Clinical trial results:
A randomized, Phase II, placebo controlled study of GDC-0068, an inhibitor to Akt, in combination with fluoropyrimidine plus oxaliplatin in patients with locally advanced or metastatic gastric or gastroesophageal junction adenocarcinoma

Summary

EudraCT number	2012-002080-10
Trial protocol	GB DE IT ES
Global end of trial date	

Results information

Result version number	v1
This version publication date	09 June 2016
First version publication date	09 June 2016

Trial information

Trial identification

Sponsor protocol code	GO28341

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01896531
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	F. Hoffmann-La Roche AG
Sponsor organisation address	Grenzacherstrasse 124, Basel, Switzerland, CH-4070
Public contact	Roche Trial Information Hotline, F. Hoffmann-La Roche AG, 41 61 6878333, global.trial_information@roche.com
Scientific contact	Roche Trial Information Hotline, F. Hoffmann-La Roche AG, 41 61 6878333, global.trial_information@roche.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	Interim
Date of interim/final analysis	03 June 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	03 June 2015
Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

To estimate the efficacy of ipatasertib (GDC-0068) combined with modified 5-fluorouracil (bolus and infusional), leucovorin, and oxaliplatin (mFOLFOX6) chemotherapy compared with placebo combined with mFOLFOX6 chemotherapy in participants with inoperable locally advanced or metastatic gastric or gastroesophageal junction (GEJ) adenocarcinoma, as measured by progression-free survival.

Protection of trial subjects:

This study was conducted in accordance with the United States Food and Drugs Administration regulations, the International Conference on Harmonization (ICH) E6 Good Clinical Practice (GCP), and applicable local, state, and federal laws, as well as other applicable country laws.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	14 August 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 9
Country: Number of subjects enrolled	United Kingdom: 10
Country: Number of subjects enrolled	France: 3
Country: Number of subjects enrolled	Germany: 9
Country: Number of subjects enrolled	Italy: 5
Country: Number of subjects enrolled	United States: 31
Country: Number of subjects enrolled	Hong Kong: 1
Country: Number of subjects enrolled	Korea, Republic of: 64
Country: Number of subjects enrolled	Malaysia: 5
Country: Number of subjects enrolled	Singapore: 7
Country: Number of subjects enrolled	Taiwan: 9
Worldwide total number of subjects	153
EEA total number of subjects	36

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)	96
From 65 to 84 years	56
85 years and over	1

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Total 153 participants were randomized in this study, of which 152 participants received the treatment.

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, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Ipatasertib + mFOLFOX6

Arm description:

Ipatasertib was administered at a dose of 600 milligrams (mg) orally once daily, beginning on Day 1 of Cycle 1 through Day 7 of each 14-day cycle until the participant experienced disease progression or intolerable toxicity. Following ipatasertib administration on Day 1 of each cycle, the participant then received mFOLFOX6 in the following order: oxaliplatin as an 85 milligram per square-meter (mg/m^2) intravenous (IV) infusion on Day 1 every 14 days with co-administration of leucovorin at 400 mg/m^2 or equivalent substitute. The participant then received 5-fluorouracil (5-FU) as a 400 mg/m^2 bolus infusion followed by 5-FU as a 2400 mg/m^2 continuous IV infusion (or 5-FU as a 1200 mg/m^2/day continuous IV infusion). Following Cycle 8, oxaliplatin was discontinued.

Arm type	Experimental
Investigational medicinal product name	Ipatasertib
Investigational medicinal product code	GDC-0068
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Ipatasertib was administered at a dose of 600 mg orally once daily, beginning on Day 1 of Cycle 1 through Day 7 of each 14-day cycle until the participant experienced disease progression or intolerable toxicity.

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

Dosage and administration details:

Oxaliplatin was administered as an 85 mg/m^2 IV infusion on Day 1 every 14 days up to Cycle 8 until the participant experienced disease progression or intolerable toxicity.

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

Dosage and administration details:

Leucovorin was administered at a dose of 400 mg/m^2 as an intravenous infusion on Day 1 every 14 days until the participant experienced disease progression or intolerable toxicity.

Investigational medicinal product name	5-fluorouracil
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion, Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

5-fluorouracil (5-FU) was administered as a 400 mg/m^2 bolus infusion followed by 5-FU as a 2400 mg/m^2 continuous IV infusion (or 5-FU as a 1200 mg/m^2/day continuous IV infusion) from Days 1 to 3 of each cycle (over approximately a 46-hour period) until the participant experienced disease progression or intolerable toxicity.

Arm title	Placebo + mFOLFOX6

Arm description:

Placebo matched to ipatasertib was administered orally once daily, beginning on Day 1 of Cycle 1 through Day 7 of each 14-day cycle until the participant experienced disease progression or intolerable toxicity. Following placebo administration on Day 1 of each cycle, the participant then received mFOLFOX6 in the following order: oxaliplatin as an 85 mg/m^2 IV infusion on Day 1 every 14 days with co-administration of leucovorin at 400 mg/m^2 or equivalent substitute. The participant then received 5-FU as a 400 mg/m^2 bolus infusion followed by 5-FU as a 2400 mg/m^2 continuous IV infusion (or 5-FU as a 1200 mg/m^2/day continuous IV infusion). Following Cycle 8, oxaliplatin was discontinued.

Arm type	Placebo
Investigational medicinal product name	Placebo matched to ipatasertib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Placebo matched to ipatasertib was administered orally once daily, beginning on Day 1 of Cycle 1 through Day 7 of each 14-day cycle until the participant experienced disease progression or intolerable toxicity.

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

Dosage and administration details:

Oxaliplatin was administered as an 85 mg/m^2 IV infusion on Day 1 every 14 days up to Cycle 8 until the participant experienced disease progression or intolerable toxicity.

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

Dosage and administration details:

Leucovorin was administered at a dose of 400 mg/m^2 as an intravenous infusion on Day 1 every 14 days until the participant experienced disease progression or intolerable toxicity.

Investigational medicinal product name	5-fluorouracil
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection, Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

5-fluorouracil (5-FU) was administered as a 400 mg/m^2 bolus infusion followed by 5-FU as a 2400 mg/m^2 continuous IV infusion (or 5-FU as a 1200 mg/m^2/day continuous IV infusion) from Days 1 to 3 of each cycle (over approximately a 46-hour period) until the participant experienced disease progression or intolerable toxicity.

Number of subjects in period 1	Ipatasertib + mFOLFOX6	Placebo + mFOLFOX6
Started	71	82
Treated	70	82
Completed	0	0
Not completed	71	82
Consent withdrawn by subject	3	2
Death	40	29
Unspecified	1	2
Ongoing in the study	25	49
Lost to follow-up	2	-

Baseline characteristics

Reporting groups	
Reporting group title	Ipatasertib + mFOLFOX6

Reporting group description:

Ipatasertib was administered at a dose of 600 milligrams (mg) orally once daily, beginning on Day 1 of Cycle 1 through Day 7 of each 14-day cycle until the participant experienced disease progression or intolerable toxicity. Following ipatasertib administration on Day 1 of each cycle, the participant then received mFOLFOX6 in the following order: oxaliplatin as an 85 milligram per square-meter (mg/m^2) intravenous (IV) infusion on Day 1 every 14 days with co-administration of leucovorin at 400 mg/m^2 or equivalent substitute. The participant then received 5-fluorouracil (5-FU) as a 400 mg/m^2 bolus infusion followed by 5-FU as a 2400 mg/m^2 continuous IV infusion (or 5-FU as a 1200 mg/m^2/day continuous IV infusion). Following Cycle 8, oxaliplatin was discontinued.

Reporting group title	Placebo + mFOLFOX6

Reporting group description:

Placebo matched to ipatasertib was administered orally once daily, beginning on Day 1 of Cycle 1 through Day 7 of each 14-day cycle until the participant experienced disease progression or intolerable toxicity. Following placebo administration on Day 1 of each cycle, the participant then received mFOLFOX6 in the following order: oxaliplatin as an 85 mg/m^2 IV infusion on Day 1 every 14 days with co-administration of leucovorin at 400 mg/m^2 or equivalent substitute. The participant then received 5-FU as a 400 mg/m^2 bolus infusion followed by 5-FU as a 2400 mg/m^2 continuous IV infusion (or 5-FU as a 1200 mg/m^2/day continuous IV infusion). Following Cycle 8, oxaliplatin was discontinued.

Reporting group values	Ipatasertib + mFOLFOX6	Placebo + mFOLFOX6	Total
Number of subjects	71	82	153
Age categorical			
Units: Subjects			

Age continuous			
Units: years			
arithmetic mean	57.5	61.3	
standard deviation	± 11.4	± 10.9	-
Gender categorical			
Units: Subjects			
Female	19	22	41
Male	52	60	112

End points

End points reporting groups

Reporting group title	Ipatasertib + mFOLFOX6

Reporting group description:

Ipatasertib was administered at a dose of 600 milligrams (mg) orally once daily, beginning on Day 1 of Cycle 1 through Day 7 of each 14-day cycle until the participant experienced disease progression or intolerable toxicity. Following ipatasertib administration on Day 1 of each cycle, the participant then received mFOLFOX6 in the following order: oxaliplatin as an 85 milligram per square-meter (mg/m^2) intravenous (IV) infusion on Day 1 every 14 days with co-administration of leucovorin at 400 mg/m^2 or equivalent substitute. The participant then received 5-fluorouracil (5-FU) as a 400 mg/m^2 bolus infusion followed by 5-FU as a 2400 mg/m^2 continuous IV infusion (or 5-FU as a 1200 mg/m^2/day continuous IV infusion). Following Cycle 8, oxaliplatin was discontinued.

Reporting group title	Placebo + mFOLFOX6

Reporting group description:

Placebo matched to ipatasertib was administered orally once daily, beginning on Day 1 of Cycle 1 through Day 7 of each 14-day cycle until the participant experienced disease progression or intolerable toxicity. Following placebo administration on Day 1 of each cycle, the participant then received mFOLFOX6 in the following order: oxaliplatin as an 85 mg/m^2 IV infusion on Day 1 every 14 days with co-administration of leucovorin at 400 mg/m^2 or equivalent substitute. The participant then received 5-FU as a 400 mg/m^2 bolus infusion followed by 5-FU as a 2400 mg/m^2 continuous IV infusion (or 5-FU as a 1200 mg/m^2/day continuous IV infusion). Following Cycle 8, oxaliplatin was discontinued.

Primary: Percentage of Participants With Disease Progression or Death

End point title	Percentage of Participants With Disease Progression or Death[1]

End point description:

Tumor response was assessed by investigator using Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1. Progressive disease (PD): At least a 20 percent (%) increase in the sum of diameters of target lesions, and the sum must also demonstrate an absolute increase of at least 5 millimeter (mm) or progression of non-target lesions. Death on study was defined as death from any cause within 30 days of the last dose of study treatment regimen. Analysis population included all randomized participants. Data were reported for all randomized participants and for participants with phosphatase and tensin homolog (PTEN) loss tumors.

End point type	Primary

End point timeframe:

Screening, at the end of Cycle 4 and every fourth cycle thereafter until disease progression or death, whichever occurred first, assessed up to approximately 1.75 years

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis was planned for this end point.

End point values	Ipatasertib + mFOLFOX6	Placebo + mFOLFOX6		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	71[2]	82[3]		
Units: percentage of participants				
number (not applicable)				
All randomized participants	67.6	69.5		
Participants with PTEN loss tumors	73.3	61.9		

Notes:

[2] - Number of participants analyzed=15 for PTEN loss tumors

[3] - Number of participants analyzed=21 for PTEN loss tumors

Statistical analyses

No statistical analyses for this end point

Primary: Progression-free Survival (PFS)

End point title	Progression-free Survival (PFS)

End point description:

PFS was defined as the time from randomization to the first occurrence of disease progression (as determined using RECIST Version 1.1 and assessed by the investigator), or death from any cause on study. PD: At least a 20% increase in the sum of diameters of target lesions, and the sum must also demonstrate an absolute increase of at least 5 mm or progression of non-target lesions. Death on study was defined as death from any cause within 30 days of the last dose of study treatment regimen. Kaplan−Meier estimates were used for evaluation. Analysis population included all randomized participants. Data were reported for all randomized participants and for participants with PTEN loss tumors.

End point type	Primary

End point timeframe:

Screening, at the end of Cycle 4 and every fourth cycle thereafter until disease progression or death, whichever occurred first, assessed up to approximately 1.75 years

End point values	Ipatasertib + mFOLFOX6	Placebo + mFOLFOX6		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	71[4]	82[5]		
Units: months				
median (confidence interval 90%)				
All randomized participants	6.57 (5.72 to 7.52)	7.52 (6.24 to 8.11)		
Participants with PTEN loss tumors	7.1 (5.39 to 9.92)	7.39 (6.51 to 14.69)		

Notes:

[4] - Number of participants analyzed=15 for PTEN loss tumors

[5] - Number of participants analyzed=21 for PTEN loss tumors

Statistical analyses

Statistical analysis title	PFS: Ipatasertib + mFOLFOX6 vs. Placebo + mFOLFOX6

Statistical analysis description:

All randomized participants

Comparison groups	Ipatasertib + mFOLFOX6 v Placebo + mFOLFOX6
Number of subjects included in analysis	153
Analysis specification	Pre-specified
Analysis type	superiority[6]
P-value	= 0.56
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.12
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.81
upper limit	1.55

Notes:

[6] - Unstratified analysis

Statistical analysis title	PFS: Ipatasertib + mFOLFOX6 vs. Placebo + mFOLFOX6

Statistical analysis description:

Participants with PTEN loss tumors. Number of participants with PTEN loss tumors in this analysis = 15 (Ipatasertib + mFOLFOX6) + 21 (Placebo + mFOLFOX6) = 36

Comparison groups	Ipatasertib + mFOLFOX6 v Placebo + mFOLFOX6
Number of subjects included in analysis	153
Analysis specification	Pre-specified
Analysis type	superiority[7]
P-value	= 0.86
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.07
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.54
upper limit	2.11

Notes:

[7] - Unstratified analysis

Secondary: Percentage of Participants Who Died

End point title	Percentage of Participants Who Died

End point description:

Death on study was defined as death from any cause within 30 days of the last dose of study treatment regimen. Analysis population included all randomized participants.

End point type	Secondary

End point timeframe:

Baseline until death (assessed up to approximately 1.75 years)

End point values	Ipatasertib + mFOLFOX6	Placebo + mFOLFOX6		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	71	82		
Units: percentage of participants				
number (not applicable)	54.9	35.4		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival (OS)

End point title	Overall survival (OS)

End point description:

OS was defined as the time from the date of randomization to the date of death from any cause. Death on study was defined as death from any cause within 30 days of the last dose of study treatment regimen. Kaplan−Meier estimates were used for evaluation. Analysis population included all randomized participants.

End point type	Secondary

End point timeframe:

Baseline until death (assessed up to approximately 1.75 years)

End point values	Ipatasertib + mFOLFOX6	Placebo + mFOLFOX6		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	71	82		
Units: months				
median (confidence interval 90%)	12.12 (10.28 to 14.55)	15.67 (13.54 to 19.81)		

Statistical analyses

Statistical analysis title	OS: Ipatasertib + mFOLFOX6 vs. Placebo + mFOLFOX6
Comparison groups	Ipatasertib + mFOLFOX6 v Placebo + mFOLFOX6
Number of subjects included in analysis	153
Analysis specification	Pre-specified
Analysis type	superiority[8]
P-value	= 0.01
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.85
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.23
upper limit	2.79

Notes:

[8] - Unstratified analysis

Secondary: Percentage of Participants with Objective Tumor Response

End point title	Percentage of Participants with Objective Tumor Response

End point description:

Objective Response was defined as the participants achieving either a complete response (CR) or a partial response (PR) based on the investigator assessment using RECIST v 1.1. CR: disappearance of all target lesions and all pathological lymph nodes below 10 mm. Partial response (PR): At least a 30% decrease in the sum of diameters of target lesions. Analysis population included all randomized participants.

End point type	Secondary

End point timeframe:

Screening, at the end of Cycle 4 and every fourth cycle thereafter until disease progression or death, whichever occurred first, assessed up to approximately 1.75 years

End point values	Ipatasertib + mFOLFOX6	Placebo + mFOLFOX6		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[9]	0[10]		
Units: percentage of participants				
number (not applicable)				

Notes:

[9] - Due to primary efficacy endpoints not met, secondary efficacy endpoints were not analyzed.

[10] - Due to primary efficacy endpoints not met, secondary efficacy endpoints were not analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of objective response

End point title	Duration of objective response

End point description:

Duration of objective response in participants with measurable soft tissue disease at baseline was defined as the time from first observation of an objective tumor response until first observation of disease progression, as assessed by the investigator per modified RECIST Version 1.1. PD: At least a 20% increase in the sum of diameters of target lesions, and the sum must also demonstrate an absolute increase of at least 5 mm or progression of non-target lesions. Analysis population included all randomized participants.

End point type	Secondary

End point timeframe:

Screening, at the end of Cycle 4 and every fourth cycle thereafter until disease progression or death, whichever occurred first, assessed up to approximately 1.75 years

End point values	Ipatasertib + mFOLFOX6	Placebo + mFOLFOX6		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[11]	0[12]		
Units: months				
arithmetic mean (standard deviation)	()	()		

Notes:

[11] - Due to primary efficacy endpoints not met, secondary efficacy endpoints were not analyzed.

[12] - Due to primary efficacy endpoints not met, secondary efficacy endpoints were not analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Time to disease progression

End point title	Time to disease progression

End point description:

Time to disease progression was defined as the time from randomization to the first occurrence of disease progression, as determined by investigator review of tumor assessments by RECIST Version 1.1. PD: At least a 20% increase in the sum of diameters of target lesions, and the sum must also demonstrate an absolute increase of at least 5 mm or progression of non-target lesions. Analysis

population included all randomized participants.

End point type	Secondary

End point timeframe:

Screening, at the end of Cycle 4 and every fourth cycle thereafter until disease progression or death, whichever occurred first, assessed up to approximately 1.75 years

End point values	Ipatasertib + mFOLFOX6	Placebo + mFOLFOX6		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[13]	0[14]		
Units: months				
median (confidence interval 90%)	(to)	(to)		

Notes:

[13] - Due to primary efficacy endpoints not met, secondary efficacy endpoints were not analyzed.

[14] - Due to primary efficacy endpoints not met, secondary efficacy endpoints were not analyzed.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline until 30 days after the last dose of study treatment or until initiation of another anti-cancer therapy, whichever occurred first (up to approximately 1.75 years)

Adverse event reporting additional description:

One participant in Ipatasertib + mFOLFOX6 group was randomized prior to site notification of participant's death.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	Ipatasertib + mFOLFOX6

Reporting group description:

Ipatasertib was administered at a dose of 600 milligrams (mg) orally once daily, beginning on Day 1 of Cycle 1 through Day 7 of each 14-day cycle until the participant experienced disease progression or intolerable toxicity. Following ipatasertib administration on Day 1 of each cycle, the participant then received mFOLFOX6 in the following order: oxaliplatin as an 85 milligram per square-meter (mg/m^2) intravenous (IV) infusion on Day 1 every 14 days with co-administration of leucovorin at 400 mg/m^2 or equivalent substitute. The participant then received 5-fluorouracil (5-FU) as a 400 mg/m^2 bolus infusion followed by 5-FU as a 2400 mg/m^2 continuous IV infusion (or 5-FU as a 1200 mg/m^2/day continuous IV infusion). Following Cycle 8, oxaliplatin was discontinued.

Reporting group title	Placebo + mFOLFOX6

Reporting group description:

Placebo matched to ipatasertib was administered orally once daily, beginning on Day 1 of Cycle 1 through Day 7 of each 14-day cycle until the participant experienced disease progression or intolerable toxicity. Following placebo administration on Day 1 of each cycle, the participant then received mFOLFOX6 in the following order: oxaliplatin as an mg/m^2 IV infusion on Day 1 every 14 days with co-administration of leucovorin at 400 mg/m^2 or equivalent substitute. The participant then received 5-FU as a 400 mg/m^2 bolus infusion followed by 5-FU as a 2400 mg/m^2 continuous IV infusion (or 5-FU as a 1200 mg/m^2/day continuous IV infusion). Following Cycle 8, oxaliplatin was discontinued.

Serious adverse events	Ipatasertib + mFOLFOX6	Placebo + mFOLFOX6	
Total subjects affected by serious adverse events			
subjects affected / exposed	38 / 70 (54.29%)	35 / 82 (42.68%)	
number of deaths (all causes)	39	29	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Gastric cancer			
subjects affected / exposed	2 / 70 (2.86%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 2	0 / 1	
Tumour pain			

subjects affected / exposed	1 / 70 (1.43%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Venous thrombosis			
subjects affected / exposed	0 / 70 (0.00%)	1 / 82 (1.22%)	
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	1 / 70 (1.43%)	2 / 82 (2.44%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	1 / 70 (1.43%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Obstruction			
subjects affected / exposed	1 / 70 (1.43%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	3 / 70 (4.29%)	3 / 82 (3.66%)	
occurrences causally related to treatment / all	1 / 4	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 70 (1.43%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			

subjects affected / exposed	0 / 70 (0.00%)	3 / 82 (3.66%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	1 / 70 (1.43%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Investigations			
Platelet count decreased			
subjects affected / exposed	1 / 70 (1.43%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Weight decreased			
subjects affected / exposed	1 / 70 (1.43%)	0 / 82 (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			
Chemical peritonitis			
subjects affected / exposed	0 / 70 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pubis fracture			
subjects affected / exposed	0 / 70 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal compression fracture			
subjects affected / exposed	0 / 70 (0.00%)	2 / 82 (2.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Pyloric stenosis			

subjects affected / exposed	1 / 70 (1.43%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac arrest			
subjects affected / exposed	1 / 70 (1.43%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Nervous system disorders			
Cerebral gas embolism			
subjects affected / exposed	0 / 70 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Diabetic hyperosmolar coma			
subjects affected / exposed	1 / 70 (1.43%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorder			
subjects affected / exposed	1 / 70 (1.43%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraparesis			
subjects affected / exposed	1 / 70 (1.43%)	0 / 82 (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	1 / 70 (1.43%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	1 / 70 (1.43%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Neutropenia			
subjects affected / exposed	1 / 70 (1.43%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	1 / 70 (1.43%)	0 / 82 (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 distension			
subjects affected / exposed	0 / 70 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	3 / 70 (4.29%)	4 / 82 (4.88%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	0 / 70 (0.00%)	2 / 82 (2.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	1 / 70 (1.43%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colonic pseudo−obstruction			
subjects affected / exposed	1 / 70 (1.43%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	5 / 70 (7.14%)	3 / 82 (3.66%)	
occurrences causally related to treatment / all	5 / 6	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			

subjects affected / exposed	1 / 70 (1.43%)	2 / 82 (2.44%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteritis			
subjects affected / exposed	1 / 70 (1.43%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric perforation			
subjects affected / exposed	1 / 70 (1.43%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer			
subjects affected / exposed	1 / 70 (1.43%)	0 / 82 (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	2 / 70 (2.86%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	3 / 70 (4.29%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	1 / 70 (1.43%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jejunal perforation			
subjects affected / exposed	1 / 70 (1.43%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestinal obstruction			

subjects affected / exposed	1 / 70 (1.43%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine perforation			
subjects affected / exposed	1 / 70 (1.43%)	0 / 82 (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 / 70 (5.71%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	5 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obstruction gastric			
subjects affected / exposed	1 / 70 (1.43%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal fistula			
subjects affected / exposed	0 / 70 (0.00%)	1 / 82 (1.22%)	
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 / 70 (0.00%)	2 / 82 (2.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	2 / 70 (2.86%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	4 / 70 (5.71%)	4 / 82 (4.88%)	
occurrences causally related to treatment / all	2 / 4	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Bile duct obstruction			

subjects affected / exposed	1 / 70 (1.43%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaundice cholestatic			
subjects affected / exposed	1 / 70 (1.43%)	0 / 82 (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			
Acute kidney injury			
subjects affected / exposed	2 / 70 (2.86%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	2 / 70 (2.86%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydronephrosis			
subjects affected / exposed	1 / 70 (1.43%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal colic			
subjects affected / exposed	1 / 70 (1.43%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	1 / 70 (1.43%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract disorder			
subjects affected / exposed	1 / 70 (1.43%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			

Back pain			
subjects affected / exposed	1 / 70 (1.43%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bursitis			
subjects affected / exposed	0 / 70 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Flank pain			
subjects affected / exposed	0 / 70 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Appendicitis perforated			
subjects affected / exposed	0 / 70 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopulmonary aspergillosis			
subjects affected / exposed	1 / 70 (1.43%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	0 / 70 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	1 / 70 (1.43%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infectious colitis			
subjects affected / exposed	0 / 70 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			

subjects affected / exposed	1 / 70 (1.43%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic sepsis			
subjects affected / exposed	0 / 70 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oral candidiasis			
subjects affected / exposed	0 / 70 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			
subjects affected / exposed	0 / 70 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngitis			
subjects affected / exposed	1 / 70 (1.43%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 70 (0.00%)	2 / 82 (2.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary tuberculosis			
subjects affected / exposed	0 / 70 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 70 (1.43%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tuberculosis			

subjects affected / exposed	0 / 70 (0.00%)	1 / 82 (1.22%)	
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	0 / 70 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Cachexia			
subjects affected / exposed	0 / 70 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Decreased appetite			
subjects affected / exposed	3 / 70 (4.29%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	4 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	3 / 70 (4.29%)	2 / 82 (2.44%)	
occurrences causally related to treatment / all	0 / 3	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Failure to thrive			
subjects affected / exposed	1 / 70 (1.43%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	3 / 70 (4.29%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperosmolar hyperglycaemic state			
subjects affected / exposed	1 / 70 (1.43%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	1 / 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	Ipatasertib + mFOLFOX6	Placebo + mFOLFOX6	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	70 / 70 (100.00%)	79 / 82 (96.34%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	5 / 70 (7.14%)	4 / 82 (4.88%)	
occurrences (all)	5	4	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	14 / 70 (20.00%)	16 / 82 (19.51%)	
occurrences (all)	18	27	
Catheter site pain			
subjects affected / exposed	4 / 70 (5.71%)	5 / 82 (6.10%)	
occurrences (all)	4	7	
Chest discomfort			
subjects affected / exposed	6 / 70 (8.57%)	1 / 82 (1.22%)	
occurrences (all)	7	2	
Chest pain			
subjects affected / exposed	4 / 70 (5.71%)	6 / 82 (7.32%)	
occurrences (all)	5	8	
Fatigue			
subjects affected / exposed	43 / 70 (61.43%)	37 / 82 (45.12%)	
occurrences (all)	110	81	
Influenza like illness			
subjects affected / exposed	4 / 70 (5.71%)	3 / 82 (3.66%)	
occurrences (all)	4	4	
Mucosal inflammation			
subjects affected / exposed	13 / 70 (18.57%)	15 / 82 (18.29%)	
occurrences (all)	46	20	
Oedema peripheral			
subjects affected / exposed	7 / 70 (10.00%)	8 / 82 (9.76%)	
occurrences (all)	10	13	
Pyrexia			

subjects affected / exposed	15 / 70 (21.43%)	9 / 82 (10.98%)	
occurrences (all)	17	10	
Temperature intolerance			
subjects affected / exposed	7 / 70 (10.00%)	11 / 82 (13.41%)	
occurrences (all)	8	12	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	7 / 70 (10.00%)	10 / 82 (12.20%)	
occurrences (all)	8	13	
Dyspnoea			
subjects affected / exposed	10 / 70 (14.29%)	14 / 82 (17.07%)	
occurrences (all)	16	20	
Epistaxis			
subjects affected / exposed	5 / 70 (7.14%)	5 / 82 (6.10%)	
occurrences (all)	6	5	
Hiccups			
subjects affected / exposed	7 / 70 (10.00%)	5 / 82 (6.10%)	
occurrences (all)	10	6	
Oropharyngeal pain			
subjects affected / exposed	4 / 70 (5.71%)	6 / 82 (7.32%)	
occurrences (all)	5	7	
Rhinorrhoea			
subjects affected / exposed	5 / 70 (7.14%)	4 / 82 (4.88%)	
occurrences (all)	5	4	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	5 / 70 (7.14%)	3 / 82 (3.66%)	
occurrences (all)	5	3	
Insomnia			
subjects affected / exposed	12 / 70 (17.14%)	13 / 82 (15.85%)	
occurrences (all)	20	20	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	7 / 70 (10.00%)	6 / 82 (7.32%)	
occurrences (all)	9	8	
Aspartate aminotransferase increased			

subjects affected / exposed	5 / 70 (7.14%)	10 / 82 (12.20%)	
occurrences (all)	7	15	
Blood creatinine increased			
subjects affected / exposed	6 / 70 (8.57%)	4 / 82 (4.88%)	
occurrences (all)	8	6	
Blood triglycerides increased			
subjects affected / exposed	1 / 70 (1.43%)	5 / 82 (6.10%)	
occurrences (all)	1	8	
Glycosylated haemoglobin increased			
subjects affected / exposed	1 / 70 (1.43%)	5 / 82 (6.10%)	
occurrences (all)	1	5	
Neutrophil count decreased			
subjects affected / exposed	5 / 70 (7.14%)	12 / 82 (14.63%)	
occurrences (all)	7	18	
Platelet count decreased			
subjects affected / exposed	6 / 70 (8.57%)	5 / 82 (6.10%)	
occurrences (all)	11	18	
Weight decreased			
subjects affected / exposed	16 / 70 (22.86%)	10 / 82 (12.20%)	
occurrences (all)	21	15	
White blood cell count decreased			
subjects affected / exposed	3 / 70 (4.29%)	5 / 82 (6.10%)	
occurrences (all)	4	7	
Nervous system disorders			
Dizziness			
subjects affected / exposed	15 / 70 (21.43%)	13 / 82 (15.85%)	
occurrences (all)	18	19	
Dysgeusia			
subjects affected / exposed	13 / 70 (18.57%)	15 / 82 (18.29%)	
occurrences (all)	13	15	
Headache			
subjects affected / exposed	6 / 70 (8.57%)	7 / 82 (8.54%)	
occurrences (all)	19	14	
Neuropathy peripheral			
subjects affected / exposed	27 / 70 (38.57%)	38 / 82 (46.34%)	
occurrences (all)	47	99	

Paraesthesia			
subjects affected / exposed	6 / 70 (8.57%)	6 / 82 (7.32%)	
occurrences (all)	10	6	
Peripheral sensory neuropathy			
subjects affected / exposed	10 / 70 (14.29%)	14 / 82 (17.07%)	
occurrences (all)	17	23	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	14 / 70 (20.00%)	15 / 82 (18.29%)	
occurrences (all)	27	22	
Granulocytopenia			
subjects affected / exposed	4 / 70 (5.71%)	6 / 82 (7.32%)	
occurrences (all)	6	10	
Leukopenia			
subjects affected / exposed	1 / 70 (1.43%)	6 / 82 (7.32%)	
occurrences (all)	4	10	
Neutropenia			
subjects affected / exposed	21 / 70 (30.00%)	33 / 82 (40.24%)	
occurrences (all)	38	66	
Thrombocytopenia			
subjects affected / exposed	8 / 70 (11.43%)	11 / 82 (13.41%)	
occurrences (all)	14	22	
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	6 / 70 (8.57%)	2 / 82 (2.44%)	
occurrences (all)	6	3	
Abdominal distension			
subjects affected / exposed	9 / 70 (12.86%)	7 / 82 (8.54%)	
occurrences (all)	10	8	
Abdominal pain			
subjects affected / exposed	18 / 70 (25.71%)	20 / 82 (24.39%)	
occurrences (all)	25	34	
Abdominal pain upper			
subjects affected / exposed	10 / 70 (14.29%)	6 / 82 (7.32%)	
occurrences (all)	11	9	
Constipation			

subjects affected / exposed	26 / 70 (37.14%)	25 / 82 (30.49%)	
occurrences (all)	58	49	
Diarrhoea			
subjects affected / exposed	57 / 70 (81.43%)	34 / 82 (41.46%)	
occurrences (all)	203	68	
Dry mouth			
subjects affected / exposed	4 / 70 (5.71%)	8 / 82 (9.76%)	
occurrences (all)	6	9	
Dyspepsia			
subjects affected / exposed	9 / 70 (12.86%)	17 / 82 (20.73%)	
occurrences (all)	11	22	
Dysphagia			
subjects affected / exposed	7 / 70 (10.00%)	8 / 82 (9.76%)	
occurrences (all)	13	9	
Flatulence			
subjects affected / exposed	2 / 70 (2.86%)	5 / 82 (6.10%)	
occurrences (all)	3	6	
Gastrooesophageal reflux disease			
subjects affected / exposed	6 / 70 (8.57%)	5 / 82 (6.10%)	
occurrences (all)	6	10	
Nausea			
subjects affected / exposed	51 / 70 (72.86%)	51 / 82 (62.20%)	
occurrences (all)	117	133	
Stomatitis			
subjects affected / exposed	17 / 70 (24.29%)	8 / 82 (9.76%)	
occurrences (all)	26	12	
Vomiting			
subjects affected / exposed	43 / 70 (61.43%)	33 / 82 (40.24%)	
occurrences (all)	105	78	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	13 / 70 (18.57%)	20 / 82 (24.39%)	
occurrences (all)	13	22	
Dry skin			
subjects affected / exposed	5 / 70 (7.14%)	8 / 82 (9.76%)	
occurrences (all)	7	10	

Palmar−plantar erythrodysaesthesia syndrome			
subjects affected / exposed	5 / 70 (7.14%)	3 / 82 (3.66%)	
occurrences (all)	5	6	
Pruritus			
subjects affected / exposed	10 / 70 (14.29%)	4 / 82 (4.88%)	
occurrences (all)	11	4	
Rash			
subjects affected / exposed	20 / 70 (28.57%)	10 / 82 (12.20%)	
occurrences (all)	34	18	
Skin discolouration			
subjects affected / exposed	4 / 70 (5.71%)	0 / 82 (0.00%)	
occurrences (all)	6	0	
Skin hyperpigmentation			
subjects affected / exposed	7 / 70 (10.00%)	1 / 82 (1.22%)	
occurrences (all)	7	1	
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	5 / 70 (7.14%)	3 / 82 (3.66%)	
occurrences (all)	7	5	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 70 (1.43%)	7 / 82 (8.54%)	
occurrences (all)	3	9	
Back pain			
subjects affected / exposed	8 / 70 (11.43%)	14 / 82 (17.07%)	
occurrences (all)	14	23	
Flank pain			
subjects affected / exposed	3 / 70 (4.29%)	6 / 82 (7.32%)	
occurrences (all)	6	6	
Muscle spasms			
subjects affected / exposed	1 / 70 (1.43%)	5 / 82 (6.10%)	
occurrences (all)	1	7	
Musculoskeletal pain			
subjects affected / exposed	6 / 70 (8.57%)	3 / 82 (3.66%)	
occurrences (all)	6	3	
Myalgia			

subjects affected / exposed	4 / 70 (5.71%)	1 / 82 (1.22%)	
occurrences (all)	8	1	
Pain in extremity			
subjects affected / exposed	3 / 70 (4.29%)	6 / 82 (7.32%)	
occurrences (all)	4	10	
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	7 / 70 (10.00%)	3 / 82 (3.66%)	
occurrences (all)	10	3	
Urinary tract infection			
subjects affected / exposed	9 / 70 (12.86%)	5 / 82 (6.10%)	
occurrences (all)	10	10	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	41 / 70 (58.57%)	41 / 82 (50.00%)	
occurrences (all)	117	92	
Dehydration			
subjects affected / exposed	5 / 70 (7.14%)	5 / 82 (6.10%)	
occurrences (all)	5	6	
Hyperglycaemia			
subjects affected / exposed	14 / 70 (20.00%)	15 / 82 (18.29%)	
occurrences (all)	23	28	
Hyperkalaemia			
subjects affected / exposed	6 / 70 (8.57%)	5 / 82 (6.10%)	
occurrences (all)	7	6	
Hypoalbuminaemia			
subjects affected / exposed	4 / 70 (5.71%)	2 / 82 (2.44%)	
occurrences (all)	4	4	
Hypocalcaemia			
subjects affected / exposed	4 / 70 (5.71%)	2 / 82 (2.44%)	
occurrences (all)	5	2	
Hypokalaemia			
subjects affected / exposed	11 / 70 (15.71%)	8 / 82 (9.76%)	
occurrences (all)	14	11	
Hypomagnesaemia			

subjects affected / exposed	6 / 70 (8.57%)	4 / 82 (4.88%)	
occurrences (all)	12	7	
Hyponatraemia			
subjects affected / exposed	4 / 70 (5.71%)	2 / 82 (2.44%)	
occurrences (all)	7	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 March 2013	Version 2: Updated information related to the ipatasertib/placebo formulation had been added. Updated safety and clinical data from the Phase Ib study of ipatasertib in combination with chemotherapy, including mFOLFOX6, (Study PAM4983g) had been included. Dose-modification guidelines for the management of adverse events related to mFOLFOX6 chemotherapy and/or to ipatasertib had been updated to improve clarity and consistency. Medical monitor contact information for sites in Europe and Asia had been added.
26 August 2014	Version 3: The sample size for this study had been increased from approximately 120 participants to approximately 150 patients. The primary reason to increase the sample size was to maintain the target PFS events by accounting for the unexpected discontinuations for surgery and/or radiofrequency ablation in some participants left with minimal disease following treatment on this study. The adjusted increase in sample size enabled a robust estimate of the primary endpoint with the preplanned PFS events for the overall population and for the diagnostic-positive (Dx+) sub-population.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported