Clinical trial results:
A PHASE II RANDOMIZED, DOUBLE-BLIND, STUDY OF IPATASERTIB (GDC0068), AN INHIBITOR TO AKT, IN COMBINATION WITH PACLITAXEL AS NEOADJUVANT TREATMENT FOR PATIENTS WITH EARLY STAGE TRIPLE NEGATIVE BREAST CANCER

Summary

EudraCT number	2014-003029-16
Trial protocol	ES PT
Global end of trial date	02 August 2017

Results information

Result version number	v1 (current)
This version publication date	11 August 2018
First version publication date	11 August 2018

Trial information

Trial identification

Sponsor protocol code	GO29505

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02301988
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 616878333, global.trial_information@roche.com
Scientific contact	F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, +41 616878333, 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	02 August 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	02 August 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This is a randomized, double-blind, placebo-controlled, multicenter, pre-operative Phase II study designed to estimate the efficacy of ipatasertib combined with paclitaxel chemotherapy versus placebo combined with paclitaxel chemotherapy in women with Stage Ia - IIIa triple-negative breast adenocarcinoma. The anticipated time on study treatment is 12 weeks.

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	17 February 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 91
Country: Number of subjects enrolled	Portugal: 12
Country: Number of subjects enrolled	United States: 48
Worldwide total number of subjects	151
EEA total number of subjects	103

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)	123
From 65 to 84 years	28

85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

151 subjects were randomized to either receive 400 mg ipatasertib + paclitaxel (76 subjects) or placebo + paclitaxel (75 subjects).

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 + Paclitaxel

Arm description:

Participants received ipatasertib orally daily on Days 1-21 of each 28-day cycle for 3 cycles and paclitaxel intravenous (IV) infusion every week (QW) for 3 cycles (12 total doses).

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

Dosage and administration details:

Paclitaxel will be administered at a dose of 80 milligrams per square meter (mg/m^2) as IV infusion QW for 3 cycles.

Investigational medicinal product name	Ipatasertib
Investigational medicinal product code	
Other name	GDC0068
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Ipatasertib will be administered at a dose of 400 milligrams (mg) orally daily on Days 1-21 of each 28-day cycle for 3 cycles.

Arm title	Placebo + Paclitaxel

Arm description:

Participants received placebo (matching to ipatasertib) orally daily on Days 1-21 of each 28-day cycle for 3 cycles and paclitaxel IV infusion QW for 3 cycles (12 total doses).

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

Dosage and administration details:

Paclitaxel will be administered at a dose of 80 milligrams per square meter (mg/m^2) as IV infusion QW for 3 cycles.

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants will receive placebo (matching to ipatasertib) orally daily on Days 1-21 of each 28-day cycle for 3 cycles.

Number of subjects in period 1	Ipatasertib + Paclitaxel	Placebo + Paclitaxel
Started	76	75
Completed	66	66
Not completed	10	9
Adverse event, serious fatal	1	-
Consent withdrawn by subject	2	1
Physician decision	2	2
Unknown Reason	1	3
Adverse event, non-fatal	1	1
Lack of efficacy	3	2

Baseline characteristics

Reporting groups	
Reporting group title	Ipatasertib + Paclitaxel
Reporting group description:	
Participants received ipatasertib orally daily on Days 1-21 of each 28-day cycle for 3 cycles and paclitaxel intravenous (IV) infusion every week (QW) for 3 cycles (12 total doses).	
Reporting group title	Placebo + Paclitaxel
Reporting group description:	
Participants received placebo (matching to ipatasertib) orally daily on Days 1-21 of each 28-day cycle for 3 cycles and paclitaxel IV infusion QW for 3 cycles (12 total doses).	

Reporting group values	Ipatasertib + Paclitaxel	Placebo + Paclitaxel	Total
Number of subjects	76	75	151
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	62	61	123
From 65-84 years	14	14	28
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	53.8	53.8	
standard deviation	± 10.9	± 12.0	-
Sex: Female, Male Units: Subjects			
Female	76	75	151
Male	0	0	0
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	1	1
Native Hawaiian or Other Pacific Islander	1	0	1
Black or African American	2	3	5
White	71	70	141
More than one race	0	0	0
Unknown or Not Reported	2	1	3

End points

End points reporting groups

Reporting group title	Ipatasertib + Paclitaxel
Reporting group description:	
Participants received ipatasertib orally daily on Days 1-21 of each 28-day cycle for 3 cycles and paclitaxel intravenous (IV) infusion every week (QW) for 3 cycles (12 total doses).	
Reporting group title	Placebo + Paclitaxel
Reporting group description:	
Participants received placebo (matching to ipatasertib) orally daily on Days 1-21 of each 28-day cycle for 3 cycles and paclitaxel IV infusion QW for 3 cycles (12 total doses).	

Primary: Percentage of Participants With Pathological Complete Response (pCR) in Breast and Axilla as Defined by ypT0/Tis ypN0 in the American Joint Committee on Cancer Staging System (in All Participants)

End point title	Percentage of Participants With Pathological Complete Response (pCR) in Breast and Axilla as Defined by ypT0/Tis ypN0 in the American Joint Committee on Cancer Staging System (in All Participants)
End point description:	
pCR was defined by ypT0/Tis ypN0 in the American Joint Committee on Cancer (AJCC) Staging System with the following determination for breast and axilla by local pathology laboratory evaluation: T0: no evidence of primary tumor; Tis: early cancer that has not spread to neighboring tissue and N0: no cancer found in the lymph nodes.	
End point type	Primary
End point timeframe:	
Surgery visit (at approximately Weeks 14 to 19)	

End point values	Ipatasertib + Paclitaxel	Placebo + Paclitaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	76	75		
Units: percentage of participants				
number (confidence interval 95%)	17.1 (9.82 to 27.25)	13.3 (6.58 to 22.86)		

Statistical analyses

Statistical analysis title	pCR in Breast and Axilla for All Participants
Statistical analysis description:	
Unstratified Analysis	
Comparison groups	Ipatasertib + Paclitaxel v Placebo + Paclitaxel

Number of subjects included in analysis	151
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.519
Method	Chi-squared
Parameter estimate	Difference in Response Rates
Point estimate	3.77
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.99
upper limit	16.54

Primary: Percentage of Participants With pCR in Breast and Axilla as Defined by ypT0/Tis ypN0 in the American Joint Committee on Cancer Staging System (in Participants Who Have Phosphatase and Tensin Homolog [PTEN]-low Tumors)

End point title	Percentage of Participants With pCR in Breast and Axilla as Defined by ypT0/Tis ypN0 in the American Joint Committee on Cancer Staging System (in Participants Who Have Phosphatase and Tensin Homolog [PTEN]-low Tumors)

End point description:

pCR was defined by ypT0/Tis ypN0 in the AJCC Staging System with the following determination for breast and axilla by local pathology laboratory evaluation: T0: no evidence of primary tumor; Tis: early cancer that has not spread to neighboring tissue and N0: no cancer found in the lymph nodes.

End point type	Primary

End point timeframe:

Surgery visit (at approximately Weeks 14 to 19)

End point values	Ipatasertib + Paclitaxel	Placebo + Paclitaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	16		
Units: percentage of participants				
number (confidence interval 95%)	15.8 (4.45 to 38.36)	12.5 (2.27 to 35.43)		

Statistical analyses

Statistical analysis title	pCR in Breast and Axilla in PTEN-low Tumors

Statistical analysis description:

Unstratified analysis

Comparison groups	Ipatasertib + Paclitaxel v Placebo + Paclitaxel

Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.7817
Method	Chi-squared
Parameter estimate	Difference in response rates
Point estimate	3.29
Confidence interval	
level	95 %
sides	2-sided
lower limit	-25.52
upper limit	32.1

Secondary: Percentage of Participants With pCR in Breast as Defined by ypT0/Tis in the American Joint Committee on Cancer Staging System (in All Participants)

End point title	Percentage of Participants With pCR in Breast as Defined by ypT0/Tis in the American Joint Committee on Cancer Staging System (in All Participants)

End point description:

pCR was defined by ypT0/Tis in the AJCC Staging System with the following determination for breast by local pathology laboratory evaluation: T0: no evidence of primary tumor; Tis: early cancer that has not spread to neighboring tissue.

End point type	Secondary

End point timeframe:

Surgery visit (at approximately Weeks 14 to 19)

End point values	Ipatasertib + Paclitaxel	Placebo + Paclitaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	76	75		
Units: percentage of participants				
number (confidence interval 95%)	22.4 (14.33 to 33.31)	14.7 (7.98 to 24.04)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With pCR in Breast as Defined by ypT0/Tis in the American Joint Committee on Cancer Staging System (in Participants Who Have PTEN-low Tumors)

End point title	Percentage of Participants With pCR in Breast as Defined by ypT0/Tis in the American Joint Committee on Cancer Staging System (in Participants Who Have PTEN-low Tumors)

End point description:

pCR was defined by ypT0/Tis in the AJCC Staging System with the following determination for breast by local pathology laboratory evaluation: T0: no evidence of primary tumor; Tis: early cancer that has not

spread to neighboring tissue.

End point type	Secondary

End point timeframe:

Surgery visit (at approximately Weeks 14 to 19)

End point values	Ipatasertib + Paclitaxel	Placebo + Paclitaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	16		
Units: percentage of participants				
number (confidence interval 95%)	15.8 (4.45 to 38.36)	18.8 (5.31 to 42.94)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Objective Tumor Response by Magnetic Resonance Imaging (MRI), As Assessed by Investigator per the Modified Response Evaluation Criteria in Solid Tumors (RECIST) (in All Participants)

End point title	Percentage of Participants With Objective Tumor Response by Magnetic Resonance Imaging (MRI), As Assessed by Investigator per the Modified Response Evaluation Criteria in Solid Tumors (RECIST) (in All Participants)

End point description:

ORR was based on criteria related to changes in size of target lesions according to modified RECIST. Target lesions were selected on the basis of their size (lesions with the longest diameter) as well as the feasibility of reproducible repeated measurements. ORR was the sum of complete response (CR) and partial response (PR). CR: disappearance of all target lesions. PR: at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters.

End point type	Secondary

End point timeframe:

Screening up to disease progression or death (assessed at screening, pre-surgical visit [approximately Weeks 10-12], early termination visit [up to Week 16])

End point values	Ipatasertib + Paclitaxel	Placebo + Paclitaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	76	75		
Units: percentage of participants				
number (confidence interval 95%)	67.1 (55.86 to 77.46)	56.0 (44.46 to 66.84)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Objective Tumor Response by MRI, As Assessed by Investigator per Modified RECIST (in Participants Who Have PTEN-low Tumors)

End point title	Percentage of Participants With Objective Tumor Response by MRI, As Assessed by Investigator per Modified RECIST (in Participants Who Have PTEN-low Tumors)

End point description:

ORR was based on criteria related to changes in size of target lesions according to modified RECIST. Target lesions were selected on the basis of their size (lesions with the longest diameter) as well as the feasibility of reproducible repeated measurements. ORR was the sum of complete response (CR) and partial response (PR). CR: disappearance of all target lesions. PR: at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters.

End point type	Secondary

End point timeframe:

Screening up to disease progression or death (assessed at screening, pre-surgical visit [approximately Weeks 10-12], early termination visit [up to Week 16])

End point values	Ipatasertib + Paclitaxel	Placebo + Paclitaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	16		
Units: percentage of participants				
number (confidence interval 95%)	73.7 (50.00 to 89.01)	50.0 (27.20 to 72.80)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With pCR in Breast and Axilla as Defined by ypT0/Tis ypN0 in the American Joint Committee on Cancer Staging System (in Participants Who Are Akt diagnostic positive [Dx+])

End point title	Percentage of Participants With pCR in Breast and Axilla as Defined by ypT0/Tis ypN0 in the American Joint Committee on Cancer Staging System (in Participants Who Are Akt diagnostic positive [Dx+])

End point description:

pCR was defined by ypT0/Tis ypN0 in the AJCC Staging System with the following determination for breast and axilla by local pathology laboratory evaluation: T0: no evidence of primary tumor; Tis: early cancer that has not spread to neighboring tissue and N0: no cancer found in the lymph nodes.

End point type	Secondary

End point timeframe:

Surgery visit (at approximately Weeks 14 to 19)

End point values	Ipatasertib + Paclitaxel	Placebo + Paclitaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	34		
Units: percentage of participants				
number (confidence interval 95%)	17.9 (7.31 to 35.71)	11.8 (4.12 to 27.19)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With pCR in Breast as Defined by ypT0/Tis in the American Joint Committee on Cancer Staging System (in Participants Who Are Akt Dx+)

End point title	Percentage of Participants With pCR in Breast as Defined by ypT0/Tis in the American Joint Committee on Cancer Staging System (in Participants Who Are Akt Dx+)

End point description:

pCR was defined by ypT0/Tis in the AJCC Staging System with the following determination for breast by local pathology laboratory evaluation: T0: no evidence of primary tumor; Tis: early cancer that has not spread to neighboring tissue.

End point type	Secondary

End point timeframe:

Surgery visit (at approximately Weeks 14 to 19)

End point values	Ipatasertib + Paclitaxel	Placebo + Paclitaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	34		
Units: percentage of participants				
number (confidence interval 95%)	21.4 (9.77 to 40.58)	11.8 (4.12 to 27.19)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With pCR According to American Joint Committee on Cancer Staging System, by Breast Cancer Subtype

End point title	Percentage of Participants With pCR According to American Joint Committee on Cancer Staging System, by Breast Cancer Subtype

End point description:

pCR was defined by ypT0/Tis in the AJCC Staging System with the following determination for breast subtypes by local pathology laboratory evaluation: T0: no evidence of primary tumor; Tis: early cancer that has not spread to neighboring tissue. The intrinsic molecular subtypes of breast cancer included here are luminal A (LumA), Her-2, basal-like, normal and unknown.

End point type	Secondary

End point timeframe:

Surgery visit (at approximately Weeks 14 to 19)

End point values	Ipatasertib + Paclitaxel	Placebo + Paclitaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	32		
Units: percentage of participants				
number (not applicable)				
Unknown	18.5	21.9		
Basal	22.0	10.8		
Her2	33.3	0		
LumA	0	0		
Normal	50.0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Response to Undergoing Breast Conserving Surgery (BCS) Among Participants With T2 or T3 Tumors

End point title	Percentage of Participants With Response to Undergoing Breast Conserving Surgery (BCS) Among Participants With T2 or T3 Tumors

End point description:

After neoadjuvant treatment, the number of patients who is appropriate for breast conserving surgery is reported as a measure of efficacy of the treatment to shrink the tumor enough for patients to benefit from less aggressive surgical management. Breast-conserving surgery was defined as removal of part of the breast tissue during surgery. T2 or T3 in the AJCC Staging System were defined as follows: T2: tumor was more than 2 centimeter (cm) but no more than 5 cm across; T3: tumor was larger than 5 cm across.

End point type	Secondary

End point timeframe:

Surgery visit (at approximately Weeks 14 to 19)

End point values	Ipatasertib + Paclitaxel	Placebo + Paclitaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	63		
Units: percentage of participants				
number (confidence interval 95%)	64.5 (51.93 to 76.26)	60.3 (47.20 to 71.74)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Response to Conversion to BCS Among Participants With T2 or T3 Tumors

End point title	Percentage of Participants With Response to Conversion to BCS Among Participants With T2 or T3 Tumors

End point description:

After neoadjuvant treatment, the number of patients who is appropriate for breast conserving surgery is reported as a measure of efficacy of the treatment to shrink the tumor enough for patients to benefit from less aggressive surgical management. Breast-conserving surgery was defined as removal of part of the breast tissue during surgery. T2 or T3 in the AJCC Staging System were defined as follows: T2: tumor was more than 2 centimeter (cm) but no more than 5 cm across; T3: tumor was larger than 5 cm across.

End point type	Secondary

End point timeframe:

From screening to surgery visit (at approximately Weeks 14 to 19)

End point values	Ipatasertib + Paclitaxel	Placebo + Paclitaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	16		
Units: percentage of participants				
number (confidence interval 95%)	33.3 (12.29 to 65.11)	25 (9.03 to 50.00)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Adverse Events

End point title	Percentage of Participants With Adverse Events

End point description:

An adverse event is any untoward medical occurrence in a participant 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.

End point type	Secondary

End point timeframe:

Screening up to Week 24

End point values	Ipatasertib + Paclitaxel	Placebo + Paclitaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	76	75		
Units: percentage of participants				
number (not applicable)	100	98.7		

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Concentrations of Ipatasertib on Day 1 and Day 8

End point title	Plasma Concentrations of Ipatasertib on Day 1 and Day 8[1]

End point description:

Plasma samples for pharmacokinetic characterization was collected at various timepoints in all participants.

End point type	Secondary

End point timeframe:

0.5 and 4 hours post dose on Day 1 of Cycle 1, 166 and 170 hours post dose from Day 1 of Cycle 1 (Cycle length = 28 days)

Notes:

[1] - 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: Only Plasma concentrations of ipatasertib were collected.

End point values	Ipatasertib + Paclitaxel			
Subject group type	Reporting group			
Number of subjects analysed	73			
Units: ng/mL				
arithmetic mean (standard deviation)				
0.5 hours (73 subjects analyzed)	290 (± 312)			
4 hours (72 subjects analyzed)	196 (± 93.0)			
166 hours (71 subjects analyzed)	37.5 (± 28.3)			
170 hours (71 subjects analyzed)	355 (± 204)			

Statistical analyses

No statistical analyses for this end point

Secondary: Minimum Observed Plasma Concentration (Cmin) of Ipatasertib

End point title	Minimum Observed Plasma Concentration (Cmin) of

End point description:

Plasma samples for pharmacokinetic characterization was collected on Day 1 and Day 8 in all participants.

End point type	Secondary

End point timeframe:

0.5 and 4 hours post dose on Day 1 of Cycle 1, 166 and 170 hours post dose from Day 1 of Cycle 1

(Cycle length = 28 days)

Notes:

[2] - 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: Only Plasma concentrations of ipatasertib were collected.

End point values	Ipatasertib + Paclitaxel			
Subject group type	Reporting group			
Number of subjects analysed	71			
Units: ng/mL				
arithmetic mean (standard deviation)	37.5 (± 28.3)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

2 years and 6 months

Adverse event reporting additional description:

The safety population was identical to the ITT population. The ITT population comprised all 151 randomized patients.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	Ipatasertib + Paclitaxel

Reporting group description:

Participants received ipatasertib orally daily on Days 1-21 of each 28-day cycle for 3 cycles and paclitaxel intravenous (IV) infusion every week (QW) for 3 cycles (12 total doses).

Reporting group title	Placebo + Paclitaxel

Reporting group description:

Participants received placebo (matching to ipatasertib) orally daily on Days 1-21 of each 28-day cycle for 3 cycles and paclitaxel IV infusion QW for 3 cycles (12 total doses).

Serious adverse events	Ipatasertib + Paclitaxel	Placebo + Paclitaxel	
Total subjects affected by serious adverse events			
subjects affected / exposed	10 / 76 (13.16%)	3 / 75 (4.00%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events			
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 76 (1.32%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	1 / 76 (1.32%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Complication associated with device			
subjects affected / exposed	1 / 76 (1.32%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

General physical health deterioration			
subjects affected / exposed	0 / 76 (0.00%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Sickle cell anaemia with crisis			
subjects affected / exposed	1 / 76 (1.32%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 76 (1.32%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pneumonitis			
subjects affected / exposed	1 / 76 (1.32%)	0 / 75 (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			
Device related infection			
subjects affected / exposed	2 / 76 (2.63%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 76 (1.32%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Atypical pneumonia			
subjects affected / exposed	1 / 76 (1.32%)	0 / 75 (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			
Dehydration			

subjects affected / exposed	1 / 76 (1.32%)	0 / 75 (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 + Paclitaxel	Placebo + Paclitaxel	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	76 / 76 (100.00%)	73 / 75 (97.33%)	
Vascular disorders			
Flushing			
subjects affected / exposed	7 / 76 (9.21%)	4 / 75 (5.33%)	
occurrences (all)	8	4	
Hot flush			
subjects affected / exposed	6 / 76 (7.89%)	5 / 75 (6.67%)	
occurrences (all)	6	5	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	32 / 76 (42.11%)	29 / 75 (38.67%)	
occurrences (all)	52	55	
Fatigue			
subjects affected / exposed	23 / 76 (30.26%)	24 / 75 (32.00%)	
occurrences (all)	31	36	
Mucosal dryness			
subjects affected / exposed	4 / 76 (5.26%)	0 / 75 (0.00%)	
occurrences (all)	5	0	
Mucosal inflammation			
subjects affected / exposed	14 / 76 (18.42%)	5 / 75 (6.67%)	
occurrences (all)	16	7	
Oedema peripheral			
subjects affected / exposed	3 / 76 (3.95%)	5 / 75 (6.67%)	
occurrences (all)	3	6	
Pyrexia			
subjects affected / exposed	8 / 76 (10.53%)	4 / 75 (5.33%)	
occurrences (all)	9	4	

Reproductive system and breast disorders			
Amenorrhoea			
subjects affected / exposed	1 / 76 (1.32%)	5 / 75 (6.67%)	
occurrences (all)	1	5	
Breast pain			
subjects affected / exposed	4 / 76 (5.26%)	2 / 75 (2.67%)	
occurrences (all)	4	3	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	10 / 76 (13.16%)	8 / 75 (10.67%)	
occurrences (all)	13	9	
Epistaxis			
subjects affected / exposed	12 / 76 (15.79%)	9 / 75 (12.00%)	
occurrences (all)	13	14	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	3 / 76 (3.95%)	6 / 75 (8.00%)	
occurrences (all)	3	7	
Insomnia			
subjects affected / exposed	15 / 76 (19.74%)	15 / 75 (20.00%)	
occurrences (all)	19	17	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	5 / 76 (6.58%)	5 / 75 (6.67%)	
occurrences (all)	7	7	
Aspartate aminotransferase increased			
subjects affected / exposed	3 / 76 (3.95%)	4 / 75 (5.33%)	
occurrences (all)	5	4	
Neutrophil count decreased			
subjects affected / exposed	4 / 76 (5.26%)	4 / 75 (5.33%)	
occurrences (all)	9	7	
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	5 / 76 (6.58%)	4 / 75 (5.33%)	
occurrences (all)	7	4	
Nervous system disorders			

Dizziness			
subjects affected / exposed	7 / 76 (9.21%)	8 / 75 (10.67%)	
occurrences (all)	8	9	
Dysgeusia			
subjects affected / exposed	18 / 76 (23.68%)	17 / 75 (22.67%)	
occurrences (all)	20	19	
Hypoaesthesia			
subjects affected / exposed	1 / 76 (1.32%)	4 / 75 (5.33%)	
occurrences (all)	1	6	
Neuropathy peripheral			
subjects affected / exposed	14 / 76 (18.42%)	14 / 75 (18.67%)	
occurrences (all)	17	19	
Neurotoxicity			
subjects affected / exposed	9 / 76 (11.84%)	6 / 75 (8.00%)	
occurrences (all)	12	10	
Paraesthesia			
subjects affected / exposed	12 / 76 (15.79%)	9 / 75 (12.00%)	
occurrences (all)	15	13	
Peripheral sensory neuropathy			
subjects affected / exposed	8 / 76 (10.53%)	13 / 75 (17.33%)	
occurrences (all)	13	16	
Headache			
subjects affected / exposed	14 / 76 (18.42%)	15 / 75 (20.00%)	
occurrences (all)	21	20	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	14 / 76 (18.42%)	11 / 75 (14.67%)	
occurrences (all)	20	17	
Neutropenia			
subjects affected / exposed	7 / 76 (9.21%)	6 / 75 (8.00%)	
occurrences (all)	15	12	
Eye disorders			
Dry eye			
subjects affected / exposed	3 / 76 (3.95%)	4 / 75 (5.33%)	
occurrences (all)	3	4	
Lacrimation increased			

subjects affected / exposed	4 / 76 (5.26%)	1 / 75 (1.33%)	
occurrences (all)	5	1	
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	4 / 76 (5.26%)	1 / 75 (1.33%)	
occurrences (all)	4	1	
Abdominal Pain			
subjects affected / exposed	14 / 76 (18.42%)	6 / 75 (8.00%)	
occurrences (all)	14	7	
Abdominal pain upper			
subjects affected / exposed	7 / 76 (9.21%)	4 / 75 (5.33%)	
occurrences (all)	9	4	
Constipation			
subjects affected / exposed	10 / 76 (13.16%)	16 / 75 (21.33%)	
occurrences (all)	10	19	
Diarrhoea			
subjects affected / exposed	66 / 76 (86.84%)	24 / 75 (32.00%)	
occurrences (all)	194	45	
Dry mouth			
subjects affected / exposed	7 / 76 (9.21%)	6 / 75 (8.00%)	
occurrences (all)	8	11	
Gastrooesophageal reflux disease			
subjects affected / exposed	5 / 76 (6.58%)	8 / 75 (10.67%)	
occurrences (all)	6	8	
Dyspepsia			
subjects affected / exposed	12 / 76 (15.79%)	9 / 75 (12.00%)	
occurrences (all)	12	9	
Nausea			
subjects affected / exposed	36 / 76 (47.37%)	23 / 75 (30.67%)	
occurrences (all)	52	25	
Stomatitis			
subjects affected / exposed	5 / 76 (6.58%)	6 / 75 (8.00%)	
occurrences (all)	6	7	
Vomiting			
subjects affected / exposed	17 / 76 (22.37%)	4 / 75 (5.33%)	
occurrences (all)	21	5	

Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	40 / 76 (52.63%)	40 / 75 (53.33%)	
occurrences (all)	50	54	
Dermatitis Acneiform			
subjects affected / exposed	4 / 76 (5.26%)	3 / 75 (4.00%)	
occurrences (all)	5	4	
Dry skin			
subjects affected / exposed	5 / 76 (6.58%)	3 / 75 (4.00%)	
occurrences (all)	5	3	
Erythema			
subjects affected / exposed	5 / 76 (6.58%)	4 / 75 (5.33%)	
occurrences (all)	6	9	
Onycholysis			
subjects affected / exposed	5 / 76 (6.58%)	2 / 75 (2.67%)	
occurrences (all)	6	2	
Pruritus			
subjects affected / exposed	6 / 76 (7.89%)	10 / 75 (13.33%)	
occurrences (all)	7	13	
Rash			
subjects affected / exposed	19 / 76 (25.00%)	14 / 75 (18.67%)	
occurrences (all)	25	21	
Rash maculo-papular			
subjects affected / exposed	4 / 76 (5.26%)	7 / 75 (9.33%)	
occurrences (all)	7	11	
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	1 / 76 (1.32%)	5 / 75 (6.67%)	
occurrences (all)	1	6	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	8 / 76 (10.53%)	6 / 75 (8.00%)	
occurrences (all)	10	7	
Musculoskeletal pain			
subjects affected / exposed	5 / 76 (6.58%)	3 / 75 (4.00%)	
occurrences (all)	5	3	

Myalgia			
subjects affected / exposed	6 / 76 (7.89%)	12 / 75 (16.00%)	
occurrences (all)	6	13	
Pain in extremity			
subjects affected / exposed	4 / 76 (5.26%)	7 / 75 (9.33%)	
occurrences (all)	4	7	
Infections and infestations			
Conjunctivitis			
subjects affected / exposed	2 / 76 (2.63%)	5 / 75 (6.67%)	
occurrences (all)	2	5	
Folliculitis			
subjects affected / exposed	5 / 76 (6.58%)	3 / 75 (4.00%)	
occurrences (all)	5	3	
Upper respiratory tract infection			
subjects affected / exposed	3 / 76 (3.95%)	5 / 75 (6.67%)	
occurrences (all)	3	6	
Urinary tract infection			
subjects affected / exposed	8 / 76 (10.53%)	9 / 75 (12.00%)	
occurrences (all)	13	10	
Viral upper respiratory tract infection			
subjects affected / exposed	4 / 76 (5.26%)	7 / 75 (9.33%)	
occurrences (all)	4	8	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	11 / 76 (14.47%)	6 / 75 (8.00%)	
occurrences (all)	14	7	
Hyperglycaemia			
subjects affected / exposed	3 / 76 (3.95%)	5 / 75 (6.67%)	
occurrences (all)	4	6	
Hypokalaemia			
subjects affected / exposed	4 / 76 (5.26%)	2 / 75 (2.67%)	
occurrences (all)	9	3	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 July 2015	Request for tumor biopsy had been changed from optional to mandated for patients who are discontinued from study treatment prior to surgery. Evaluation of the patient's tumor sample for PTEN status by a central laboratory was clarified to indicate that it should occur prior to the initiation of study treatment even though in the absence of archival tissue, fresh tissue biopsy samples will be acceptable for eligibility. Guidance for pathology assessment in the study was added. In situ hybridization (ISH) was added as an additional optional method to study exploratory endpoints.
19 January 2016	Dosing delay due to treatment-related toxicity had been clarified that when dosing delay to paclitaxel occurs, preferred dosing for ipatasertib/placebo is to align and resume with paclitaxel dosing. Clarified that dose reductions and dose modification(s) for ipatasertib/placebo and paclitaxel are independent. Further guidance and clarification to the management of diarrhea had been provided. Grade ≥ 3 diarrhea and Grade 2 diarrhea that persists for longer than 5 days despite optimal medical management had been added as adverse event of special interest. Data entry requirements for adverse event reporting had been clarified for persistent or recurrent adverse events. A sensitivity analysis that accounts for patients whose pCR assessment cannot be ascertained had been added.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported