Clinical trial results:
A Randomized, Phase II, Placebo-controlled Study of Ipatasertib (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	26 January 2021

Results information

Result version number	v2 (current)
This version publication date	10 February 2022
First version publication date	09 June 2016
Version creation reason	

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	F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, 41 61 6878333, global.trial_information@roche.com
Scientific contact	F. Hoffmann-La Roche AG, 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	Final
Date of interim/final analysis	26 January 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	26 January 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of the efficacy of ipatasertib in combination with oxaliplatin, 5-fluorouracil, and leucovorin (modified FOLFOX6 [mFOLFOX6]) chemotherapy in participants with advanced or metastatic gastric or gastroesophageal junction (GEJ) cancer.

Protection of trial subjects:

All study subjects were required to read and sign an Informed Consent Form.

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	26

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:

The study was conducted at 33 centers in 11 countries.

Pre-assignment

Screening details:

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

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	
Other name	GDC-0068
Pharmaceutical forms	Tablet, Capsule
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
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
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet, Capsule
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	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
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.

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.

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
Study Ended by Sponsor	7	20
Death Prior to Treatment	1	-
Death	57	59
Non-compliance	-	1
Lost to follow-up	3	-

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	57.6	61.4	
standard deviation	± 11.4	± 11.0	-
Sex: Female, Male Units: Participants			
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: Progression-Free Survival (PFS) in All Randomized Participants and Participants With PTEN Loss Tumors at Primary Analysis

End point title	Progression-Free Survival (PFS) in All Randomized Participants and Participants With PTEN Loss Tumors at Primary Analysis

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. Progressive disease (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. The randomized population was defined as all participants who were randomized in the study. Randomized participants with PTEN loss tumors were also analyzed. For the primary analysis, PTEN loss was defined as the condition "Perc Cells Cytoplasmic Stain Int 0" of greater than or equal to 10. Here 'n' indicates the number analyzed for the specified population.

End point type	Primary

End point timeframe:

Screening, at the end of Cycle 4 (cycle = 14 days) 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	82		
Units: months				
median (confidence interval 90%)				
All Randomized Participants (n=71,82)	6.57 (5.72 to 7.52)	7.52 (6.24 to 8.11)		
Participants With PTEN Loss Tumors (n=15,21)	7.10 (5.39 to 9.92)	7.39 (6.51 to 14.69)		

Statistical analyses

Statistical analysis title	All randomized participants
Comparison groups	Ipatasertib + mFOLFOX6 v Placebo + mFOLFOX6
Number of subjects included in analysis	153
Analysis specification	Pre-specified
Analysis type	superiority[1]
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:

[1] - Unstratified analysis

Statistical analysis title	Participants with PTEN loss tumors

Statistical analysis description:

Total number of participants with PTEN loss tumors in this analysis is 36.

Comparison groups	Ipatasertib + mFOLFOX6 v Placebo + mFOLFOX6
Number of subjects included in analysis	153
Analysis specification	Pre-specified
Analysis type	superiority[2]
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:

[2] - Unstratified analysis

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. Kaplan−Meier estimates were used for evaluation. All randomized participants, randomized participants with PTEN loss tumors and randomized participants who were Akt diagnostic-positive (Akt Dx+) were analyzed. For the final analysis, PTEN loss was defined as the condition "Perc Cells Cytoplasmic Stain Int

0" of greater than 10. Here 'n' indicates the number analyzed for the specified population. '99999' indicates that data point was not estimable due to low number of events.

End point type	Secondary

End point timeframe:

Baseline up to end of study (up to approximately 7.5 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%)				
Randomized (n=71,82)	11.96 (10.28 to 14.55)	15.31 (13.54 to 16.92)		
PTEN Loss Tumors (n=14,15)	14.82 (11.99 to 18.40)	21.78 (14.13 to 99999)		
Akt Dx+ (n=23,23)	11.66 (9.92 to 18.40)	17.22 (12.71 to 23.29)		

Statistical analyses

Statistical analysis title	All randomized participants
Comparison groups	Ipatasertib + mFOLFOX6 v Placebo + mFOLFOX6
Number of subjects included in analysis	153
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.0234
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.52
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.12
upper limit	2.07

Notes:

[3] - Unstratified analysis

Statistical analysis title	Participants with PTEN loss tumors

Statistical analysis description:

Total number of participants with PTEN loss tumors in this analysis is 29.

Comparison groups	Ipatasertib + mFOLFOX6 v Placebo + mFOLFOX6

Number of subjects included in analysis	153
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.2867
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.66
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.75
upper limit	3.65

Statistical analysis title	Participants who are Akt Dx+

Statistical analysis description:

Total number of participants who are Akt Dx+ in this analysis is 46.

Comparison groups	Ipatasertib + mFOLFOX6 v Placebo + mFOLFOX6
Number of subjects included in analysis	153
Analysis specification	Pre-specified
Analysis type	superiority[4]
P-value	= 0.1369
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.66
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.94
upper limit	2.93

Notes:

[4] - Unstratified analysis

Secondary: Objective Response Rate (ORR)

End point title	Objective Response Rate (ORR)

End point description:

Objective Response Rate was defined as the percentage of 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. All randomized participants, randomized participants with PTEN loss tumors and randomized participants who were Akt diagnostic-positive (Akt Dx+) were analyzed. For the final analysis, PTEN loss was defined as the condition "Perc Cells Cytoplasmic Stain Int 0" of greater than 10. Here ‘n’ indicates the number analyzed for the specified population.

End point type	Secondary

End point timeframe:

Screening, at the end of Cycle 4 (cycle = 14 days) and every fourth cycle thereafter until disease progression or death, whichever occurred first, up to end of study (up to approximately 7.5 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 (confidence interval 90%)				
Randomized (n=71,82)	52.1 (41.74 to 62.35)	57.3 (48.02 to 66.59)		
PTEN Loss Tumors (n=14,15)	50.0 (26.36 to 73.64)	73.3 (50.00 to 87.82)		
Akt Dx+ (n=23,23)	52.2 (33.51 to 70.39)	56.5 (38.05 to 72.67)		

Statistical analyses

Statistical analysis title	All randomized participants
Comparison groups	Ipatasertib + mFOLFOX6 v Placebo + mFOLFOX6
Number of subjects included in analysis	153
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5202
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in Response Rates
Point estimate	-5.2
Confidence interval	
level	90 %
sides	2-sided
lower limit	-18.46
upper limit	8.06

Statistical analysis title	Participants with PTEN loss tumors
Statistical analysis description: Total number of participants with PTEN loss tumors in this analysis is 29.	
Comparison groups	Ipatasertib + mFOLFOX6 v Placebo + mFOLFOX6
Number of subjects included in analysis	153
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2035
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in Response Rates
Point estimate	-23.33
Confidence interval	
level	90 %
sides	2-sided
lower limit	-52.24
upper limit	5.58

Statistical analysis title	Participants who are Akt Dx+
Statistical analysis description:	
Total number of participants who are Akt Dx+ in this analysis is 46.	
Comparison groups	Ipatasertib + mFOLFOX6 v Placebo + mFOLFOX6
Number of subjects included in analysis	153
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7697
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in Response Rates
Point estimate	-4.35
Confidence interval	
level	90 %
sides	2-sided
lower limit	-28.48
upper limit	19.79

Secondary: Duration of Objective Tumor Response

End point title	Duration of Objective Tumor Response

End point description:

Duration of objective tumor 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. All randomized participants, randomized participants with PTEN loss tumors and randomized participants who were Akt diagnostic-positive (Akt Dx+) were analyzed. For the final analysis, PTEN loss was defined as the condition "Perc Cells Cytoplasmic Stain Int 0" of greater than 10. '99999' indicates that data point was not estimable due to low number of events. Here ‘n’ indicates the number analyzed for the specified population.

End point type	Secondary

End point timeframe:

Screening, at the end of Cycle 4 (cycle = 14 days) and every fourth cycle thereafter until disease progression or death, whichever occurred first, up to end of study (up to approximately 7.5 years)

End point values	Ipatasertib + mFOLFOX6	Placebo + mFOLFOX6		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37	47		
Units: months				
median (confidence interval 90%)				
Randomized (n=37,47)	4.63 (4.01 to 5.52)	5.85 (4.47 to 6.90)		
PTEN Loss Tumor (n=7,11)	4.70 (4.27 to 99999)	5.98 (4.86 to 10.94)		
Akt Dx+ (n=12,13)	4.70 (3.84 to 14.78)	6.80 (4.86 to 10.71)		

Statistical analyses

Statistical analysis title	All randomized participants
Comparison groups	Ipatasertib + mFOLFOX6 v Placebo + mFOLFOX6
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	= 0.5974
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.14
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.76
upper limit	1.73

Notes:

[5] - Unstratified analysis

Statistical analysis title	Participants who are Akt Dx+
Statistical analysis description:	
Total number of participants who are Akt Dx+ in this analysis is 25.	
Comparison groups	Ipatasertib + mFOLFOX6 v Placebo + mFOLFOX6
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority[6]
P-value	= 0.6097
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.78
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.35
upper limit	1.75

Notes:

[6] - Unstratified analysis

Statistical analysis title	Participants with PTEN loss tumors
Statistical analysis description:	
Total number of participants with PTEN loss tumors in this analysis is 18.	
Comparison groups	Ipatasertib + mFOLFOX6 v Placebo + mFOLFOX6

Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority[7]
P-value	= 0.5385
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.71
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.28
upper limit	1.79

Notes:

[7] - Unstratified analysis

Secondary: Number of Participants with Adverse Events (AEs)

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

End point description:

An adverse event is any untoward medical occurrence in a subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with the treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a pharmaceutical product, whether or not considered related to the pharmaceutical product. Preexisting conditions which worsen during a study are also considered as adverse events. Death on study was defined as death from any cause within 30 days of the last dose of study treatment regimen. The safety population was defined as all randomized participants who received at least one dose of ipatasertib/placebo or mFOLFOX6, with participants grouped according to the treatment actually received.

End point type	Secondary

End point timeframe:

Baseline until end of study (up to approximately 7.5 years)

End point values	Ipatasertib + mFOLFOX6	Placebo + mFOLFOX6		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	70	82		
Units: participants	70	80		

Statistical analyses

No statistical analyses for this end point

Secondary: Serum Concentration of Ipatasertib

End point title	Serum Concentration of Ipatasertib[8]

End point description:

The pharmacokinetic (PK) population was defined as all participants with evaluable PK data. Here 'n' indicates the number analyzed for the specified timepoint.

End point type	Secondary

End point timeframe:

Day 1 at 1 hour and 4 hours post-dose; Day 5, pre-dose and 2 hours post-dose

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Ipatasertib serum concentrations were only measured in the arm that received ipatasertib.

End point values	Ipatasertib + mFOLFOX6			
Subject group type	Reporting group			
Number of subjects analysed	64			
Units: ng/mL				
arithmetic mean (standard deviation)				
Day 1: 1 hour post-dose (n=63)	506 (± 550)			
Day 1: 4 hours post-dose (n=64)	389 (± 202)			
Day 5: pre-dose (n=62)	90.7 (± 61.0)			
Day 5: 2 hours post-dose (n=57)	557 (± 328)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline until end of study (up to approximately 7.5 years)

Adverse event reporting additional description:

Safety population included treated participants (i.e., participants who received at least one dose of ipatasertib/placebo or mFOLFOX6), with participants allocated to the treatment arm associated with the regimen that they actually received.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.1

Reporting groups

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 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.

Serious adverse events	Placebo+mFOLFOX6	Ipatasertib+mFOLFOX6	
Total subjects affected by serious adverse events			
subjects affected / exposed	36 / 82 (43.90%)	39 / 70 (55.71%)	
number of deaths (all causes)	59	57	
number of deaths resulting from adverse events	0	1	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
GASTRIC CANCER			
subjects affected / exposed	2 / 82 (2.44%)	2 / 70 (2.86%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 2	0 / 2	
TUMOUR PAIN			

subjects affected / exposed	0 / 82 (0.00%)	1 / 70 (1.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
VENOUS THROMBOSIS			
subjects affected / exposed	1 / 82 (1.22%)	0 / 70 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
ASTHENIA			
subjects affected / exposed	2 / 82 (2.44%)	1 / 70 (1.43%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
DEATH			
subjects affected / exposed	1 / 82 (1.22%)	1 / 70 (1.43%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
FATIGUE			
subjects affected / exposed	0 / 82 (0.00%)	1 / 70 (1.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
OBSTRUCTION			
subjects affected / exposed	0 / 82 (0.00%)	1 / 70 (1.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PYREXIA			
subjects affected / exposed	3 / 82 (3.66%)	3 / 70 (4.29%)	
occurrences causally related to treatment / all	1 / 3	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
ACUTE RESPIRATORY FAILURE			

subjects affected / exposed	0 / 82 (0.00%)	1 / 70 (1.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
DYSPNOEA			
subjects affected / exposed	1 / 82 (1.22%)	1 / 70 (1.43%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMONIA ASPIRATION			
subjects affected / exposed	1 / 82 (1.22%)	0 / 70 (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 / 82 (3.66%)	0 / 70 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
RESPIRATORY FAILURE			
subjects affected / exposed	0 / 82 (0.00%)	1 / 70 (1.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Investigations			
PLATELET COUNT DECREASED			
subjects affected / exposed	0 / 82 (0.00%)	1 / 70 (1.43%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
WEIGHT DECREASED			
subjects affected / exposed	0 / 82 (0.00%)	1 / 70 (1.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
CHEMICAL PERITONITIS			
subjects affected / exposed	1 / 82 (1.22%)	0 / 70 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

PELVIC FRACTURE			
subjects affected / exposed	1 / 82 (1.22%)	0 / 70 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SPINAL COMPRESSION FRACTURE			
subjects affected / exposed	2 / 82 (2.44%)	0 / 70 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
CARDIAC ARREST			
subjects affected / exposed	0 / 82 (0.00%)	1 / 70 (1.43%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Nervous system disorders			
CEREBRAL GAS EMBOLISM			
subjects affected / exposed	1 / 82 (1.22%)	0 / 70 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
DIABETIC HYPEROSMOLAR COMA			
subjects affected / exposed	0 / 82 (0.00%)	1 / 70 (1.43%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PARAPARESIS			
subjects affected / exposed	0 / 82 (0.00%)	1 / 70 (1.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	0 / 82 (0.00%)	1 / 70 (1.43%)	
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 / 82 (1.22%)	1 / 70 (1.43%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
NEUTROPENIA			
subjects affected / exposed	1 / 82 (1.22%)	1 / 70 (1.43%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
THROMBOCYTOPENIA			
subjects affected / exposed	0 / 82 (0.00%)	1 / 70 (1.43%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
ULCERATIVE KERATITIS			
subjects affected / exposed	1 / 82 (1.22%)	0 / 70 (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	1 / 82 (1.22%)	0 / 70 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ABDOMINAL PAIN			
subjects affected / exposed	4 / 82 (4.88%)	4 / 70 (5.71%)	
occurrences causally related to treatment / all	0 / 4	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
ASCITES			
subjects affected / exposed	2 / 82 (2.44%)	0 / 70 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
COLITIS			
subjects affected / exposed	0 / 82 (0.00%)	1 / 70 (1.43%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
DIARRHOEA			

subjects affected / exposed	3 / 82 (3.66%)	5 / 70 (7.14%)	
occurrences causally related to treatment / all	2 / 3	6 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
DYSPHAGIA			
subjects affected / exposed	2 / 82 (2.44%)	1 / 70 (1.43%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ENTERITIS			
subjects affected / exposed	1 / 82 (1.22%)	1 / 70 (1.43%)	
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	0 / 82 (0.00%)	1 / 70 (1.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTRIC ULCER			
subjects affected / exposed	0 / 82 (0.00%)	1 / 70 (1.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HAEMATEMESIS			
subjects affected / exposed	1 / 82 (1.22%)	2 / 70 (2.86%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
ILEUS			
subjects affected / exposed	0 / 82 (0.00%)	3 / 70 (4.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
INTESTINAL OBSTRUCTION			
subjects affected / exposed	1 / 82 (1.22%)	1 / 70 (1.43%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
INTESTINAL PSEUDO-OBSTRUCTION			

subjects affected / exposed	0 / 82 (0.00%)	1 / 70 (1.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
JEJUNAL PERFORATION			
subjects affected / exposed	0 / 82 (0.00%)	1 / 70 (1.43%)	
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	0 / 82 (0.00%)	1 / 70 (1.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
LARGE INTESTINE PERFORATION			
subjects affected / exposed	0 / 82 (0.00%)	1 / 70 (1.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
NAUSEA			
subjects affected / exposed	0 / 82 (0.00%)	4 / 70 (5.71%)	
occurrences causally related to treatment / all	0 / 0	5 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
OBSTRUCTION GASTRIC			
subjects affected / exposed	2 / 82 (2.44%)	2 / 70 (2.86%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
OESOPHAGEAL FISTULA			
subjects affected / exposed	1 / 82 (1.22%)	0 / 70 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SMALL INTESTINAL OBSTRUCTION			
subjects affected / exposed	2 / 82 (2.44%)	0 / 70 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
UPPER GASTROINTESTINAL HAEMORRHAGE			

subjects affected / exposed	0 / 82 (0.00%)	2 / 70 (2.86%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
VOMITING			
subjects affected / exposed	4 / 82 (4.88%)	3 / 70 (4.29%)	
occurrences causally related to treatment / all	1 / 5	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
BILIARY OBSTRUCTION			
subjects affected / exposed	0 / 82 (0.00%)	1 / 70 (1.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
JAUNDICE CHOLESTATIC			
subjects affected / exposed	0 / 82 (0.00%)	1 / 70 (1.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
ACUTE KIDNEY INJURY			
subjects affected / exposed	0 / 82 (0.00%)	2 / 70 (2.86%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
HAEMATURIA			
subjects affected / exposed	0 / 82 (0.00%)	2 / 70 (2.86%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYDRONEPHROSIS			
subjects affected / exposed	0 / 82 (0.00%)	1 / 70 (1.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
RENAL COLIC			
subjects affected / exposed	0 / 82 (0.00%)	1 / 70 (1.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
URINARY RETENTION			

subjects affected / exposed	0 / 82 (0.00%)	1 / 70 (1.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
URINARY TRACT DISORDER			
subjects affected / exposed	0 / 82 (0.00%)	1 / 70 (1.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
BACK PAIN			
subjects affected / exposed	0 / 82 (0.00%)	1 / 70 (1.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
BURSITIS			
subjects affected / exposed	1 / 82 (1.22%)	0 / 70 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
FLANK PAIN			
subjects affected / exposed	1 / 82 (1.22%)	0 / 70 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
APPENDICITIS PERFORATED			
subjects affected / exposed	1 / 82 (1.22%)	0 / 70 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
BRONCHOPULMONARY ASPERGILLOSIS			
subjects affected / exposed	0 / 82 (0.00%)	1 / 70 (1.43%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CELLULITIS			
subjects affected / exposed	1 / 82 (1.22%)	0 / 70 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

CLOSTRIDIUM DIFFICILE COLITIS			
subjects affected / exposed	0 / 82 (0.00%)	1 / 70 (1.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
LARGE INTESTINE INFECTION			
subjects affected / exposed	1 / 82 (1.22%)	0 / 70 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
LOWER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	0 / 82 (0.00%)	1 / 70 (1.43%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ORAL CANDIDIASIS			
subjects affected / exposed	1 / 82 (1.22%)	0 / 70 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PERITONITIS			
subjects affected / exposed	1 / 82 (1.22%)	0 / 70 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PHARYNGITIS			
subjects affected / exposed	0 / 82 (0.00%)	1 / 70 (1.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMONIA			
subjects affected / exposed	2 / 82 (2.44%)	0 / 70 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PULMONARY TUBERCULOSIS			
subjects affected / exposed	1 / 82 (1.22%)	0 / 70 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SEPSIS			

subjects affected / exposed	2 / 82 (2.44%)	1 / 70 (1.43%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
TUBERCULOSIS			
subjects affected / exposed	1 / 82 (1.22%)	0 / 70 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
URINARY TRACT INFECTION			
subjects affected / exposed	1 / 82 (1.22%)	0 / 70 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
VIRAL INFECTION			
subjects affected / exposed	1 / 82 (1.22%)	0 / 70 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
CACHEXIA			
subjects affected / exposed	1 / 82 (1.22%)	0 / 70 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DECREASED APPETITE			
subjects affected / exposed	0 / 82 (0.00%)	3 / 70 (4.29%)	
occurrences causally related to treatment / all	0 / 0	4 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
DEHYDRATION			
subjects affected / exposed	2 / 82 (2.44%)	3 / 70 (4.29%)	
occurrences causally related to treatment / all	1 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
FAILURE TO THRIVE			
subjects affected / exposed	0 / 82 (0.00%)	1 / 70 (1.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPERGLYCAEMIA			

subjects affected / exposed	0 / 82 (0.00%)	3 / 70 (4.29%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPERGLYCAEMIC HYPEROSMOLAR NONKETOTIC SYNDROME			
subjects affected / exposed	0 / 82 (0.00%)	1 / 70 (1.43%)	
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	Placebo+mFOLFOX6	Ipatasertib+mFOLFOX6	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	79 / 82 (96.34%)	70 / 70 (100.00%)	
Vascular disorders			
DEEP VEIN THROMBOSIS			
subjects affected / exposed	5 / 82 (6.10%)	2 / 70 (2.86%)	
occurrences (all)	5	2	
HYPERTENSION			
subjects affected / exposed	5 / 82 (6.10%)	4 / 70 (5.71%)	
occurrences (all)	5	4	
General disorders and administration site conditions			
ASTHENIA			
subjects affected / exposed	16 / 82 (19.51%)	13 / 70 (18.57%)	
occurrences (all)	27	17	
CATHETER SITE PAIN			
subjects affected / exposed	5 / 82 (6.10%)	4 / 70 (5.71%)	
occurrences (all)	7	4	
CHEST DISCOMFORT			
subjects affected / exposed	2 / 82 (2.44%)	5 / 70 (7.14%)	
occurrences (all)	3	6	
CHEST PAIN			
subjects affected / exposed	6 / 82 (7.32%)	4 / 70 (5.71%)	
occurrences (all)	8	5	
FATIGUE			

subjects affected / exposed	37 / 82 (45.12%)	44 / 70 (62.86%)	
occurrences (all)	83	112	
INFLUENZA LIKE ILLNESS			
subjects affected / exposed	3 / 82 (3.66%)	4 / 70 (5.71%)	
occurrences (all)	4	4	
MUCOSAL INFLAMMATION			
subjects affected / exposed	15 / 82 (18.29%)	13 / 70 (18.57%)	
occurrences (all)	20	46	
OEDEMA PERIPHERAL			
subjects affected / exposed	8 / 82 (9.76%)	7 / 70 (10.00%)	
occurrences (all)	13	10	
PYREXIA			
subjects affected / exposed	9 / 82 (10.98%)	15 / 70 (21.43%)	
occurrences (all)	10	18	
TEMPERATURE INTOLERANCE			
subjects affected / exposed	11 / 82 (13.41%)	7 / 70 (10.00%)	
occurrences (all)	12	8	
Respiratory, thoracic and mediastinal disorders			
COUGH			
subjects affected / exposed	12 / 82 (14.63%)	7 / 70 (10.00%)	
occurrences (all)	15	8	
DYSPNOEA			
subjects affected / exposed	15 / 82 (18.29%)	10 / 70 (14.29%)	
occurrences (all)	21	16	
EPISTAXIS			
subjects affected / exposed	5 / 82 (6.10%)	5 / 70 (7.14%)	
occurrences (all)	5	6	
HICCUPS			
subjects affected / exposed	5 / 82 (6.10%)	7 / 70 (10.00%)	
occurrences (all)	6	10	
OROPHARYNGEAL PAIN			
subjects affected / exposed	6 / 82 (7.32%)	4 / 70 (5.71%)	
occurrences (all)	7	5	
RHINORRHOEA			

subjects affected / exposed	4 / 82 (4.88%)	6 / 70 (8.57%)	
occurrences (all)	5	6	
Psychiatric disorders			
ANXIETY			
subjects affected / exposed	3 / 82 (3.66%)	5 / 70 (7.14%)	
occurrences (all)	3	5	
INSOMNIA			
subjects affected / exposed	13 / 82 (15.85%)	12 / 70 (17.14%)	
occurrences (all)	20	18	
Investigations			
ALANINE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	6 / 82 (7.32%)	7 / 70 (10.00%)	
occurrences (all)	8	9	
ASPARTATE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	10 / 82 (12.20%)	5 / 70 (7.14%)	
occurrences (all)	15	7	
BLOOD CREATININE INCREASED			
subjects affected / exposed	4 / 82 (4.88%)	6 / 70 (8.57%)	
occurrences (all)	6	8	
BLOOD TRIGLYCERIDES INCREASED			
subjects affected / exposed	5 / 82 (6.10%)	1 / 70 (1.43%)	
occurrences (all)	8	1	
GLYCOSYLATED HAEMOGLOBIN INCREASED			
subjects affected / exposed	5 / 82 (6.10%)	1 / 70 (1.43%)	
occurrences (all)	5	1	
NEUTROPHIL COUNT DECREASED			
subjects affected / exposed	12 / 82 (14.63%)	5 / 70 (7.14%)	
occurrences (all)	18	7	
PLATELET COUNT DECREASED			
subjects affected / exposed	5 / 82 (6.10%)	6 / 70 (8.57%)	
occurrences (all)	18	10	
WEIGHT DECREASED			
subjects affected / exposed	9 / 82 (10.98%)	16 / 70 (22.86%)	
occurrences (all)	13	21	
WHITE BLOOD CELL COUNT			

DECREASED			
subjects affected / exposed	5 / 82 (6.10%)	3 / 70 (4.29%)	
occurrences (all)	7	4	
Nervous system disorders			
DIZZINESS			
subjects affected / exposed	13 / 82 (15.85%)	15 / 70 (21.43%)	
occurrences (all)	19	18	
DYSGEUSIA			
subjects affected / exposed	8 / 82 (9.76%)	5 / 70 (7.14%)	
occurrences (all)	8	5	
HEADACHE			
subjects affected / exposed	8 / 82 (9.76%)	7 / 70 (10.00%)	
occurrences (all)	16	20	
NEUROPATHY PERIPHERAL			
subjects affected / exposed	38 / 82 (46.34%)	27 / 70 (38.57%)	
occurrences (all)	100	46	
PARAESTHESIA			
subjects affected / exposed	6 / 82 (7.32%)	6 / 70 (8.57%)	
occurrences (all)	6	10	
PERIPHERAL SENSORY NEUROPATHY			
subjects affected / exposed	14 / 82 (17.07%)	10 / 70 (14.29%)	
occurrences (all)	24	17	
TASTE DISORDER			
subjects affected / exposed	7 / 82 (8.54%)	8 / 70 (11.43%)	
occurrences (all)	7	8	
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	15 / 82 (18.29%)	14 / 70 (20.00%)	
occurrences (all)	22	27	
GRANULOCYTOPENIA			
subjects affected / exposed	6 / 82 (7.32%)	4 / 70 (5.71%)	
occurrences (all)	10	6	
LEUKOPENIA			
subjects affected / exposed	6 / 82 (7.32%)	1 / 70 (1.43%)	
occurrences (all)	10	4	
NEUTROPENIA			

subjects affected / exposed	33 / 82 (40.24%)	21 / 70 (30.00%)	
occurrences (all)	71	38	
THROMBOCYTOPENIA			
subjects affected / exposed	11 / 82 (13.41%)	8 / 70 (11.43%)	
occurrences (all)	22	14	
Eye disorders			
VISION BLURRED			
subjects affected / exposed	5 / 82 (6.10%)	2 / 70 (2.86%)	
occurrences (all)	11	2	
Gastrointestinal disorders			
ABDOMINAL DISCOMFORT			
subjects affected / exposed	3 / 82 (3.66%)	6 / 70 (8.57%)	
occurrences (all)	5	6	
ABDOMINAL DISTENSION			
subjects affected / exposed	7 / 82 (8.54%)	9 / 70 (12.86%)	
occurrences (all)	9	10	
ABDOMINAL PAIN			
subjects affected / exposed	20 / 82 (24.39%)	19 / 70 (27.14%)	
occurrences (all)	34	26	
ABDOMINAL PAIN UPPER			
subjects affected / exposed	7 / 82 (8.54%)	9 / 70 (12.86%)	
occurrences (all)	10	10	
CONSTIPATION			
subjects affected / exposed	24 / 82 (29.27%)	27 / 70 (38.57%)	
occurrences (all)	48	59	
DIARRHOEA			
subjects affected / exposed	34 / 82 (41.46%)	57 / 70 (81.43%)	
occurrences (all)	73	202	
DRY MOUTH			
subjects affected / exposed	8 / 82 (9.76%)	4 / 70 (5.71%)	
occurrences (all)	10	6	
DYSPEPSIA			
subjects affected / exposed	17 / 82 (20.73%)	9 / 70 (12.86%)	
occurrences (all)	22	11	
DYSPHAGIA			

subjects affected / exposed	7 / 82 (8.54%)	7 / 70 (10.00%)	
occurrences (all)	8	13	
FLATULENCE			
subjects affected / exposed	5 / 82 (6.10%)	2 / 70 (2.86%)	
occurrences (all)	6	3	
GASTROOESOPHAGEAL REFLUX DISEASE			
subjects affected / exposed	5 / 82 (6.10%)	6 / 70 (8.57%)	
occurrences (all)	10	6	
NAUSEA			
subjects affected / exposed	51 / 82 (62.20%)	51 / 70 (72.86%)	
occurrences (all)	133	117	
STOMATITIS			
subjects affected / exposed	8 / 82 (9.76%)	17 / 70 (24.29%)	
occurrences (all)	12	26	
VOMITING			
subjects affected / exposed	33 / 82 (40.24%)	43 / 70 (61.43%)	
occurrences (all)	87	104	
Skin and subcutaneous tissue disorders			
ALOPECIA			
subjects affected / exposed	20 / 82 (24.39%)	13 / 70 (18.57%)	
occurrences (all)	22	13	
DRY SKIN			
subjects affected / exposed	8 / 82 (9.76%)	5 / 70 (7.14%)	
occurrences (all)	11	7	
PALMAR-PLANTAR ERYTHRODYSAESTHESIA SYNDROME			
subjects affected / exposed	4 / 82 (4.88%)	5 / 70 (7.14%)	
occurrences (all)	9	5	
PRURITUS			
subjects affected / exposed	6 / 82 (7.32%)	10 / 70 (14.29%)	
occurrences (all)	6	11	
RASH			
subjects affected / exposed	11 / 82 (13.41%)	20 / 70 (28.57%)	
occurrences (all)	20	34	
SKIN DISCOLOURATION			

subjects affected / exposed	0 / 82 (0.00%)	4 / 70 (5.71%)	
occurrences (all)	0	6	
SKIN HYPERPIGMENTATION			
subjects affected / exposed	1 / 82 (1.22%)	7 / 70 (10.00%)	
occurrences (all)	1	7	
Renal and urinary disorders			
PROTEINURIA			
subjects affected / exposed	3 / 82 (3.66%)	5 / 70 (7.14%)	
occurrences (all)	5	7	
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
subjects affected / exposed	10 / 82 (12.20%)	6 / 70 (8.57%)	
occurrences (all)	12	9	
BACK PAIN			
subjects affected / exposed	14 / 82 (17.07%)	8 / 70 (11.43%)	
occurrences (all)	23	14	
FLANK PAIN			
subjects affected / exposed	7 / 82 (8.54%)	3 / 70 (4.29%)	
occurrences (all)	8	6	
MUSCLE SPASMS			
subjects affected / exposed	5 / 82 (6.10%)	1 / 70 (1.43%)	
occurrences (all)	7	1	
MYALGIA			
subjects affected / exposed	1 / 82 (1.22%)	4 / 70 (5.71%)	
occurrences (all)	1	8	
PAIN IN EXTREMITY			
subjects affected / exposed	6 / 82 (7.32%)	3 / 70 (4.29%)	
occurrences (all)	11	4	
Infections and infestations			
UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	3 / 82 (3.66%)	7 / 70 (10.00%)	
occurrences (all)	3	10	
URINARY TRACT INFECTION			
subjects affected / exposed	4 / 82 (4.88%)	10 / 70 (14.29%)	
occurrences (all)	9	11	
Metabolism and nutrition disorders			

DECREASED APPETITE			
subjects affected / exposed	41 / 82 (50.00%)	41 / 70 (58.57%)	
occurrences (all)	92	115	
DEHYDRATION			
subjects affected / exposed	5 / 82 (6.10%)	5 / 70 (7.14%)	
occurrences (all)	6	5	
HYPERGLYCAEMIA			
subjects affected / exposed	15 / 82 (18.29%)	14 / 70 (20.00%)	
occurrences (all)	28	23	
HYPERKALAEMIA			
subjects affected / exposed	5 / 82 (6.10%)	6 / 70 (8.57%)	
occurrences (all)	7	7	
HYPOALBUMINAEMIA			
subjects affected / exposed	2 / 82 (2.44%)	4 / 70 (5.71%)	
occurrences (all)	4	4	
HYPOCALCAEMIA			
subjects affected / exposed	2 / 82 (2.44%)	4 / 70 (5.71%)	
occurrences (all)	2	5	
HYPOKALAEMIA			
subjects affected / exposed	8 / 82 (9.76%)	11 / 70 (15.71%)	
occurrences (all)	11	14	
HYPOMAGNESAEMIA			
subjects affected / exposed	4 / 82 (4.88%)	7 / 70 (10.00%)	
occurrences (all)	7	13	
HYPONATRAEMIA			
subjects affected / exposed	2 / 82 (2.44%)	4 / 70 (5.71%)	
occurrences (all)	2	7	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 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.
25 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.
01 April 2016	Version 4: The main purpose of this amendment was to provide a high-level summary of the primary analysis results for Study GO28341 and describe the management plan for ongoing participants. The primary analysis for safety and efficacy showed that ipatasertib+mFOLFOX6, compared with placebo +mFOLFOX6, did not improve progression-free survival (primary endpoint) or overall survival (secondary endpoint) in either the randomized population or the subset of participants who had tumors with loss of the tumor suppressor phosphatase and tensin homolog (PTEN loss) meeting pre-defined criteria by immunohistochemistry prior to the primary analysis. Safety data from this study were consistent with the known safety profiles for ipatasertib and mFOLFOX6 chemotherapy. The overall safety profile and the risks associated with ipatasertib had not changed. As of 11 January 2016, the Sponsor provided all investigators with the unblinded study treatment assignments and a summary of the primary analysis results to allow investigators to share this information and discuss future treatment plans with the 7 ongoing participants in the study. Because of a lack of clinical benefit, the Sponsor recommended discontinuation of ipatasertib/placebo treatment. Allowed for certain laboratory assessments scheduled during the treatment period (glycosylated hemoglobin, fasting lipid profile, coagulation, and urinalysis) to be performed only if clinically indicated, at the discretion of the investigator, for participants who continue to receive ipatasertib with or without mFOLFOX6 treatment in the study. Eliminated exploratory assessments, survival follow-up and assessment of new anti-cancer therapies for all participants.
26 October 2017	Version 5: GDC-0068 was updated to reflect the international nonproprietary name “ipatasertib”. The Protocol was amended to provide an update on the formulation of ipatasertib (previously capsule; tablet formulation effective no later than March, 2018) and to simplify the study assessment schedule for the 1 ongoing participant in the study (at approximately every 3-4 months, or more frequently if clinically indicated). As of 1 October 2017, the study was unblinded following primary analysis; 1 participant remained on study treatment receiving ipatasertib.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported