall response rate (ORR) was defined as complete response (CR) + partial response (PR) per investigator assessment.

Comparison groups	Ibrutinib+Nab-paclitaxel+Gemcitabine v Placebo+Nab-paclitaxel+Gemcitabine
Number of subjects included in analysis	424
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0058 [3]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Rate Ratio
Point estimate	0.695
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.535
upper limit	0.903

Notes:

[3] - P-value for rate ratio is based on Cochran-Mantel-Haenszel (CMH) test adjusted for the three randomization stratification factors.

Secondary: Carbohydrate Antigen 19-9 response rate

End point title	Carbohydrate Antigen 19-9 response rate

End point description:

Carbohydrate antigen 19-9 (CA19-9) response rate for 60% reduction was defined as the proportion of subjects with at least a 60% decrease from baseline.

End point type	Secondary

End point timeframe:

The median time on study was 24.3 months for subjects in the Ibr+n-P/G arm and 25.3 months for subjects in the Pbo+n-P/G arm. The median time on treatment was 3.9 months for subjects in the Ibr+n-P/G arm and 5.5 months for subjects in the Pbo+n-P/G arm.

End point values	Ibrutinib+Nab-paclitaxel+Gemcitabine	Placebo+Nab-paclitaxel+Gemcitabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	211	213		
Units: percent				
number (confidence interval 95%)	53.6 (46.6 to 60.4)	62.9 (56.0 to 69.4)		

Statistical analyses

Statistical analysis title	CA19-9 Response Rate
Comparison groups	Ibrutinib+Nab-paclitaxel+Gemcitabine v Placebo+Nab-paclitaxel+Gemcitabine
Number of subjects included in analysis	424
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0488 [4]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Rate Ratio
Point estimate	0.85
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.722
upper limit	1

Notes:

[4] - p-value for rate ratio is based on Cochran-Mantel Haenszel (CMH) test adjusted for the 3 randomization stratification factors.

Secondary: TUDD1 in EORTC Global Health Status

End point title	TUDD1 in EORTC Global Health Status

End point description:

Time until definitive deterioration (TUDD1) was defined as the time interval between randomization and the first occurrence of a decrease in QLQ-C30.

End point type	Secondary

End point timeframe:

The median time on study was 24.3 months for subjects in the Ibr+n-P/G arm and 25.3 months for subjects in the Pbo+n-P/G arm. The median time on treatment was 3.9 months for subjects in the Ibr+n-P/G arm and 5.5 months for subjects in the Pbo+n-P/G arm.

End point values	Ibrutinib+Nab-paclitaxel+Gemcitabine	Placebo+Nab-paclitaxel+Gemcitabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	211	213		
Units: months				
number (confidence interval 95%)	4.21 (2.86 to 5.82)	6.14 (4.86 to 8.21)		

Statistical analyses

Statistical analysis title	TUDD1
Comparison groups	Ibrutinib+Nab-paclitaxel+Gemcitabine v Placebo+Nab-paclitaxel+Gemcitabine
Number of subjects included in analysis	424
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0782 [5]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.265
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.975
upper limit	1.642

Notes:

[5] - P-value is from log-rank test stratified by the three randomization stratification factors.

Secondary: Rate of Venous Thromboembolic Events

End point title	Rate of Venous Thromboembolic Events

End point description:

VTE was defined as the proportion of subjects with TEAE VTE of any grade defined by SMQ terms.

End point type	Secondary

End point timeframe:

The median time on study was 24.3 months for subjects in the Ibr+n-P/G arm and 25.3 months for subjects in the Pbo+n-P/G arm. The median time on treatment was 3.9 months for subjects in the Ibr+n-P/G arm and 5.5 months for subjects in the Pbo+n-P/G arm.

End point values	Ibrutinib+Nab-paclitaxel+Gemcitabine	Placebo+Nab-paclitaxel+Gemcitabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	211	213		
Units: percent				
number (confidence interval 95%)	8.11 (4.8 to 12.6)	10.8 (7.0 to 15.8)		

Statistical analyses

Statistical analysis title	Rate of VTEs
Statistical analysis description: VTEs are adverse events defined by SMQ terms as 'embolic and thrombotic events, venous'.	
Comparison groups	Ibrutinib+Nab-paclitaxel+Gemcitabine v Placebo+Nab-paclitaxel+Gemcitabine
Number of subjects included in analysis	424
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3343
Method	Chi-squared

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs were reported from the time the subject signs the Informed Consent Form until 30 days following last dose of study drug. All new malignant tumors were to be reported as adverse events through Long Term Follow-up for OS.

Adverse event reporting additional description:

An AE is any untoward medical occurrence in a subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups

Reporting group title	Ibrutinib + Nab-Paclitaxel + Gemcitabine

Reporting group description:

Ibrutinib 560 mg (4 x 140-mg capsules) once daily until disease progression or unacceptable toxicity.

Reporting group title	Placebo + Nab-Paclitaxel + Gemcitabine

Reporting group description:

Ibrutinib Placebo (4 capsules) once daily until disease progression or unacceptable toxicity.

Serious adverse events	Ibrutinib + Nab-Paclitaxel + Gemcitabine	Placebo + Nab-Paclitaxel + Gemcitabine	
Total subjects affected by serious adverse events			
subjects affected / exposed	112 / 208 (53.85%)	126 / 212 (59.43%)	
number of deaths (all causes)	189	188	
number of deaths resulting from adverse events	20	18	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma pancreas			
subjects affected / exposed	2 / 208 (0.96%)	3 / 212 (1.42%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 2	0 / 1	
Cancer pain			
subjects affected / exposed	2 / 208 (0.96%)	4 / 212 (1.89%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatic carcinoma			

subjects affected / exposed	6 / 208 (2.88%)	6 / 212 (2.83%)	
occurrences causally related to treatment / all	0 / 7	0 / 8	
deaths causally related to treatment / all	0 / 5	0 / 4	
Pancreatic carcinoma metastatic			
subjects affected / exposed	5 / 208 (2.40%)	5 / 212 (2.36%)	
occurrences causally related to treatment / all	0 / 6	0 / 8	
deaths causally related to treatment / all	0 / 5	0 / 4	
Tumour haemorrhage			
subjects affected / exposed	0 / 208 (0.00%)	1 / 212 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour pain			
subjects affected / exposed	1 / 208 (0.48%)	0 / 212 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Arterial haemorrhage			
subjects affected / exposed	0 / 208 (0.00%)	1 / 212 (0.47%)	
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	0 / 208 (0.00%)	1 / 212 (0.47%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolism			
subjects affected / exposed	1 / 208 (0.48%)	0 / 212 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	2 / 208 (0.96%)	0 / 212 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jugular vein thrombosis			

subjects affected / exposed	0 / 208 (0.00%)	1 / 212 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral ischaemia			
subjects affected / exposed	1 / 208 (0.48%)	0 / 212 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous thrombosis			
subjects affected / exposed	0 / 208 (0.00%)	1 / 212 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous thrombosis limb			
subjects affected / exposed	0 / 208 (0.00%)	1 / 212 (0.47%)	
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	6 / 208 (2.88%)	7 / 212 (3.30%)	
occurrences causally related to treatment / all	5 / 8	2 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	0 / 208 (0.00%)	1 / 212 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chills			
subjects affected / exposed	0 / 208 (0.00%)	1 / 212 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	1 / 208 (0.48%)	0 / 212 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gait disturbance			

subjects affected / exposed	0 / 208 (0.00%)	1 / 212 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	4 / 208 (1.92%)	5 / 212 (2.36%)	
occurrences causally related to treatment / all	1 / 5	0 / 6	
deaths causally related to treatment / all	0 / 2	0 / 1	
Generalised oedema			
subjects affected / exposed	0 / 208 (0.00%)	1 / 212 (0.47%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperthermia			
subjects affected / exposed	0 / 208 (0.00%)	1 / 212 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucosal inflammation			
subjects affected / exposed	2 / 208 (0.96%)	0 / 212 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	0 / 208 (0.00%)	1 / 212 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	13 / 208 (6.25%)	17 / 212 (8.02%)	
occurrences causally related to treatment / all	2 / 16	5 / 20	
deaths causally related to treatment / all	0 / 0	0 / 0	
Systemic inflammatory response syndrome			
subjects affected / exposed	1 / 208 (0.48%)	1 / 212 (0.47%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			

Acute respiratory distress syndrome			
subjects affected / exposed	1 / 208 (0.48%)	0 / 212 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	1 / 208 (0.48%)	2 / 212 (0.94%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea exertional			
subjects affected / exposed	0 / 208 (0.00%)	1 / 212 (0.47%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	0 / 208 (0.00%)	1 / 212 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial lung disease			
subjects affected / exposed	1 / 208 (0.48%)	0 / 212 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infiltration			
subjects affected / exposed	1 / 208 (0.48%)	0 / 212 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oropharyngeal pain			
subjects affected / exposed	0 / 208 (0.00%)	1 / 212 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 208 (0.48%)	2 / 212 (0.94%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			

subjects affected / exposed	1 / 208 (0.48%)	0 / 212 (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	3 / 208 (1.44%)	3 / 212 (1.42%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 2	0 / 1	
Pulmonary oedema			
subjects affected / exposed	0 / 208 (0.00%)	1 / 212 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pulmonary thrombosis			
subjects affected / exposed	1 / 208 (0.48%)	0 / 212 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	2 / 208 (0.96%)	1 / 212 (0.47%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachypnoea			
subjects affected / exposed	0 / 208 (0.00%)	1 / 212 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Confusional state			
subjects affected / exposed	0 / 208 (0.00%)	1 / 212 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
subjects affected / exposed	0 / 208 (0.00%)	1 / 212 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicide attempt			

subjects affected / exposed	0 / 208 (0.00%)	1 / 212 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 208 (0.48%)	0 / 212 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 208 (0.00%)	1 / 212 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood bilirubin increased			
subjects affected / exposed	1 / 208 (0.48%)	2 / 212 (0.94%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood creatinine increased			
subjects affected / exposed	1 / 208 (0.48%)	1 / 212 (0.47%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutrophil count decreased			
subjects affected / exposed	0 / 208 (0.00%)	1 / 212 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transaminases increased			
subjects affected / exposed	0 / 208 (0.00%)	2 / 212 (0.94%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Bone contusion			
subjects affected / exposed	0 / 208 (0.00%)	1 / 212 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Joint dislocation			
subjects affected / exposed	1 / 208 (0.48%)	0 / 212 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Patella fracture			
subjects affected / exposed	0 / 208 (0.00%)	1 / 212 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin laceration			
subjects affected / exposed	1 / 208 (0.48%)	0 / 212 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxicity to various agents			
subjects affected / exposed	1 / 208 (0.48%)	0 / 212 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	3 / 208 (1.44%)	4 / 212 (1.89%)	
occurrences causally related to treatment / all	1 / 4	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	0 / 208 (0.00%)	3 / 212 (1.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	0 / 208 (0.00%)	1 / 212 (0.47%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left ventricular failure			
subjects affected / exposed	1 / 208 (0.48%)	1 / 212 (0.47%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus tachycardia			

subjects affected / exposed	0 / 208 (0.00%)	1 / 212 (0.47%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	1 / 208 (0.48%)	0 / 212 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebral infarction			
subjects affected / exposed	0 / 208 (0.00%)	1 / 212 (0.47%)	
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	1 / 208 (0.48%)	0 / 212 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy			
subjects affected / exposed	0 / 208 (0.00%)	1 / 212 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Guillain-Barre syndrome			
subjects affected / exposed	1 / 208 (0.48%)	0 / 212 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage intracranial			
subjects affected / exposed	1 / 208 (0.48%)	1 / 212 (0.47%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	1 / 1	0 / 0	
Hydrocephalus			
subjects affected / exposed	1 / 208 (0.48%)	0 / 212 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic cerebral infarction			

subjects affected / exposed	1 / 208 (0.48%)	0 / 212 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	1 / 208 (0.48%)	0 / 212 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolic encephalopathy			
subjects affected / exposed	0 / 208 (0.00%)	1 / 212 (0.47%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral sensorimotor neuropathy			
subjects affected / exposed	1 / 208 (0.48%)	0 / 212 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	1 / 208 (0.48%)	0 / 212 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	3 / 208 (1.44%)	2 / 212 (0.94%)	
occurrences causally related to treatment / all	0 / 3	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wernicke's encephalopathy			
subjects affected / exposed	1 / 208 (0.48%)	0 / 212 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	7 / 208 (3.37%)	9 / 212 (4.25%)	
occurrences causally related to treatment / all	3 / 7	1 / 13	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disseminated intravascular coagulation			

subjects affected / exposed	0 / 208 (0.00%)	1 / 212 (0.47%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	1 / 208 (0.48%)	3 / 212 (1.42%)	
occurrences causally related to treatment / all	1 / 1	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic diathesis			
subjects affected / exposed	0 / 208 (0.00%)	1 / 212 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	6 / 208 (2.88%)	3 / 212 (1.42%)	
occurrences causally related to treatment / all	3 / 7	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	0 / 208 (0.00%)	1 / 212 (0.47%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	4 / 208 (1.92%)	4 / 212 (1.89%)	
occurrences causally related to treatment / all	8 / 8	5 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Cataract			
subjects affected / exposed	1 / 208 (0.48%)	0 / 212 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	4 / 208 (1.92%)	11 / 212 (5.19%)	
occurrences causally related to treatment / all	0 / 7	0 / 12	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			

subjects affected / exposed	1 / 208 (0.48%)	2 / 212 (0.94%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	0 / 208 (0.00%)	3 / 212 (1.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	2 / 208 (0.96%)	1 / 212 (0.47%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	14 / 208 (6.73%)	9 / 212 (4.25%)	
occurrences causally related to treatment / all	14 / 17	8 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal obstruction			
subjects affected / exposed	3 / 208 (1.44%)	1 / 212 (0.47%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal stenosis			
subjects affected / exposed	1 / 208 (0.48%)	1 / 212 (0.47%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer haemorrhage			
subjects affected / exposed	2 / 208 (0.96%)	1 / 212 (0.47%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspepsia			
subjects affected / exposed	0 / 208 (0.00%)	1 / 212 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis			

subjects affected / exposed	1 / 208 (0.48%)	0 / 212 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Flatulence			
subjects affected / exposed	1 / 208 (0.48%)	0 / 212 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric haemorrhage			
subjects affected / exposed	2 / 208 (0.96%)	0 / 212 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer			
subjects affected / exposed	1 / 208 (0.48%)	0 / 212 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	4 / 208 (1.92%)	1 / 212 (0.47%)	
occurrences causally related to treatment / all	5 / 6	2 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Gastrointestinal obstruction			
subjects affected / exposed	0 / 208 (0.00%)	1 / 212 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematemesis			
subjects affected / exposed	0 / 208 (0.00%)	1 / 212 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia strangulated			
subjects affected / exposed	1 / 208 (0.48%)	0 / 212 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			

subjects affected / exposed	3 / 208 (1.44%)	0 / 212 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intussusception			
subjects affected / exposed	1 / 208 (0.48%)	0 / 212 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Irritable bowel syndrome			
subjects affected / exposed	0 / 208 (0.00%)	1 / 212 (0.47%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestinal obstruction			
subjects affected / exposed	1 / 208 (0.48%)	1 / 212 (0.47%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Melaena			
subjects affected / exposed	1 / 208 (0.48%)	0 / 212 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mesenteric vein thrombosis			
subjects affected / exposed	0 / 208 (0.00%)	1 / 212 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	3 / 208 (1.44%)	7 / 212 (3.30%)	
occurrences causally related to treatment / all	5 / 6	2 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic colitis			
subjects affected / exposed	1 / 208 (0.48%)	0 / 212 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obstruction gastric			

subjects affected / exposed	0 / 208 (0.00%)	3 / 212 (1.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	0 / 208 (0.00%)	2 / 212 (0.94%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritoneal haemorrhage			
subjects affected / exposed	0 / 208 (0.00%)	1 / 212 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pneumoperitoneum			
subjects affected / exposed	1 / 208 (0.48%)	0 / 212 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			
subjects affected / exposed	1 / 208 (0.48%)	0 / 212 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retching			
subjects affected / exposed	0 / 208 (0.00%)	1 / 212 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	0 / 208 (0.00%)	1 / 212 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal ulcer haemorrhage			
subjects affected / exposed	1 / 208 (0.48%)	0 / 212 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			

subjects affected / exposed	1 / 208 (0.48%)	0 / 212 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	1 / 208 (0.48%)	0 / 212 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	5 / 208 (2.40%)	6 / 212 (2.83%)	
occurrences causally related to treatment / all	4 / 9	2 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Bile duct obstruction			
subjects affected / exposed	0 / 208 (0.00%)	4 / 212 (1.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biliary dilatation			
subjects affected / exposed	0 / 208 (0.00%)	1 / 212 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangitis			
subjects affected / exposed	9 / 208 (4.33%)	4 / 212 (1.89%)	
occurrences causally related to treatment / all	0 / 14	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangitis acute			
subjects affected / exposed	1 / 208 (0.48%)	3 / 212 (1.42%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	1 / 208 (0.48%)	2 / 212 (0.94%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			

subjects affected / exposed	1 / 208 (0.48%)	0 / 212 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic function abnormal			
subjects affected / exposed	1 / 208 (0.48%)	0 / 212 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatotoxicity			
subjects affected / exposed	1 / 208 (0.48%)	0 / 212 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperbilirubinaemia			
subjects affected / exposed	2 / 208 (0.96%)	0 / 212 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaundice			
subjects affected / exposed	1 / 208 (0.48%)	2 / 212 (0.94%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaundice cholestatic			
subjects affected / exposed	1 / 208 (0.48%)	1 / 212 (0.47%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Rash maculo-papular			
subjects affected / exposed	0 / 208 (0.00%)	2 / 212 (0.94%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 208 (0.00%)	4 / 212 (1.89%)	
occurrences causally related to treatment / all	0 / 0	2 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Azotaemia			

subjects affected / exposed	0 / 208 (0.00%)	1 / 212 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	0 / 208 (0.00%)	1 / 212 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydronephrosis			
subjects affected / exposed	0 / 208 (0.00%)	1 / 212 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	3 / 208 (1.44%)	0 / 212 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	1 / 208 (0.48%)	2 / 212 (0.94%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	0 / 208 (0.00%)	1 / 212 (0.47%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 208 (0.00%)	1 / 212 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis			
subjects affected / exposed	0 / 208 (0.00%)	1 / 212 (0.47%)	
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	4 / 208 (1.92%)	1 / 212 (0.47%)	
occurrences causally related to treatment / all	0 / 6	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular weakness			
subjects affected / exposed	0 / 208 (0.00%)	2 / 212 (0.94%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal pain			
subjects affected / exposed	0 / 208 (0.00%)	1 / 212 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myalgia			
subjects affected / exposed	1 / 208 (0.48%)	1 / 212 (0.47%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abdominal sepsis			
subjects affected / exposed	1 / 208 (0.48%)	0 / 212 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal abscess			
subjects affected / exposed	0 / 208 (0.00%)	1 / 212 (0.47%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			
subjects affected / exposed	3 / 208 (1.44%)	0 / 212 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biliary sepsis			
subjects affected / exposed	1 / 208 (0.48%)	3 / 212 (1.42%)	
occurrences causally related to treatment / all	1 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biliary tract infection			

subjects affected / exposed	2 / 208 (0.96%)	1 / 212 (0.47%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis bacterial			
subjects affected / exposed	0 / 208 (0.00%)	1 / 212 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Candida sepsis			
subjects affected / exposed	1 / 208 (0.48%)	0 / 212 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cellulitis			
subjects affected / exposed	4 / 208 (1.92%)	1 / 212 (0.47%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile infection			
subjects affected / exposed	1 / 208 (0.48%)	1 / 212 (0.47%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis			
subjects affected / exposed	1 / 208 (0.48%)	0 / 212 (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	0 / 208 (0.00%)	4 / 212 (1.89%)	
occurrences causally related to treatment / all	0 / 0	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	0 / 208 (0.00%)	1 / 212 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Empyema			

subjects affected / exposed	1 / 208 (0.48%)	0 / 212 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterobacter bacteraemia			
subjects affected / exposed	1 / 208 (0.48%)	0 / 212 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	0 / 208 (0.00%)	1 / 212 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia bacteraemia			
subjects affected / exposed	0 / 208 (0.00%)	1 / 212 (0.47%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia sepsis			
subjects affected / exposed	3 / 208 (1.44%)	1 / 212 (0.47%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	2 / 208 (0.96%)	1 / 212 (0.47%)	
occurrences causally related to treatment / all	1 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal infection			
subjects affected / exposed	1 / 208 (0.48%)	0 / 212 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	4 / 208 (1.92%)	1 / 212 (0.47%)	
occurrences causally related to treatment / all	1 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infectious colitis			

subjects affected / exposed	1 / 208 (0.48%)	0 / 212 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral discitis			
subjects affected / exposed	0 / 208 (0.00%)	1 / 212 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver abscess			
subjects affected / exposed	4 / 208 (1.92%)	0 / 212 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	1 / 208 (0.48%)	0 / 212 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic sepsis			
subjects affected / exposed	2 / 208 (0.96%)	2 / 212 (0.94%)	
occurrences causally related to treatment / all	1 / 2	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis bacterial			
subjects affected / exposed	0 / 208 (0.00%)	1 / 212 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngotonsillitis			
subjects affected / exposed	1 / 208 (0.48%)	0 / 212 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumocystis jirovecii pneumonia			
subjects affected / exposed	1 / 208 (0.48%)	4 / 212 (1.89%)	
occurrences causally related to treatment / all	0 / 1	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			

subjects affected / exposed	13 / 208 (6.25%)	8 / 212 (3.77%)	
occurrences causally related to treatment / all	3 / 14	9 / 11	
deaths causally related to treatment / all	0 / 0	1 / 1	
Pneumonia bacterial			
subjects affected / exposed	1 / 208 (0.48%)	1 / 212 (0.47%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pseudomonal sepsis			
subjects affected / exposed	1 / 208 (0.48%)	0 / 212 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary sepsis			
subjects affected / exposed	1 / 208 (0.48%)	0 / 212 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pyelonephritis			
subjects affected / exposed	1 / 208 (0.48%)	0 / 212 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis acute			
subjects affected / exposed	1 / 208 (0.48%)	0 / 212 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	2 / 208 (0.96%)	0 / 212 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 208 (0.00%)	4 / 212 (1.89%)	
occurrences causally related to treatment / all	0 / 0	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 1	
Septic shock			

subjects affected / exposed	1 / 208 (0.48%)	3 / 212 (1.42%)	
occurrences causally related to treatment / all	0 / 2	2 / 4	
deaths causally related to treatment / all	0 / 1	1 / 1	
Staphylococcal sepsis			
subjects affected / exposed	0 / 208 (0.00%)	1 / 212 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Urinary tract infection			
subjects affected / exposed	4 / 208 (1.92%)	2 / 212 (0.94%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular device infection			
subjects affected / exposed	1 / 208 (0.48%)	1 / 212 (0.47%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 208 (0.48%)	0 / 212 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	1 / 208 (0.48%)	5 / 212 (2.36%)	
occurrences causally related to treatment / all	0 / 1	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus			
subjects affected / exposed	1 / 208 (0.48%)	0 / 212 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus inadequate control			
subjects affected / exposed	0 / 208 (0.00%)	1 / 212 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enzyme abnormality			

subjects affected / exposed	0 / 208 (0.00%)	1 / 212 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	1 / 208 (0.48%)	1 / 212 (0.47%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malnutrition			
subjects affected / exposed	0 / 208 (0.00%)	1 / 212 (0.47%)	
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	1 / 208 (0.48%)	0 / 212 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelet count decreased			
subjects affected / exposed	0 / 208 (0.00%)	1 / 212 (0.47%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Ibrutinib + Nab-Paclitaxel + Gemcitabine	Placebo + Nab-Paclitaxel + Gemcitabine	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	208 / 208 (100.00%)	212 / 212 (100.00%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	11 / 208 (5.29%)	13 / 212 (6.13%)	
occurrences (all)	33	34	
Hypotension			
subjects affected / exposed	12 / 208 (5.77%)	13 / 212 (6.13%)	
occurrences (all)	15	15	
General disorders and administration site conditions			

Asthenia			
subjects affected / exposed	100 / 208 (48.08%)	93 / 212 (43.87%)	
occurrences (all)	311	283	
Chills			
subjects affected / exposed	21 / 208 (10.10%)	15 / 212 (7.08%)	
occurrences (all)	24	21	
Fatigue			
subjects affected / exposed	78 / 208 (37.50%)	65 / 212 (30.66%)	
occurrences (all)	149	170	
Mucosal inflammation			
subjects affected / exposed	24 / 208 (11.54%)	19 / 212 (8.96%)	
occurrences (all)	36	29	
Oedema peripheral			
subjects affected / exposed	60 / 208 (28.85%)	77 / 212 (36.32%)	
occurrences (all)	97	143	
Pyrexia			
subjects affected / exposed	85 / 208 (40.87%)	82 / 212 (38.68%)	
occurrences (all)	150	181	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	15 / 208 (7.21%)	42 / 212 (19.81%)	
occurrences (all)	19	47	
Dyspnoea			
subjects affected / exposed	25 / 208 (12.02%)	43 / 212 (20.28%)	
occurrences (all)	34	64	
Epistaxis			
subjects affected / exposed	36 / 208 (17.31%)	21 / 212 (9.91%)	
occurrences (all)	41	27	
Pleural effusion			
subjects affected / exposed	9 / 208 (4.33%)	16 / 212 (7.55%)	
occurrences (all)	14	22	
Productive cough			
subjects affected / exposed	7 / 208 (3.37%)	12 / 212 (5.66%)	
occurrences (all)	7	16	
Psychiatric disorders			

Insomnia			
subjects affected / exposed	20 / 208 (9.62%)	34 / 212 (16.04%)	
occurrences (all)	23	36	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	12 / 208 (5.77%)	25 / 212 (11.79%)	
occurrences (all)	16	42	
Aspartate aminotransferase increased			
subjects affected / exposed	8 / 208 (3.85%)	18 / 212 (8.49%)	
occurrences (all)	12	34	
Neutrophil count decreased			
subjects affected / exposed	11 / 208 (5.29%)	19 / 212 (8.96%)	
occurrences (all)	19	48	
Weight decreased			
subjects affected / exposed	14 / 208 (6.73%)	21 / 212 (9.91%)	
occurrences (all)	19	33	
Nervous system disorders			
Dizziness			
subjects affected / exposed	20 / 208 (9.62%)	20 / 212 (9.43%)	
occurrences (all)	22	22	
Dysgeusia			
subjects affected / exposed	19 / 208 (9.13%)	26 / 212 (12.26%)	
occurrences (all)	24	33	
Headache			
subjects affected / exposed	21 / 208 (10.10%)	20 / 212 (9.43%)	
occurrences (all)	25	24	
Neuropathy peripheral			
subjects affected / exposed	15 / 208 (7.21%)	14 / 212 (6.60%)	
occurrences (all)	33	28	
Neurotoxicity			
subjects affected / exposed	14 / 208 (6.73%)	18 / 212 (8.49%)	
occurrences (all)	40	47	
Paraesthesia			
subjects affected / exposed	27 / 208 (12.98%)	20 / 212 (9.43%)	
occurrences (all)	79	42	
Peripheral motor neuropathy			

subjects affected / exposed	13 / 208 (6.25%)	11 / 212 (5.19%)	
occurrences (all)	30	23	
Peripheral sensory neuropathy			
subjects affected / exposed	69 / 208 (33.17%)	63 / 212 (29.72%)	
occurrences (all)	171	153	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	90 / 208 (43.27%)	95 / 212 (44.81%)	
occurrences (all)	289	309	
Leukopenia			
subjects affected / exposed	15 / 208 (7.21%)	18 / 212 (8.49%)	
occurrences (all)	19	61	
Neutropenia			
subjects affected / exposed	68 / 208 (32.69%)	84 / 212 (39.62%)	
occurrences (all)	139	328	
Thrombocytopenia			
subjects affected / exposed	75 / 208 (36.06%)	55 / 212 (25.94%)	
occurrences (all)	221	208	
Eye disorders			
Vision blurred			
subjects affected / exposed	17 / 208 (8.17%)	15 / 212 (7.08%)	
occurrences (all)	20	18	
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	13 / 208 (6.25%)	13 / 212 (6.13%)	
occurrences (all)	15	13	
Abdominal pain			
subjects affected / exposed	63 / 208 (30.29%)	67 / 212 (31.60%)	
occurrences (all)	94	99	
Abdominal pain upper			
subjects affected / exposed	38 / 208 (18.27%)	27 / 212 (12.74%)	
occurrences (all)	64	40	
Ascites			
subjects affected / exposed	21 / 208 (10.10%)	25 / 212 (11.79%)	
occurrences (all)	30	35	
Constipation			

subjects affected / exposed	68 / 208 (32.69%)	78 / 212 (36.79%)	
occurrences (all)	91	96	
Diarrhoea			
subjects affected / exposed	147 / 208 (70.67%)	109 / 212 (51.42%)	
occurrences (all)	357	240	
Dyspepsia			
subjects affected / exposed	34 / 208 (16.35%)	21 / 212 (9.91%)	
occurrences (all)	38	26	
Nausea			
subjects affected / exposed	116 / 208 (55.77%)	107 / 212 (50.47%)	
occurrences (all)	228	242	
Stomatitis			
subjects affected / exposed	36 / 208 (17.31%)	21 / 212 (9.91%)	
occurrences (all)	50	28	
Vomiting			
subjects affected / exposed	85 / 208 (40.87%)	86 / 212 (40.57%)	
occurrences (all)	169	184	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	90 / 208 (43.27%)	87 / 212 (41.04%)	
occurrences (all)	130	119	
Dry skin			
subjects affected / exposed	14 / 208 (6.73%)	6 / 212 (2.83%)	
occurrences (all)	16	7	
Pruritus			
subjects affected / exposed	8 / 208 (3.85%)	25 / 212 (11.79%)	
occurrences (all)	8	36	
Rash erythematous			
subjects affected / exposed	12 / 208 (5.77%)	15 / 212 (7.08%)	
occurrences (all)	16	21	
Rash maculo-papular			
subjects affected / exposed	23 / 208 (11.06%)	28 / 212 (13.21%)	
occurrences (all)	28	42	
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	17 / 208 (8.17%)	26 / 212 (12.26%)	
occurrences (all)	20	30	
Back pain			
subjects affected / exposed	25 / 208 (12.02%)	25 / 212 (11.79%)	
occurrences (all)	31	38	
Musculoskeletal chest pain			
subjects affected / exposed	5 / 208 (2.40%)	11 / 212 (5.19%)	
occurrences (all)	5	15	
Musculoskeletal pain			
subjects affected / exposed	11 / 208 (5.29%)	11 / 212 (5.19%)	
occurrences (all)	13	13	
Myalgia			
subjects affected / exposed	28 / 208 (13.46%)	35 / 212 (16.51%)	
occurrences (all)	36	58	
Pain in extremity			
subjects affected / exposed	17 / 208 (8.17%)	24 / 212 (11.32%)	
occurrences (all)	24	31	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	7 / 208 (3.37%)	15 / 212 (7.08%)	
occurrences (all)	10	17	
Urinary tract infection			
subjects affected / exposed	16 / 208 (7.69%)	16 / 212 (7.55%)	
occurrences (all)	23	25	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	85 / 208 (40.87%)	76 / 212 (35.85%)	
occurrences (all)	135	129	
Dehydration			
subjects affected / exposed	5 / 208 (2.40%)	12 / 212 (5.66%)	
occurrences (all)	5	14	
Hypoalbuminaemia			
subjects affected / exposed	17 / 208 (8.17%)	16 / 212 (7.55%)	
occurrences (all)	24	28	
Hypokalaemia			

subjects affected / exposed	25 / 208 (12.02%)	20 / 212 (9.43%)	
occurrences (all)	37	32	
Hypomagnesaemia			
subjects affected / exposed	11 / 208 (5.29%)	7 / 212 (3.30%)	
occurrences (all)	14	16	
Platelet count decreased			
subjects affected / exposed	13 / 208 (6.25%)	17 / 212 (8.02%)	
occurrences (all)	26	61	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 June 2015	· Updated language on randomization; certain criteria for inclusion (ie, added ECOG 0-1 population) and exclusion (ie, decrease in albumin ≥20%); ibrutinib overdose language for consistency with USPI; statistical analysis section · Removal of Child-Pugh score as criteria for excluding subject participation · Inclusion of "maximum clinical benefit" derived from nab-paclitaxel and gemcitabine as a criterion for discontinuing treatment from either of these study treatments. · Revision of Grade 3-4 nausea, vomiting, or diarrhea events to include time limit >3 days before implementing dose modifications · Modified language in DMC section to state that a safety signal would be considered if Grade 3-4 AEs of longer duration and or frequency occurred because of study treatment.
25 August 2015	· Revised protocol to remove "maximum clinical benefit" defined as "a plateau in radiographic plateau or CA-19-9," as a criterion to discontinue chemotherapy
18 September 2015	· Updated inclusion criteria to align abstinence language with MHRA guidance and to modify birth control measures for females and males in accordance with nab-paclitaxel and gemcitabine labeling · Updated eligibility criteria to exclude subjects who received a live vaccination within 4 weeks prior to randomization in alignment with gemcitabine labeling
16 September 2016	· Implemented updates for sections on concomitant therapy, pharmacokinetics, product metabolism, summary of clinical safety, risks per revised ibrutinib IB · Updated contraception methods per current labeling for nab-paclitaxel and gemcitabine · Included live vaccinations in list of prohibited concomitant medications for alignment with gemcitabine labeling · Included instruction if tumor pseudoprogression was suspected · Excluded subjects with currently active and clinically significant hepatic impairment
16 December 2016	· Increased sample size in alignment with DMC agreement · Removed interim analysis for safety and efficacy in alignment with DMC agreement to mitigate the insufficient power for OS analysis at the planned IA analysis time
19 July 2017	· Conversion of OS from secondary objective to primary objective · Inclusion of VTE rate as secondary objective · Updated sections for alignment with latest version of ibrutinib IB
20 December 2017	· Added requirement to periodically monitor subjects clinically for atrial fibrillation · Added requirement to monitor closely and take appropriate actions for subjects at risk of tumor lysis syndrome

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported