Clinical trial results:
A Randomized, Phase II, Multicenter, Placebo-Controlled Study of Ipatasertib (GDC-0068), an Inhibitor of Akt, in Combination with Paclitaxel as Front-Line Treatment for Patients with Metastatic Triple-Negative Breast Cancer

Summary

EudraCT number	2014-000469-35
Trial protocol	IT BE ES FR
Global end of trial date	

Results information

Result version number	v1
This version publication date	24 June 2017
First version publication date	24 June 2017

Trial information

Trial identification

Sponsor protocol code	GO29227

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02162719
WHO universal trial number (UTN)	-
Other trial identifiers	LOTUS: Alias ID

Notes:

Sponsors

Sponsor organisation name	Hoffmann-La Roche
Sponsor organisation address	Grenzacherstrasse 124, Basel, Switzerland, CH4070
Public contact	Medical Communications, Hoffmann-La Roche, +41 616878333, global.trial_information@roche.com
Scientific contact	Medical Communications, Hoffmann-La Roche, +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	Interim
Date of interim/final analysis	07 June 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	07 June 2016
Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

To estimate the efficacy of ipatasertib combined with paclitaxel compared with placebo combined with paclitaxel in subjects with inoperable locally advanced metastatic triple-negative breast cancer (mTNBC), as measured by PFS in all subjects and in subjects with PTEN-low tumors.

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	19 August 2014
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	24 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 31
Country: Number of subjects enrolled	Spain: 13
Country: Number of subjects enrolled	France: 14
Country: Number of subjects enrolled	Belgium: 1
Country: Number of subjects enrolled	Korea, Democratic People's Republic of: 41
Country: Number of subjects enrolled	Taiwan: 11
Country: Number of subjects enrolled	Singapore: 7
Country: Number of subjects enrolled	Italy: 6
Worldwide total number of subjects	124
EEA total number of subjects	34

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)	101
From 65 to 84 years	23
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 166 subjects were screened, out of which 42 subjects failed screening. A total of 124 subjects were enrolled at 44 sites. Results are reported here up to clinical cut-off date of 7 June 2016.

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 and Paclitaxel

Arm description:

Subjects received paclitaxel 80 mg/m^2, intravenously on Days 1, 8, and 15 along with ipatasertib 400 mg, orally, once daily from Days 1-21 in each cycle of 28 days until disease progression, intolerable toxicity, elective withdrawal from the study, or study completion or termination.

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

Dosage and administration details:

Ipatasertib 400 mg once daily (QD), beginning on Cycle 1, Day 1 through Day 21 of each 28-day cycle until disease progression or intolerable toxicity.

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 80 mg/m^2 as intravenous (IV) infusion on Days 1, 8, and 15 of each cycle of 28 days.

Arm title	Placebo and Paclitaxel

Arm description:

Subjects received paclitaxel 80 mg/m^2, intravenously on Days 1, 8, and 15 along with ipatasertib matching placebo, orally, once daily from Days 1-21 in each cycle of 28 days until disease progression, intolerable toxicity, elective withdrawal from the study, or study completion or termination.

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

Dosage and administration details:

Ipatasertib matching placebo orally, once daily on Cycle 1, Day 1 through Day 21 of each 28-day cycle until disease progression or intolerable toxicity.

Investigational medicinal product name	Paclitaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Paclitaxel 80 mg/m^2 as intravenous (IV) infusion on Days 1, 8, and 15 of each cycle of 28 days.

Number of subjects in period 1	Ipatasertib and Paclitaxel	Placebo and Paclitaxel
Started	62	62
Treated	61	62
Completed	0	0
Not completed	62	62
Death	9	17
Ongoing	49	41
Withdrawal by Subject	3	3
Lost to follow-up	-	1
Reason not Specified	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Ipatasertib and Paclitaxel
Reporting group description:	
Subjects received paclitaxel 80 mg/m^2, intravenously on Days 1, 8, and 15 along with ipatasertib 400 mg, orally, once daily from Days 1-21 in each cycle of 28 days until disease progression, intolerable toxicity, elective withdrawal from the study, or study completion or termination.	
Reporting group title	Placebo and Paclitaxel
Reporting group description:	
Subjects received paclitaxel 80 mg/m^2, intravenously on Days 1, 8, and 15 along with ipatasertib matching placebo, orally, once daily from Days 1-21 in each cycle of 28 days until disease progression, intolerable toxicity, elective withdrawal from the study, or study completion or termination.	

Reporting group values	Ipatasertib and Paclitaxel	Placebo and Paclitaxel	Total
Number of subjects	62	62	124
Age categorical Units: Subjects			
Adults (18-40 years)	10	5	15
From 41-64 years	40	46	86
65 years and over	12	11	23
Age continuous Units: years			
arithmetic mean	53.6	54.3	
standard deviation	± 13.3	± 10.9	-
Gender categorical Units: Subjects			
Female	62	62	124

End points

End points reporting groups

Reporting group title	Ipatasertib and Paclitaxel
Reporting group description:	
Subjects received paclitaxel 80 mg/m^2, intravenously on Days 1, 8, and 15 along with ipatasertib 400 mg, orally, once daily from Days 1-21 in each cycle of 28 days until disease progression, intolerable toxicity, elective withdrawal from the study, or study completion or termination.	
Reporting group title	Placebo and Paclitaxel
Reporting group description:	
Subjects received paclitaxel 80 mg/m^2, intravenously on Days 1, 8, and 15 along with ipatasertib matching placebo, orally, once daily from Days 1-21 in each cycle of 28 days until disease progression, intolerable toxicity, elective withdrawal from the study, or study completion or termination.	

Primary: Progression Free Survival (PFS)

End point title	Progression Free Survival (PFS)
End point description:	
PFS was defined as the time from randomization to the first occurrence of disease progression, as determined by investigator review of tumor assessments by RECIST, v1.1 or death on study (<=30 days after the last dose of study treatment regimen) from any cause, whichever occurred first. Intent to treat population included all randomized subjects allocated to the treatment arm to which they were randomized.	
End point type	Primary
End point timeframe:	
Baseline up to 30 days after the last dose of study drug administration (clinical cut off date: 07 June 2016)	

End point values	Ipatasertib and Paclitaxel	Placebo and Paclitaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	62		
Units: Months				
median (confidence interval 90%)	6.18 (4.57 to 7.33)	4.93 (3.58 to 5.36)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Ipatasertib and Paclitaxel v Placebo and Paclitaxel
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0372 [1]
Method	Logrank
Parameter estimate	Hazard Ratio (Stratified Analysis)
Point estimate	0.6

Confidence interval	
level	90 %
sides	2-sided
lower limit	0.4
upper limit	0.91

Notes:

[1] - Stratification variables were adjuvant/neoadjuvant treatment including treatment with or without radiation, disease-free interval from last dose (<=12 vs >12 months vs. no prior chemotherapy), PTEN status of tumor (H-score 0, vs. 1 to 150, vs. >150).

Primary: PFS in Subjects with Phosphatase and Tensin Homolog (PTEN)-Low Tumors

End point title	PFS in Subjects with Phosphatase and Tensin Homolog (PTEN)-Low Tumors

End point description:

PFS was defined as the time from randomization to the first occurrence of disease progression, as determined by investigator review of tumor assessments by RECIST, v1.1 or death on study (<=30 days after the last dose of study treatment regimen) from any cause, whichever occurred first. ITT population included all randomized subjects allocated to the treatment arm to which they were randomized. Subjects with PTEN-low tumors were evaluated for this endpoint.

End point type	Primary

End point timeframe:

Baseline up to 30 days after the last dose of study drug administration (clinical cut off date: 07 June 2016)

End point values	Ipatasertib and Paclitaxel	Placebo and Paclitaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	23		
Units: Months				
median (confidence interval 90%)	6.18 (3.65 to 9.1)	3.65 (2.53 to 5.75)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Ipatasertib and Paclitaxel v Placebo and Paclitaxel
Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1753 [2]
Method	Logrank
Parameter estimate	Hazard Ratio (Stratified Analysis)
Point estimate	0.59
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.3
upper limit	1.16

Notes:

[2] - Stratification variables were adjuvant/neoadjuvant treatment including treatment with or without radiation, disease-free interval from last dose (<=12 vs >12 months vs. no prior chemotherapy), PTEN status of tumor (H-score 0, vs. 1 to 150, vs. >150).

Secondary: PFS in Subjects with Phosphatidylinositol-4,5-bisphosphate 3-kinase Catalytic Subunit Alpha (PIK3CA)/ Protein Kinase B (AKT1)/ PTEN-altered Tumors

End point title	PFS in Subjects with Phosphatidylinositol-4,5-bisphosphate 3-kinase Catalytic Subunit Alpha (PIK3CA)/ Protein Kinase B (AKT1)/ PTEN-altered Tumors

End point description:

PFS was defined as the time from randomization to the first occurrence of disease progression, as determined by investigator review of tumor assessments by RECIST, v1.1 or death on study (<=30 days after the last dose of study treatment regimen) from any cause, whichever occurred first. ITT population included all randomized subjects allocated to the treatment arm to which they were randomized. Subjects with PIK3CA/AKT1/PTEN-altered tumors were evaluated for this endpoint.

End point type	Secondary

End point timeframe:

Baseline up to 30 days after the last dose of study drug administration (clinical cut off date: 07 June 2016)

End point values	Ipatasertib and Paclitaxel	Placebo and Paclitaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26	16		
Units: Months				
median (confidence interval 90%)	9.03 (4.57 to 12.88)	4.93 (3.58 to 5.39)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Ipatasertib and Paclitaxel v Placebo and Paclitaxel
Number of subjects included in analysis	42
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.3636
Method	Logrank
Parameter estimate	Hazard Ratio (Unstratified Analysis)
Point estimate	0.76
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.46
upper limit	1.27

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. ITT population included all randomized subjects allocated to the treatment arm to which they were randomized. Data for this endpoint is not reported as it is not yet mature. Data will be reported at final results posting.

End point type	Secondary

End point timeframe:

Baseline to up to clinical cut off date: 07 June 2016

End point values	Ipatasertib and Paclitaxel	Placebo and Paclitaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[3]	0[4]		
Units: months				
median (confidence interval 90%)				
Overall Survival	(to)	(to)		

Notes:

[3] - Data will be reported at final results posting.

[4] - Data will be reported at final results posting.

Statistical analyses

No statistical analyses for this end point

Secondary: OS in Subjects with PTEN-Low Tumors

End point title	OS in Subjects with PTEN-Low Tumors

End point description:

OS was defined as the time from the date of randomization to the date of death from any cause. ITT population included all randomized subjects allocated to the treatment arm to which they were randomized. Subjects with PTEN-low tumor were evaluated for this endpoint. Data for this endpoint is not reported as it is not yet mature. Data will be reported at final results posting.

End point type	Secondary

End point timeframe:

Baseline to up to clinical cut off date: 07 June 2016

End point values	Ipatasertib and Paclitaxel	Placebo and Paclitaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[5]	0[6]		
Units: months				
median (confidence interval 90%)				
Overall Survival	(to)	(to)		

Notes:

[5] - Data will be reported at final results posting.

[6] - Data will be reported at final results posting.

Statistical analyses

No statistical analyses for this end point

Secondary: OS in Subjects with PIK3CA/AKT1/PTEN-altered Tumors

End point title	OS in Subjects with PIK3CA/AKT1/PTEN-altered Tumors

End point description:

OS was defined as the time from the date of randomization to the date of death from any cause. ITT population included all randomized subjects allocated to the treatment arm to which they were randomized. Subjects with PIK3CA/AKT1/PTEN-altered tumors were evaluated for this endpoint. Data for this endpoint is not reported as it is not yet mature. Data will be reported at final results posting.

End point type	Secondary

End point timeframe:

Baseline to up to clinical cut off date: 07 June 2016

End point values	Ipatasertib and Paclitaxel	Placebo and Paclitaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[7]	0[8]		
Units: months				
median (confidence interval 90%)				
Overall Survival	(to)	(to)		

Notes:

[7] - Data will be reported at final results posting.

[8] - Data will be reported at final results posting.

Statistical analyses

No statistical analyses for this end point

Secondary: Objective Response Rate (ORR)

End point title	Objective Response Rate (ORR)

End point description:

Confirmed tumor ORR in subjects with measurable disease at baseline was assessed by the investigator per RECIST, v1.1. Confirmed ORR was defined as the percentage of subjects who achieved either a complete response or partial response based on the investigator assessment that was confirmed by a repeat assessment no less than 4 weeks after the criteria for response was first met. Subjects for whom no records of post-baseline tumor assessments were reported were counted as non-responders. Complete response (CR): disappearance of all target lesions, any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm. Partial response (PR): at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters. ITT population included all randomized subjects allocated to the treatment arm to which they were randomized.

End point type	Secondary

End point timeframe:

Baseline up to every 8 weeks until documented disease progression (up to clinical cut off: 07 June 2016)

End point values	Ipatasertib and Paclitaxel	Placebo and Paclitaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	62		
Units: percentage of subjects				
number (confidence interval 90%)	40.3 (30.64 to 50.9)	32.3 (23.35 to 42.36)		

Statistical analyses

No statistical analyses for this end point

Secondary: ORR in Subjects with PTEN-Low Tumors

End point title	ORR in Subjects with PTEN-Low Tumors

End point description:

Confirmed tumor ORR in subjects with measurable disease at baseline was assessed by the investigator per RECIST, v1.1. Confirmed ORR was defined as the percentage of subjects who achieved either a complete response or partial response based on the investigator assessment that was confirmed by a repeat assessment no less than 4 weeks after the criteria for response was first met. Subjects for whom no records of post-baseline tumor assessments were reported were counted as non-responders. Complete response (CR): disappearance of all target lesions, any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm. Partial response (PR): at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters. ITT population included all randomized subjects allocated to the treatment arm to which they were randomized. Subjects with PTEN-Low Tumors were evaluated for this endpoint.

End point type	Secondary

End point timeframe:

Baseline up to every 8 weeks until documented disease progression (up to clinical cut off: 07 June 2016)

End point values	Ipatasertib and Paclitaxel	Placebo and Paclitaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	23		
Units: percentage of subjects				
number (confidence interval 90%)	48 (30.73 to 64)	26.1 (12.02 to 43.12)		

Statistical analyses

No statistical analyses for this end point

Secondary: ORR in Subjects with PIK3CA/AKT1/PTEN-altered Tumors

End point title	ORR in Subjects with PIK3CA/AKT1/PTEN-altered Tumors

End point description:

Confirmed tumor ORR in subjects with measurable disease at baseline was assessed by the investigator per RECIST, v1.1. Confirmed ORR was defined as the percentage of subjects who achieved either a complete response or partial response based on the investigator assessment that was confirmed by a repeat assessment no less than 4 weeks after the criteria for response was first met. Subjects for whom no records of post-baseline tumor assessments were reported were counted as non-responders.

Complete response (CR): disappearance of all target lesions, any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm. Partial response (PR): at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters. ITT population included all randomized subjects allocated to the treatment arm to which they were randomized. Subjects with PIK3CA/AKT1/PTEN-altered tumors were evaluated for this endpoint.

End point type	Secondary

End point timeframe:

Baseline up to every 8 weeks until documented disease progression (up to clinical cut off: 07 June 2016)

End point values	Ipatasertib and Paclitaxel	Placebo and Paclitaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26	16		
Units: percentage of subjects				
number (confidence interval 90%)	50 (34.24 to 65.76)	43.8 (23.53 to 66.66)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response

End point title	Duration of Response

End point description:

Duration of objective response in subjects with measurable 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, v1.1. Only subjects who achieved a confirmed objective response were included in the analysis. ITT population included all randomized subjects allocated to the treatment arm to which they were randomized. Here, 99999 indicates that upper limit of duration of response was not reached due to low number of subjects with events.

End point type	Secondary

End point timeframe:

Baseline up to every 8 weeks until documented disease progression (up to clinical cut off: 07 June 2016)

End point values	Ipatasertib and Paclitaxel	Placebo and Paclitaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	20		
Units: months				
median (confidence interval 90%)	7.85 (5.65 to 99999)	7.43 (3.88 to 9.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response in Subjects with PTEN-Low Tumors

End point title	Duration of Response in Subjects with PTEN-Low Tumors

End point description:

Duration of objective response in subjects with measurable 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, v1.1. Only subjects who achieved a confirmed objective response were included in the analysis. ITT population included all randomized subjects allocated to the treatment arm to which they were randomized. Subjects with PTEN-low tumors were evaluated for this endpoint. Here, 99999 indicates that upper limit of duration of response was not reached due to low number of subjects with events.

End point type	Secondary

End point timeframe:

Baseline up to every 8 weeks until documented disease progression (up to clinical cut off: 07 June 2016)

End point values	Ipatasertib and Paclitaxel	Placebo and Paclitaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	6		
Units: Months				
median (confidence interval 90%)	6.54 (4.44 to 99999)	7.49 (7.29 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response in Subjects with PIK3CA/AKT1/PTEN-altered Tumors

End point title	Duration of Response in Subjects with PIK3CA/AKT1/PTEN-altered Tumors

End point description:

Duration of objective response in subjects with measurable 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, v1.1. Only subjects who achieved a confirmed objective response were included in the analysis. ITT population included all randomized subjects allocated to the treatment arm to which they were randomized. Subjects with PIK3CA/AKT1/PTEN-altered tumors were evaluated for this endpoint. Here, 99999 indicates that upper limit of duration of response was not reached due to low number of subjects with events.

End point type	Secondary

End point timeframe:

Baseline up to every 8 weeks until documented disease progression (up to clinical cut off: 07 June 2016)

End point values	Ipatasertib and Paclitaxel	Placebo and Paclitaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	7		
Units: Months				
median (confidence interval 90%)	11.24 (5.59 to 99999)	6.06 (3.78 to 7.56)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Disease Progression

End point title	Time to Disease Progression

End point description:

Time to disease progression was defined as the time from randomization to the first occurrence of disease progression, as determined by investigator review of tumor assessments by RECIST, v1.1. ITT population included all randomized subjects allocated to the treatment arm to which they were randomized.

End point type	Secondary

End point timeframe:

Baseline up to every 8 weeks until documented disease progression (up to clinical cut off: 07 June 2016)

End point values	Ipatasertib and Paclitaxel	Placebo and Paclitaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	62		
Units: Months				
median (confidence interval 90%)	6.18 (4.57 to 7.33)	4.96 (3.61 to 5.39)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Disease Progression in Subjects with PTEN-Low Tumors

End point title	Time to Disease Progression in Subjects with PTEN-Low Tumors

End point description:

Time to disease progression was defined as the time from randomization to the first occurrence of disease progression, as determined by investigator review of tumor assessments by RECIST, v1.1. ITT population included all randomized subjects allocated to the treatment arm to which they were randomized. Subjects with PTEN low tumors were evaluated for this endpoint.

End point type	Secondary

End point timeframe:

Baseline to first occurrence of disease progression

End point values	Ipatasertib and Paclitaxel	Placebo and Paclitaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	23		
Units: Months				
median (confidence interval 90%)	6.18 (3.65 to 9.1)	3.94 (2.53 to 7.33)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Disease Progression in Subjects with PIK3CA/AKT1/PTEN-altered Tumors

End point title	Time to Disease Progression in Subjects with PIK3CA/AKT1/PTEN-altered Tumors

End point description:

Time to disease progression was defined as the time from randomization to the first occurrence of disease progression, as determined by investigator review of tumor assessments by RECIST, v1.1. ITT population included all randomized subjects allocated to the treatment arm to which they were randomized. Subjects with PIK3CA/AKT1/PTEN-altered tumors were evaluated for this endpoint.

End point type	Secondary

End point timeframe:

Baseline up to every 8 weeks until documented disease progression (up to clinical cut off: 07 June 2016)

End point values	Ipatasertib and Paclitaxel	Placebo and Paclitaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26	16		
Units: Months				
median (confidence interval 90%)	9.03 (4.57 to 12.88)	4.93 (3.58 to 5.39)		

Statistical analyses

No statistical analyses for this end point

Secondary: Safety: Percentage of Subjects with Adverse Events

End point title	Safety: Percentage of Subjects with Adverse Events

End point description:

An adverse event was defined as any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. Safety analyses population included all

treated subjects with subjects allocated to the treatment arm associated with the regimen that they actually received.

End point type	Secondary

End point timeframe:

Baseline up to 30 days after the last dose of study drug administration (up to clinical cut off date: 07 June 2016)

End point values	Ipatasertib and Paclitaxel	Placebo and Paclitaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61	62		
Units: percentage of subjects				
number (not applicable)	100	96.8		

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic Endpoint: Apparent Clearance Following Oral Dosing (CL/F) of Ipatasertib

End point title	Pharmacokinetic Endpoint: Apparent Clearance Following Oral Dosing (CL/F) of Ipatasertib

End point description:

The pharmacokinetic (PK) analysis population consisted of all subjects who had evaluable PK data. PK parameters were not calculated due to sparse PK sampling.

End point type	Secondary

End point timeframe:

Cycle 1 Day 1, Cycle 1 Day 8

End point values	Ipatasertib and Paclitaxel	Placebo and Paclitaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[9]	0[10]		
Units: ml/hr				

Notes:

[9] - PK parameters were not calculated due to sparse PK sampling.

[10] - PK parameters were not calculated due to sparse PK sampling.

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic Endpoint: Area Under the Plasma Concentration-time Curve Over the Time Interval From Zero to 24 Hours (AUC0-24h) of Ipatasertib

End point title	Pharmacokinetic Endpoint: Area Under the Plasma Concentration-time Curve Over the Time Interval From Zero to 24 Hours (AUC0-24h) of Ipatasertib

End point description:

The pharmacokinetic (PK) analysis population consisted of all subjects who had evaluable PK data. PK parameters were not calculated due to sparse PK sampling.

End point type	Secondary

End point timeframe:

Cycle 1 Day 1, Cycle 1 Day 8

End point values	Ipatasertib and Paclitaxel	Placebo and Paclitaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[11]	0[12]		
Units: h*ng/mL/mg				

Notes:

[11] - PK parameters were not calculated due to sparse PK sampling.

[12] - PK parameters were not calculated due to sparse PK sampling.

Statistical analyses

No statistical analyses for this end point

Secondary: Patient Reported Outcome (PRO) Measure: Mean Change from Baseline in European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30-item (EORTC QLQ-C30) Score

End point title	Patient Reported Outcome (PRO) Measure: Mean Change from Baseline in European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30-item (EORTC QLQ-C30) Score

End point description:

EORTC QLQ-C30 included functional scales (physical, role, cognitive, emotional, and social), global health status, symptom scales (fatigue, pain, nausea/vomiting), single items (dyspnoea, appetite loss, insomnia, constipation/diarrhea, financial difficulties). Most questions used 4-point scale (1=Not at all to 4=Very much; 2 questions used 7-point scale [1=very poor to 7=Excellent]). Scores averaged, transformed to 0-100 scale; a higher score=better level of functioning. For symptom scale scores, higher level=severe level of symptoms. "A change of at least 10 points from baseline is considered clinically meaningful (Osoba D, Rodrigues G, Myles J, et al. Interpreting the significance of changes in health-related quality of life score. J Clin Oncol 1998;16:139−44). PRO measures were analyzed from baseline up to cycle 5. Scores from later timepoints were not analyzed due to attrition (in both arms, fewer than 50% of subjects remained on treatment beyond cycle 5). ITT population.

End point type	Secondary

End point timeframe:

Baseline (Cycle 1 Day 1) up to Cycle 5 Day 1

End point values	Ipatasertib and Paclitaxel	Placebo and Paclitaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	62		
Units: unit on a scale				
arithmetic mean (standard deviation)				
Appetite loss:Cycle 2 Day 1 (n=57, 53)	7.6 (± 28.18)	-0.63 (± 24.88)		

Appetite loss:Cycle 3 Day 1 (n=46, 43)	9.42 (± 21.84)	-3.88 (± 24.35)		
Appetite loss:Cycle 4 Day 1 (n=49,40)	5.44 (± 23.91)	-4.17 (± 25.25)		
Appetite loss:Cycle 5 Day 1 (n=35,30)	0 (± 18.08)	-1.11 (± 25.5)		
Cognitive Functioning: Cycle 2 Day 1 (n=57, 53)	1.17 (± 14.04)	0.63 (± 17.28)		
Cognitive Functioning: Cycle 3 Day 1 (n=46, 43)	-1.81 (± 19.64)	-1.81 (± 19.64)		
Cognitive Functioning: Cycle 4 Day 1 (n=49, 40)	-3.4 (± 15.95)	0 (± 20.32)		
Cognitive Functioning: Cycle 3 Day 1 (n=36, 30)	0 (± 13.8)	-4.44 (± 19.54)		
Constipation: Cycle 2 Day 1 (n=57, 53)	5.85 (± 24.5)	0.63 (± 25.73)		
Constipation: Cycle 3 Day 1 (n=46, 42)	2.9 (± 19.66)	1.59 (± 22.03)		
Constipation: Cycle 4 Day 1 (n=48, 40)	1.39 (± 16.78)	0.83 (± 30.65)		
Constipation: Cycle 5 Day 1 (n=36, 30)	2.78 (± 14.64)	1.11 (± 20.5)		
Diarrhoea: Cycle 2 Day 1 (n=57, 53)	17.54 (± 30.28)	1.89 (± 15.21)		
Diarrhoea: Cycle 3 Day 1 (n=46, 43)	23.91 (± 34.9)	3.88 (± 18.13)		
Diarrhoea: Cycle 4 Day 1 (n=49, 40)	19.73 (± 34.64)	0.83 (± 15.99)		
Diarrhoea: Cycle 5 Day 1 (n=35, 30)	21.9 (± 37.87)	1.11 (± 16.34)		
Dyspnea: Cycle 2 Day 1 (n=57, 52)	2.92 (± 19.19)	0 (± 18.67)		
Dyspnea: Cycle 3 Day 1 (n=46, 41)	5.07 (± 23.27)	2.44 (± 22.84)		
Dyspnea: Cycle 4 Day 1 (n=49, 39)	3.4 (± 25.68)	5.13 (± 22.35)		
Dyspnea: Cycle 2 Day 1 (n=36, 28)	5.56 (± 25.82)	4.76 (± 23.51)		
Emotional Functioning: Cycle 2 Day 1 (n=57, 53)	12.09 (± 15.9)	4.72 (± 16.87)		
Emotional Functioning: Cycle 3 Day 1 (n=46, 43)	7.37 (± 17.18)	3.88 (± 20.36)		
Emotional Functioning: Cycle 4 Day 1 (n=49, 40)	8.22 (± 16.53)	2.71 (± 21.47)		
Emotional Functioning: Cycle 5 Day 1 (n=35, 30)	8.73 (± 16.3)	1.39 (± 17.79)		
Fatigue: Cycle 2 Day 1 (n=57, 53)	7.99 (± 22.69)	-1.36 (± 16.98)		
Fatigue: Cycle 3 Day 1 (n=46, 43)	9.18 (± 22.63)	1.42 (± 19.44)		
Fatigue: Cycle 4 Day 1 (n=49, 39)	7.94 (± 20.91)	1.85 (± 21.64)		
Fatigue: Cycle 5 Day 1 (n=35, 30)	10.32 (± 20.35)	1.67 (± 20.59)		
Financial difficulties Cycle 2 Day 1 (n=56, 52)	3.57 (± 21.72)	0 (± 20.87)		
Financial difficulties Cycle 3 Day 1 (n=46, 43)	0.72 (± 22.76)	-3.88 (± 24.35)		
Financial difficulties Cycle 4 Day 1 (n=49, 40)	3.4 (± 23.81)	-0.83 (± 29.71)		
Financial difficulties Cycle 5 Day 1 (n=36, 30)	2.78 (± 25.67)	1.11 (± 26.96)		
Nausea/Vomiting Cycle 2 Day 1 (n=57, 53)	9.06 (± 19.43)	2.83 (± 15.24)		
Nausea/Vomiting Cycle 3 Day 1 (n=46, 43)	6.52 (± 14.26)	3.1 (± 14.21)		
Nausea/Vomiting Cycle 4 Day 1 (n=49, 40)	6.8 (± 17.32)	3.75 (± 17.5)		
Nausea/Vomiting Cycle 5 Day 1 (n=36, 30)	3.7 (± 7.03)	0 (± 23.16)		
Pain Cycle 2 Day 1 (n=57, 53)	-3.8 (± 22.93)	-7.86 (± 23.02)		

Pain Cycle 3 Day 1 (n=46, 43)	-4.71 (± 26.45)	-7.36 (± 26.8)		
Pain Cycle 4 Day 1 (n=49, 40)	1.36 (± 28.63)	-3.33 (± 31.62)		
Pain Cycle 5 Day 1 (n=36, 30)	0 (± 26.13)	-5.56 (± 25.27)		
Physical Functioning Cycle 2 Day 1 (n=57, 53)	-4.53 (± 14.23)	-0.16 (± 12.96)		
Physical Functioning Cycle 3 Day 1 (n=46, 43)	-5.94 (± 15.54)	-1.71 (± 13.88)		
Physical Functioning Cycle 4 Day 1 (n=49, 40)	-9.12 (± 13.92)	-3.17 (± 16.54)		
Physical Functioning Cycle 5 Day 1 (n=36, 30)	-8.56 (± 13.47)	-4.44 (± 14.26)		
Global health status Cycle 2 Day 1 (n=57, 53)	-4.68 (± 22.33)	4.72 (± 18.38)		
Global health status Cycle 3 Day 1 (n=46, 43)	-8.15 (± 21.55)	3.29 (± 21.37)		
Global health status Cycle 4 Day 1 (n=49, 40)	-8.5 (± 21.62)	-1.46 (± 26.61)		
Global health status Cycle 5 Day 1 (n=36, 30)	-6.48 (± 22.55)	-5 (± 21.62)		
Role Functioning Cycle 2 Day 1 (n=57, 53)	-5.85 (± 20.04)	0.63 (± 22.4)		
Role Functioning Cycle 3 Day 1 (n=46, 43)	-10.51 (± 24.43)	-2.71 (± 22.69)		
Role Functioning Cycle 4 Day 1 (n=49, 40)	-13.95 (± 25.76)	-6.25 (± 26.34)		
Role Functioning Cycle 5 Day 1 (n=36, 30)	-11.57 (± 21.76)	-7.22 (± 21.3)		
Social Functioning Cycle 2 Day 1 (n=57, 53)	-2.05 (± 26.92)	0 (± 23.34)		
Social Functioning Cycle 3 Day 1 (n=46, 43)	-2.17 (± 23.99)	-3.49 (± 26.11)		
Social Functioning Cycle 4 Day 1 (n=49, 40)	-7.14 (± 27)	-5.83 (± 23.74)		
Social Functioning Cycle 5 Day 1 (n=35, 30)	-4.76 (± 31.72)	-9.44 (± 24.24)		
Insomnia Cycle 2 Day 1 (n=57, 53)	2.92 (± 31.67)	-5.03 (± 24.8)		
Insomnia Cycle 3 Day 1 (n=46, 43)	2.9 (± 25.17)	-3.1 (± 25)		
Insomnia Cycle 4 Day 1 (n=46, 43)	7.48 (± 28.27)	5.83 (± 31.02)		
Insomnia Cycle 5 Day 1 (n=36, 30)	1.85 (± 34.68)	-5.56 (± 29.14)		

Statistical analyses

No statistical analyses for this end point

Secondary: PRO Measure: Percentage of Subject With Improved, Worsened, or Remained Stable for Bothersome Side Effects of Treatment Measured by the Scales of the EORTC QLQ-C30

End point title	PRO Measure: Percentage of Subject With Improved, Worsened, or Remained Stable for Bothersome Side Effects of Treatment Measured by the Scales of the EORTC QLQ-C30

End point description:

Subjects reporting >/= 10-point increase compared to baseline (Cycle 1 Day 1) were considered "improved", those reporting <10-point difference were considered "remained stable", and those

reporting >/=10-point decrease were considered “worsened”. A change of at least 10 points from baseline is considered clinically meaningful (Osoba D, Rodrigues G, Myles J, et al. Interpreting the significance of changes in health-related quality of life score. J Clin Oncol 1998;16:139−44). Patient reported outcome measures were analyzed from baseline up to and including cycle 5. Scores from later timepoints were not analyzed due to attrition (in both arms, fewer than 50% of subjects remained on treatment beyond cycle 5). ITT population included all randomized subjects allocated to treatment arm to which they were randomized.

End point type	Secondary

End point timeframe:

Baseline (Cycle 1 Day 1) up to Cycle 5 Day 1

End point values	Ipatasertib and Paclitaxel	Placebo and Paclitaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	57	53		
Units: Percentage of subjects				
number (not applicable)				
Improved Appetite Loss: Cycle 2 (n=57, 53)	10.5	18.9		
Maintained Appetite Loss: Cycle 2 (n=57, 53)	64.9	66		
Worsened Appetite Loss: Cycle 2 (n=57, 53)	24.6	15.1		
Improved Appetite Loss: Cycle 3 (n=46, 43)	8.7	27.9		
Maintained Appetite Loss: Cycle 3 (n=46, 43)	56.5	53.5		
Worsened Appetite Loss: Cycle 3 (n=46, 43)	34.8	18.6		
Improved Appetite Loss: Cycle 4 (n=49, 40)	10.2	30		
Maintained Appetite Loss: Cycle 4 (n=49, 40)	65.3	57.5		
Worsened Appetite Loss: Cycle 4 (n=49, 40)	24.5	12.5		
Improved Appetite Loss: Cycle 5 (n=35, 30)	8.6	26.7		
Maintained Appetite Loss: Cycle 5 (n=35, 30)	80	53.3		
Wirsened Appetite Loss: Cycle 5 (n=35, 30)	11.4	20		
Improved Diarrhea: Cycle 2 (n=57, 53)	3.5	7.5		
Maintained Diarrhea: Cycle 2 (n=57, 53)	50.9	79.2		
Worsened Diarrhea: Cycle 2 (n=57, 53)	45.6	13.2		
Improved Diarrhea: Cycle 3 (n=46, 43)	8.7	9.3		
Maintained Diarrhea: Cycle 3 (n=46, 43)	39.1	69.8		
Worsened Diarrhea: Cycle 3 (n=46, 43)	52.2	20.9		
Improved Diarrhea: Cycle 4 (n=49, 40)	10.2	10		
Maintained Diarrhea: Cycle 4 (n=49, 40)	38.8	77.5		
Worsened Diarrhea: Cycle 4 (n=49, 40)	51	12.5		
Improved Diarrhea: Cycle 5 (n=35, 30)	14.3	10		
Maintained Diarrhea: Cycle 5 (n=35, 30)	34.3	76.7		

Worsened Diarrhea: Cycle 5 (n=35, 30)	51.4	13.3		
Improved Fatigue: Cycle 2 (n=57, 53)	21.1	34		
Maintained Fatigue: Cycle 2 (n=57, 53)	29.85	30.2		
Worsened Fatigue: Cycle 2 (n=57, 53)	49.1	35.8		
Improved Fatigue: Cycle 3 (n=46, 43)	23.9	34.9		
Maintained Fatigue: Cycle 3 (n=57, 53)	15.2	30.2		
Worsened Fatigue: Cycle 3 (n=57, 53)	60.9	34.9		
Improved Fatigue: Cycle 4 (n=46, 43)	24.5	28.2		
Maintained Fatigue: Cycle 4 (n=46, 43)	28.6	28.2		
Worsened Fatigue: Cycle 4 (n=46, 43)	46.9	43.6		
Improved Fatigue: Cycle 5 (n=46, 43)	20	30		
Maintained Fatigue: Cycle 5 (n=46, 43)	20	43.3		
Worsened Fatigue: Cycle 5 (n=46, 43)	60	26.7		
Improved Nausea/Vomiting Cycle 2 (n=57,53)	3.5	11.3		
Maintained Nausea/Vomiting Cycle 2 (n=57,53)	61.4	64.2		
Worsened Nausea/Vomiting Cycle 2 (n=57,53)	35.1	24.5		
Improved Nausea/Vomiting Cycle 3 (n=46,43)	4.3	9.3		
Maintained Nausea/Vomiting Cycle 3 (n=46,43)	65.2	62.8		
Worsened Nausea/Vomiting Cycle 3 (n=46,43)	30.4	27.9		
Improved Nausea/Vomiting Cycle 4 (n=49,39)	2	7.5		
Maintained Nausea/Vomiting Cycle 4 (n=49,39)	73.5	67.5		
Worsened Nausea/Vomiting Cycle 4 (n=49,39)	24.5	25		
Improved Nausea/Vomiting Cycle 5 (n=36,30)	0	16.7		
Maintained Nausea/Vomiting Cycle 5 (n=36,30)	77.8	60		
Worsened Nausea/Vomiting Cycle 5 (n=36,30)	22.2	23.3		
Improved Cognitive Functioning Cycle 2 (n=57,53)	22.8	17		
Maintained Cognitive Function Cycle 2 (n=57,53)	61.4	60.4		
Worsened Cognitive Function Cycle 2 (n=57,53)	15.8	22.6		
Improved Cognitive Functioning Cycle 3 (n=46,43)	26.1	16.3		
Maintained Cognitive Functioning Cycle 3 (n=46,43)	47.8	53.5		
Worsened Cognitive Functioning Cycle 3 (n=46,43)	26.1	30.2		
Improved Cognitive Functioning Cycle 4 (n=49,40)	20.4	22.5		
Maintained Cognitive Functioning Cycle 4 (n=49,40)	51	52.5		
Worsened Cognitive Functioning Cycle 4 (n=49,40)	28.6	25		
Improved Cognitive Functioning Cycle 5 (n=36,30)	19.4	20		
Maintained Cognitive Functioning Cycle 5 (n=36,30)	58.3	46.7		

Worsened Cognitive Functioning Cycle 5 (n=36,30)	22.2	33.3		
Improved Constipation Cycle 2 (n=57,53)	8.8	17		
Maintained Constipation Cycle 2 (n=57,53)	73.7	64.2		
Worsened Constipation Cycle 2 (n=57,53)	17.5	18.9		
Improved Constipation Cycle 3 (n=46,42)	10.9	9.5		
Maintained Constipation Cycle 3 (n=46,42)	71.7	71.4		
Worsened Constipation Cycle 3 (n=46,42)	17.4	19		
Improved Constipation Cycle 4 (n=48,40)	10.4	15		
Maintained Constipation Cycle 4 (n=48,40)	75	60		
Worsened Constipation Cycle 4 (n=48,40)	14.6	25		
Improved Constipation Cycle 5 (n=36,30)	5.6	13.3		
Maintained Constipation Cycle 5 (n=36,30)	80.6	73.3		
Worsened Constipation Cycle 5 (n=36,30)	13.9	13.3		
Improved Dyspnea Cycle 2 (n=57,52)	5.3	15.4		
Maintained Dyspnea Cycle 2 (n=57,52)	77.2	69.2		
Worsened Dyspnea Cycle 2 (n=57,52)	17.5	15.4		
Improved Dyspnea Cycle 3 (n=46,41)	6.5	14.6		
Maintained Dyspnea Cycle 3 (n=46,41)	67.4	68.3		
Worsened Dyspnea Cycle 3 (n=46,41)	26.1	17.1		
Improved Dyspnea Cycle 4 (n=49,39)	10.2	12.8		
Maintained Dyspnea Cycle 4 (n=49,39)	69.4	61.5		
Worsened Dyspnea Cycle 4 (n=49,39)	20.4	25.6		
Improved Dyspnea Cycle 5 (n=36,28)	8.3	14.3		
Maintained Dyspnea Cycle 5 (n=36,28)	69.4	60.7		
Worsened Dyspnea Cycle 5 (n=36,28)	22.2	25		
Improved Emotional Functioning Cycle 2 (n=57,53)	50.9	35.8		
Maintained Emotional Functioning Cycle 2 (n=57,53)	43.9	50.9		
Worsened Emotional Functioning Cycle 2 (n=57,53)	5.3	13.2		
Improved Emotional Functioning Cycle 3 (n=46,43)	45.7	37.2		
Maintained Emotional Functioning Cycle 3 (n=46,43)	45.7	41.9		
Worsened Emotional Functioning Cycle 3 (n=46,43)	8.7	20.9		
Improved Emotional Functioning Cycle 4 (n=49,40)	42.9	30		
Maintained Emotional Functioning Cycle 4 (n=49,40)	49	45		
Worsened Emotional Functioning Cycle 4 (n=49,40)	8.2	25		
Improved Emotional Functioning Cycle 5 (n=35,30)	42.9	36.7		
Maintained Emotional Functioning Cycle 5 (n=35,30)	48.6	36.7		

Worsened Emotional Functioning Cycle 5 (n=35,30)	8.6	26.7		
Improved Financial Difficulties Cycle 2 (n=56,52)	10.7	13.5		
Maintained Financial Difficulties Cycle 2(n=56,52)	73.2	73.1		
Worsened Financial Difficulties Cycle 2 (n=56,52)	16.1	13.5		
Improved Financial Difficulties Cycle 3 (n=46,43)	13	18.6		
Maintained Financial Difficulties Cycle 3(n=46,43)	73.9	72.1		
Worsened Financial Difficulties Cycle 3 (n=46,43)	13	9.3		
Improved Financial Difficulties Cycle 4 (n=49,40)	10.2	17.5		
Maintained Financial Difficulties Cycle 4(n=49,40)	73.5	70		
Worsened Financial Difficulties Cycle 4 (n=49,40)	16.3	12.5		
Improved Financial Difficulties Cycle 5 (n=36,30)	13.9	20		
Maintained Financial Difficulties Cycle 5(n=36,30)	66.7	63.3		
Worsened Financial Difficulties Cycle 5 (n=36,30)	19.4	16.7		
Improved Pain Cycle 2 (n=57,53)	35.1	35.8		
Maintained Pain Cycle 2 (n=57,53)	40.4	45.3		
Worsened Pain Cycle 2 (n=57,53)	24.6	18.9		
Improved Pain Cycle 3 (n=46,43)	37	39.5		
Maintained Pain Cycle 3 (n=46,43)	39.1	39.5		
Worsened Pain Cycle (n=46,43)	23.9	20.9		
Improved Pain Cycle 4 (n=49,40)	32.7	37.5		
Maintained Pain Cycle 4 (n=49,40)	32.7	35		
Worsened Pain Cycle 4 (n=49,40)	34.7	27.5		
Improved Pain Cycle 5 (n=36,30)	33.3	33.3		
Maintained Pain Cycle 5 (n=36,30)	30.6	40		
Worsened Pain Cycle 5 (n=36,30)	36.1	26.7		
Improved Physical Functioning Cycle 2 (n= 57,53)	7	13.2		
Maintained Physical Functioning Cycle 2 (n= 57,53)	68.4	75.5		
Worsened Physical Functioning Cycle 2 (n= 57,53)	24.6	11.3		
Improved Physical Functioning Cycle 3 (n= 46,43)	8.7	16.3		
Maintained Physical Functioning Cycle 3 (n= 46,43)	67.4	60.5		
Worsened Physical Functioning Cycle 3 (n= 46,43)	23.9	23.3		
Improved Physical Functioning Cycle 4 (n= 49,40)	4.1	17.5		
Maintained Physical Functioning Cycle 4 (n= 49,40)	55.1	57.5		
Worsened Physical Functioning Cycle 4 (n= 49,40)	40.8	25		
Improved Physical Functioning Cycle 5 (n= 36,30)	8.3	16.7		
Maintained Physical Functioning Cycle 5 (n= 36,30)	44.4	46.7		

Worsened Physical Functioning Cycle 5 (n= 36,30)	47.2	36.7		
Improved Global Health Status/QoL Cycle 2(n=57,53)	19.3	26.4		
Maintained Global Health Status/QoL Cycle2(n=57,53	45.6	58.5		
Worsened Global Health Status/QoL Cycle 2(n=57,53)	35.1	15.1		
Improved Global Health Status/QoL Cycle 3(n=46,43)	17.4	25.6		
Maintained Global Health Status/QoL Cycle3(n=46,43	37	60.5		
Worsened Global Health Status/QoL Cycle 3(n=46,43)	45.7	14		
Improved Global Health Status/QoL Cycle 4(n=49,40)	14.3	25		
Maintained Global Health Status/QoL Cycle4(n=49,40	51	42.5		
Worsened Global Health Status/QoL Cycle 4(n=49,40)	34.7	32.5		
Improved Global Health Status/QoL Cycle 5(n=36,30)	11.1	20		
Maintained Global Health Status/QoL Cycle5(n=36,30	58.3	46.7		
Worsened Global Health Status/QoL Cycle 5(n=36,30)	30.6	33.3		
Improved Role Functioning Cycle 2 (n=57,53)	17.5	24.5		
Maintained Role Functioning Cycle 2 (n=57,53)	52.6	45.3		
Worsened Role Functioning Cycle 2 (n=57,53)	29.8	30.2		
Improved Role Functioning Cycle 3 (n=46,43)	13	27.9		
Maintained Role Functioning Cycle 3 (n=46,43)	47.8	46.5		
Worsened Role Functioning Cycle 3 (n=46,43)	39.1	25.6		
Improved Role Functioning Cycle 4 (n=49,40)	12.2	25		
Maintained Role Functioning Cycle 4 (n=49,40)	38.8	37.5		
Worsened Role Functioning Cycle 4 (n=49,40)	49	37.5		
Improved Role Functioning Cycle 5 (n=36,30)	11.1	16.7		
Maintained Role Functioning Cycle 5 (n=36,30)	47.2	40		
Worsened Role Functioning Cycle 5 (n=36,30)	41.7	43.3		
Improved Social Functioning Cycle 2 (n=57, 53)	21.1	22.6		
Maintained Social Functioning Cycle 2 (n=57, 53)	49.1	49.1		
Worsened Social Functioning Cycle 2 (n=57, 53)	29.8	28.3		
Improved Social Functioning Cycle 3 (n=46, 43)	17.4	16.3		
Maintained Social Functioning Cycle 3 (n=46, 43)	52.2	53.5		
Worsened Social Functioning Cycle 3 (n=46, 43)	30.4	30.2		

Improved Social Functioning Cycle 4 (n=49, 40)	16.3	10		
Maintained Social Functioning Cycle 4 (n=49, 40)	49	47.5		
Worsened Social Functioning Cycle 4 (n=49, 40)	34.7	42.5		
Improved Social Functioning Cycle 5 (n=35, 30)	17.1	13.3		
Maintained Social Functioning Cycle 5 (n=35, 30)	48.6	36.7		
Worsened Social Functioning Cycle 5 (n=35, 30)	34.3	50		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From screening up to 30 days post-dose after the last dose of study drug. Serious adverse events considered related to study treatment were collected until end of survival follow up (up to clinical cut off date: 07 June 2016)

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	Ipatasertib and Paclitaxel

Reporting group description:

Subjects received paclitaxel 80 mg/m^2, intravenously on Days 1, 8, and 15 along with ipatasertib 400 mg, orally, once daily from Days 1-21 in each cycle of 28 days until disease progression, intolerable toxicity, elective withdrawal from the study, or study completion or termination.

Reporting group title	Placebo and Paclitaxel

Reporting group description:

Subjects received paclitaxel 80 mg/m^2, intravenously on Days 1, 8, and 15 along with ipatasertib matching placebo, orally, once daily from Days 1-21 in each cycle of 28 days until disease progression, intolerable toxicity, elective withdrawal from the study, or study completion or termination.

Serious adverse events	Ipatasertib and Paclitaxel	Placebo and Paclitaxel	
Total subjects affected by serious adverse events			
subjects affected / exposed	17 / 61 (27.87%)	9 / 62 (14.52%)	
number of deaths (all causes)	1	3	
number of deaths resulting from adverse events	0	1	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast Cancer Metastatic			
subjects affected / exposed	0 / 61 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Vascular disorders			
Embolism			
subjects affected / exposed	1 / 61 (1.64%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Death			

subjects affected / exposed	0 / 61 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pyrexia			
subjects affected / exposed	1 / 61 (1.64%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fever	Additional description: Adverse event raw term instead of MedDRA preferred term is used.		
subjects affected / exposed	0 / 61 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 61 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 61 (1.64%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Neutrophil Count Decreased			
subjects affected / exposed	1 / 61 (1.64%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Spinal Cord Compression			
subjects affected / exposed	1 / 61 (1.64%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Pancytopenia			

subjects affected / exposed	0 / 61 (0.00%)	1 / 62 (1.61%)	
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	2 / 61 (3.28%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	0 / 61 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	3 / 61 (4.92%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	1 / 61 (1.64%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	1 / 61 (1.64%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholestasis			
subjects affected / exposed	0 / 61 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Musculoskeletal and connective tissue disorders			
Bone Pain			
subjects affected / exposed	0 / 61 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Infections and infestations			
Atypical Pneumonia			
subjects affected / exposed	1 / 61 (1.64%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis			
subjects affected / exposed	0 / 61 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device Related Infection			
subjects affected / exposed	1 / 61 (1.64%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	0 / 61 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	0 / 61 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	3 / 61 (4.92%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Retroperitoneal Infection			
subjects affected / exposed	1 / 61 (1.64%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tuberculosis			
subjects affected / exposed	1 / 61 (1.64%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper Respiratory Tract Infection			

subjects affected / exposed	1 / 61 (1.64%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound Infection			
subjects affected / exposed	1 / 61 (1.64%)	0 / 62 (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			
Cell Death			
subjects affected / exposed	0 / 61 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Decreased Appetite			
subjects affected / exposed	1 / 61 (1.64%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	0 / 61 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Ipatasertib and Paclitaxel	Placebo and Paclitaxel	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	61 / 61 (100.00%)	59 / 62 (95.16%)	
Investigations			
Alanine Aminotransferase Increased			
subjects affected / exposed	3 / 61 (4.92%)	4 / 62 (6.45%)	
occurrences (all)	4	4	
Neutrophil Count Decreased			
subjects affected / exposed	8 / 61 (13.11%)	9 / 62 (14.52%)	
occurrences (all)	15	20	
Aspartate Aminotransferase Increased			

subjects affected / exposed	5 / 61 (8.20%)	3 / 62 (4.84%)	
occurrences (all)	7	6	
Vascular disorders			
Flushing			
subjects affected / exposed	4 / 61 (6.56%)	3 / 62 (4.84%)	
occurrences (all)	4	3	
Hot Flush			
subjects affected / exposed	5 / 61 (8.20%)	3 / 62 (4.84%)	
occurrences (all)	5	3	
Nervous system disorders			
Dizziness			
subjects affected / exposed	11 / 61 (18.03%)	9 / 62 (14.52%)	
occurrences (all)	16	10	
Dysgeusia			
subjects affected / exposed	4 / 61 (6.56%)	5 / 62 (8.06%)	
occurrences (all)	4	5	
Headache			
subjects affected / exposed	9 / 61 (14.75%)	12 / 62 (19.35%)	
occurrences (all)	12	13	
Hypoaesthesia			
subjects affected / exposed	4 / 61 (6.56%)	0 / 62 (0.00%)	
occurrences (all)	6	0	
Neuropathy Peripheral			
subjects affected / exposed	10 / 61 (16.39%)	14 / 62 (22.58%)	
occurrences (all)	12	18	
Paraesthesia			
subjects affected / exposed	5 / 61 (8.20%)	6 / 62 (9.68%)	
occurrences (all)	9	9	
Peripheral Sensory Neuropathy			
subjects affected / exposed	16 / 61 (26.23%)	10 / 62 (16.13%)	
occurrences (all)	34	14	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	8 / 61 (13.11%)	8 / 62 (12.90%)	
occurrences (all)	15	11	
Leukopenia			

subjects affected / exposed	2 / 61 (3.28%)	4 / 62 (6.45%)	
occurrences (all)	3	6	
Neutropenia			
subjects affected / exposed	13 / 61 (21.31%)	15 / 62 (24.19%)	
occurrences (all)	36	35	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	15 / 61 (24.59%)	6 / 62 (9.68%)	
occurrences (all)	28	6	
Chest Discomfort			
subjects affected / exposed	4 / 61 (6.56%)	1 / 62 (1.61%)	
occurrences (all)	4	1	
Chest Pain			
subjects affected / exposed	3 / 61 (4.92%)	6 / 62 (9.68%)	
occurrences (all)	3	6	
Fatigue			
subjects affected / exposed	16 / 61 (26.23%)	21 / 62 (33.87%)	
occurrences (all)	23	33	
Mucosal Inflammation			
subjects affected / exposed	4 / 61 (6.56%)	4 / 62 (6.45%)	
occurrences (all)	6	5	
Oedema Peripheral			
subjects affected / exposed	6 / 61 (9.84%)	5 / 62 (8.06%)	
occurrences (all)	7	6	
Pyrexia			
subjects affected / exposed	9 / 61 (14.75%)	6 / 62 (9.68%)	
occurrences (all)	9	8	
Gastrointestinal disorders			
Abdominal Pain			
subjects affected / exposed	9 / 61 (14.75%)	7 / 62 (11.29%)	
occurrences (all)	13	9	
Abdominal Pain Upper			
subjects affected / exposed	4 / 61 (6.56%)	3 / 62 (4.84%)	
occurrences (all)	4	4	
Constipation			

subjects affected / exposed	11 / 61 (18.03%)	9 / 62 (14.52%)	
occurrences (all)	13	11	
Diarrhoea			
subjects affected / exposed	56 / 61 (91.80%)	12 / 62 (19.35%)	
occurrences (all)	181	18	
Dry Mouth			
subjects affected / exposed	2 / 61 (3.28%)	5 / 62 (8.06%)	
occurrences (all)	3	5	
Dyspepsia			
subjects affected / exposed	8 / 61 (13.11%)	6 / 62 (9.68%)	
occurrences (all)	11	6	
Flatulence			
subjects affected / exposed	4 / 61 (6.56%)	2 / 62 (3.23%)	
occurrences (all)	4	2	
Gastritis			
subjects affected / exposed	4 / 61 (6.56%)	0 / 62 (0.00%)	
occurrences (all)	5	0	
Nausea			
subjects affected / exposed	30 / 61 (49.18%)	21 / 62 (33.87%)	
occurrences (all)	62	28	
Stomatitis			
subjects affected / exposed	11 / 61 (18.03%)	5 / 62 (8.06%)	
occurrences (all)	14	6	
Vomiting			
subjects affected / exposed	17 / 61 (27.87%)	14 / 62 (22.58%)	
occurrences (all)	38	15	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	7 / 61 (11.48%)	8 / 62 (12.90%)	
occurrences (all)	9	12	
Dysponea			
subjects affected / exposed	7 / 61 (11.48%)	5 / 62 (8.06%)	
occurrences (all)	10	6	
Epistaxis			

subjects affected / exposed	7 / 61 (11.48%)	2 / 62 (3.23%)	
occurrences (all)	7	2	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	33 / 61 (54.10%)	29 / 62 (46.77%)	
occurrences (all)	36	34	
Dermatitis Acneiform			
subjects affected / exposed	10 / 61 (16.39%)	5 / 62 (8.06%)	
occurrences (all)	16	5	
Nail Disorder			
subjects affected / exposed	5 / 61 (8.20%)	4 / 62 (6.45%)	
occurrences (all)	8	4	
Onycholysis			
subjects affected / exposed	4 / 61 (6.56%)	1 / 62 (1.61%)	
occurrences (all)	4	1	
Pruritus			
subjects affected / exposed	8 / 61 (13.11%)	5 / 62 (8.06%)	
occurrences (all)	11	5	
Rash			
subjects affected / exposed	16 / 61 (26.23%)	12 / 62 (19.35%)	
occurrences (all)	26	15	
Rash Maculo-Papular			
subjects affected / exposed	1 / 61 (1.64%)	4 / 62 (6.45%)	
occurrences (all)	1	6	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	2 / 61 (3.28%)	4 / 62 (6.45%)	
occurrences (all)	2	6	
Insomnia			
subjects affected / exposed	11 / 61 (18.03%)	8 / 62 (12.90%)	
occurrences (all)	15	8	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	9 / 61 (14.75%)	6 / 62 (9.68%)	
occurrences (all)	12	6	
Back Pain			

subjects affected / exposed	5 / 61 (8.20%)	6 / 62 (9.68%)	
occurrences (all)	7	7	
Musculoskeletal Chest Pain			
subjects affected / exposed	2 / 61 (3.28%)	4 / 62 (6.45%)	
occurrences (all)	2	4	
Musculoskeletal Pain			
subjects affected / exposed	2 / 61 (3.28%)	4 / 62 (6.45%)	
occurrences (all)	3	4	
Myalgia			
subjects affected / exposed	15 / 61 (24.59%)	15 / 62 (24.19%)	
occurrences (all)	34	25	
Pain in Extremity			
subjects affected / exposed	4 / 61 (6.56%)	2 / 62 (3.23%)	
occurrences (all)	4	2	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	8 / 61 (13.11%)	5 / 62 (8.06%)	
occurrences (all)	12	6	
Upper Respiratory Tract Infection			
subjects affected / exposed	6 / 61 (9.84%)	4 / 62 (6.45%)	
occurrences (all)	8	8	
Urinary Tract Infection			
subjects affected / exposed	4 / 61 (6.56%)	4 / 62 (6.45%)	
occurrences (all)	4	4	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 July 2014	This amendment was made prior to the enrollment of any subject on study: It was clarified that all subjects had to be pre-medicated prior to the infusion of paclitaxel. Criteria for the infusion of paclitaxel, including information regarding neutropenia and platelet count, were clarified. Additional pregnancy tests were added to the protocol.
05 July 2016	- Reporting criteria for events that occur after the AE reporting period (defined as 30 days after the last dose of study drug) were updated to clarify that SAEs related to study drug treatment were to be reported in Adverse Event eCRFs, and all deaths were to be reported in the Survival Follow-up and Study Discontinuation eCRFs. - Additional guidance on treatment, dose modification, supportive care, and AESI reporting was added to the diarrhea management guideline. - The criteria of non-serious AESIs were updated to include Grade ≥ 3 diarrhea as a non-serious AESI to facilitate real-time monitoring of this AE. In addition, the AESI category of Grade ≥ 3 colitis has been expanded to include enterocolitis, and the AESI category of Grade ≥ 4 hepatotoxicity has been modified to Grade 3 hepatotoxicity and Grade ≥ 3 ALT/AST elevations to align with program-level AESIs. - The assay methods were updated to include mutation detection and copy number analysis by NGS, and accordingly, the precise definition of "PTEN-low" and "PI3K/Akt pathway activated" status were to be determined prior to primary analysis. - For the EU version of Protocol Amendment 2 only, the safety analysis section was updated to explicitly state that MedDRA was the thesaurus used for mapping verbatim terms, and that MedDRA preferred terms were to be used to describe and summarize AEs.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported