



Clinical trial results:

A randomized, double-blind, placebo controlled, Phase II/III study of BKM120 plus paclitaxel in patients with HER2 negative inoperable locally advanced or metastatic breast cancer, with or without PI3K pathway activation

Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate representation of the clinical trial results. Please use <https://www.novctrd.com/CtrdWeb/home.novfor> complete trial results.

Summary

EudraCT number	2011-005932-24
Trial protocol	AT CZ ES NL GB BE HU IT DE
Global end of trial date	01 June 2015

Results information

Result version number	v1 (current)
This version publication date	18 July 2018
First version publication date	18 July 2018

Trial information

Trial identification

Sponsor protocol code	CBKM120F2202
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01572727
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma AG, 41 61324111,
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, 41 61324111,

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
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Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	01 June 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	01 June 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was to determine whether buparlisib once daily plus weeklypaclitaxel prolongs PFS as per local investigator assessment in patients with HER2- first lineinoperable LABC or MBC patients as compared to placebo plus paclitaxel in either all patients (fullpopulation) or the PI3K pathway activated subpopulation.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	16 August 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 28
Country: Number of subjects enrolled	Austria: 5
Country: Number of subjects enrolled	Belgium: 13
Country: Number of subjects enrolled	Brazil: 24
Country: Number of subjects enrolled	Canada: 1
Country: Number of subjects enrolled	Czech Republic: 6
Country: Number of subjects enrolled	France: 31
Country: Number of subjects enrolled	Germany: 10
Country: Number of subjects enrolled	United Kingdom: 11
Country: Number of subjects enrolled	Hong Kong: 8
Country: Number of subjects enrolled	Hungary: 17
Country: Number of subjects enrolled	Israel: 7
Country: Number of subjects enrolled	Italy: 16
Country: Number of subjects enrolled	Japan: 16

Country: Number of subjects enrolled	Korea, Republic of: 17
Country: Number of subjects enrolled	Netherlands: 6
Country: Number of subjects enrolled	Russian Federation: 27
Country: Number of subjects enrolled	Singapore: 8
Country: Number of subjects enrolled	Spain: 74
Country: Number of subjects enrolled	Taiwan: 9
Country: Number of subjects enrolled	United States: 82
Worldwide total number of subjects	416
EEA total number of subjects	189

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)	336
From 65 to 84 years	80
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Among 416 randomized patients, 405 patients received the study treatment. Of them, 403 patients had at least one post-baseline safety assessment.

Pre-assignment

Screening details:

A total of approximately 524 patients were to be randomized in a 1:1 ratio to one of the two treatment arms irrespective of the adaptation decision to continue in the full or PI3K pathway activated subpopulation. Randomization was stratified by PI3K activation and Hormone Receptor status.

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, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	BKM120 and paclitaxel

Arm description:

Adult females with histologically confirmed, inoperable, locally advanced or metastatic HER2- BC who received study drug plus paclitaxel

Arm type	Experimental
Investigational medicinal product name	paclitaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Paclitaxel was administered once weekly at a dose of 80 mg/m² iv in a 28-day cycle.

Investigational medicinal product name	burparlisib
Investigational medicinal product code	BKM120
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Buparlisib placebo were supplied as 100 mg and 50 mg hard gelatin capsules and was dosed on a flat scale of mg/day.

Arm title	Placebo and paclitaxel
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Arm description:

Adult females with histologically confirmed, inoperable, locally advanced or metastatic HER2- BC who received placebo plus paclitaxel

Arm type	Placebo
Investigational medicinal product name	burparlisib placebo
Investigational medicinal product code	BKM120
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Buparlisib placebo were supplied as 100 mg and 50 mg hard gelatin capsules and was dosed on a flat scale of mg/day.

Number of subjects in period 1	BKM120 and paclitaxel	Placebo and paclitaxel
Started	207	209
Completed	0	0
Not completed	207	209
Adverse event, serious fatal	2	2
Physician decision	23	9
Adverse event, non-fatal	43	15
Study terminated by sponsor	61	83
Untreated	4	7
Lost to follow-up	1	1
Progressive disease	59	82
Parent/guardian decision	14	9
Protocol deviation	-	1

Baseline characteristics

Reporting groups

Reporting group title	BKM120 and paclitaxel
Reporting group description: Adult females with histologically confirmed, inoperable, locally advanced or metastatic HER2- BC who received study drug plus paclitaxel	
Reporting group title	Placebo and paclitaxel
Reporting group description: Adult females with histologically confirmed, inoperable, locally advanced or metastatic HER2- BC who received placebo plus paclitaxel	

Reporting group values	BKM120 and paclitaxel	Placebo and paclitaxel	Total
Number of subjects	207	209	416
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)	172	164	336
From 65-84 years	35	45	80
85 years and over	0	0	0
Age Continuous Units: Years			
arithmetic mean	54.1	55.6	
standard deviation	± 11.13	± 10.48	-
Gender, Male/Female Units: Participants			
Female	207	209	416
Male	0	0	0

End points

End points reporting groups

Reporting group title	BKM120 and paclitaxel
Reporting group description:	
Adult females with histologically confirmed, inoperable, locally advanced or metastatic HER2- BC who received study drug plus paclitaxel	
Reporting group title	Placebo and paclitaxel
Reporting group description:	
Adult females with histologically confirmed, inoperable, locally advanced or metastatic HER2- BC who received placebo plus paclitaxel	

Primary: Progression-free survival (PFS) assessed by local investigator's assessment

End point title	Progression-free survival (PFS) assessed by local investigator's assessment
End point description:	
PFS was defined as the time from the date of randomization to the date of the event, defined as the first radiologically documented disease progression or death due to any cause. PFS was based on local investigator assessment per RECIST criteria v1.1	
End point type	Primary
End point timeframe:	
every 8 weeks after randomization Up to 3 months after end of Treatment	

End point values	BKM120 and paclitaxel	Placebo and paclitaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	168	170		
Units: Months				
median (confidence interval 95%)	8 (7.2 to 9.2)	9.2 (7.3 to 11)		

Statistical analyses

Statistical analysis title	Statistical Analysis for PFS
Comparison groups	Placebo and paclitaxel v BKM120 and paclitaxel
Number of subjects included in analysis	338
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	1.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.82
upper limit	1.68

Secondary: overall survival by Kaplan-Meier estimate

End point title	overall survival by Kaplan-Meier estimate
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End point description:

Overall survival (OS) was defined as the time from date of randomization to date of death due to any cause. If a patient was not known to have died by the date of analysis cut-off, OS was censored at the date of last contact.

End point type	Secondary
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End point timeframe:

every 8 weeks after randomization Up to 3 months after end of Treatment

End point values	BKM120 and paclitaxel	Placebo and paclitaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	207	209		
Units: Months				
median (confidence interval 95%)	29.5 (25 to 30)	9999.9 (-99999.99 to 99999.99)		

Statistical analyses

No statistical analyses for this end point

Secondary: overall response rate

End point title	overall response rate
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End point description:

Percentage of patients with best overall response of complete response (CR) or partial response (PR) based on local investigator's assessment according to RECIST v1.1

End point type	Secondary
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End point timeframe:

every 8 weeks after randomization Up to 3 months after end of Treatment

End point values	BKM120 and paclitaxel	Placebo and paclitaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	168	170		
Units: Percentage of participants				
number (confidence interval 95%)	22.6 (16.5 to 29.7)	27.1 (20.5 to 34.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: duration of response

End point title	duration of response
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End point description:

time from the date of the first documented response (CR or PR, which had to be confirmed subsequently) to the date of the first radiologically documented disease progression or death due to disease

End point type	Secondary
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End point timeframe:

every 8 weeks after randomization Up to 3 months after end of Treatment

End point values	BKM120 and paclitaxel	Placebo and paclitaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0 ^[1]	0 ^[2]		
Units: Months				
median (standard deviation)	()	()		

Notes:

[1] - Futility criteria met at interim analysis, analysis on other secondary endpoints not analyzed

[2] - Futility criteria met at interim analysis, analysis on other secondary endpoints not analyzed

Statistical analyses

No statistical analyses for this end point

Secondary: time to response

End point title	time to response
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End point description:

time from date of randomization until first documented response (CR or PR, which has to be confirmed subsequently).

End point type	Secondary
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End point timeframe:

every 8 weeks after randomization Up to 3 months after end of Treatment

End point values	BKM120 and paclitaxel	Placebo and paclitaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0 ^[3]	0 ^[4]		
Units: Months				
number (not applicable)				

Notes:

[3] - Futility criteria met at interim analysis, analysis on other secondary endpoints not analyzed

Statistical analyses

No statistical analyses for this end point

Secondary: clinical benefit rate (CBR)

End point title	clinical benefit rate (CBR)
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End point description:

CBR was defined as the percentage of patients with an overall response of CR or PR or SD or non-CR/non-PD lasting more than 24 weeks based on local Investigator's assessment according to RECIST v1.1.

End point type	Secondary
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End point timeframe:

every 8 weeks after randomization Up to 3 months after end of Treatment

End point values	BKM120 and paclitaxel	Placebo and paclitaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	168	170		
Units: Percentage of participants				
number (confidence interval 95%)	26.2 (19.7 to 33.5)	32.9 (25.9 to 40.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma concentration-time profiles of BKM120 - pharmacokinetics (PK)

End point title	Plasma concentration-time profiles of BKM120 - pharmacokinetics (PK)
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End point description:

Summary statistics for PK: plasma concentration-time profiles of BKM120 and appropriate individual PK parameters based on population PK model , if deemed appropriate; each cycle = 28 days

End point type	Secondary
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End point timeframe:

Cycle 1 day 1, 15, 16, 22 and Cycle 2 day 1.

End point values	BKM120 and paclitaxel	Placebo and paclitaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0 ^[5]	0 ^[6]		
Units: ng*day/mL				
median (standard deviation)	()	()		

Notes:

[5] - Futility criteria met at interim analysis, analysis on other secondary endpoints not analyzed.

[6] - Futility criteria met at interim analysis, analysis on other secondary endpoints not analyzed

Statistical analyses

No statistical analyses for this end point

Secondary: Time to definitive deterioration of ECOG performance status

End point title	Time to definitive deterioration of ECOG performance status
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End point description:

Time to definitive deterioration of the ECOG performance status from baseline

End point type	Secondary
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End point timeframe:

every 4 weeks

End point values	BKM120 and paclitaxel	Placebo and paclitaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0 ^[7]	0 ^[8]		
Units: Months				
median (standard deviation)	()	()		

Notes:

[7] - Futility criteria met at interim analysis, analysis on other secondary endpoints not analyzed

[8] - Futility criteria met at interim analysis, analysis on other secondary endpoints not analyzed

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All adverse events reported in this record are from date of First Patient First Treatment until Last Patient Last Visit.

Adverse event reporting additional description:

Consistent with EudraCT disclosure specifications, Novartis has reported under the Serious adverse events field "number of deaths resulting from adverse events" all those deaths, resulting from serious adverse events that are deemed to be causally related to treatment by the investigator.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	Placebo + Paclitaxel
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Reporting group description:

Adult females with histologically confirmed, inoperable, locally advanced or metastatic HER2- BC who received placebo plus paclitaxel

Reporting group title	Buparlisib + Paclitaxel
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Reporting group description:

Adult females with histologically confirmed, inoperable, locally advanced or metastatic HER2- BC who received study drug plus paclitaxel

Serious adverse events	Placebo + Paclitaxel	Buparlisib + Paclitaxel	
Total subjects affected by serious adverse events			
subjects affected / exposed	42 / 201 (20.90%)	61 / 202 (30.20%)	
number of deaths (all causes)	5	2	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
CANCER PAIN			
subjects affected / exposed	1 / 201 (0.50%)	0 / 202 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
METASTASES TO CENTRAL NERVOUS SYSTEM			
subjects affected / exposed	1 / 201 (0.50%)	0 / 202 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Vascular disorders			
DEEP VEIN THROMBOSIS			

subjects affected / exposed	1 / 201 (0.50%)	3 / 202 (1.49%)	
occurrences causally related to treatment / all	0 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPERTENSION			
subjects affected / exposed	0 / 201 (0.00%)	2 / 202 (0.99%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
VENA CAVA THROMBOSIS			
subjects affected / exposed	0 / 201 (0.00%)	1 / 202 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
VENOUS THROMBOSIS			
subjects affected / exposed	1 / 201 (0.50%)	2 / 202 (0.99%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
ASTHENIA			
subjects affected / exposed	0 / 201 (0.00%)	3 / 202 (1.49%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
FACE OEDEMA			
subjects affected / exposed	1 / 201 (0.50%)	0 / 202 (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	3 / 201 (1.49%)	1 / 202 (0.50%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 2	0 / 0	
LOCALISED OEDEMA			
subjects affected / exposed	0 / 201 (0.00%)	1 / 202 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
MALaise			

subjects affected / exposed	0 / 201 (0.00%)	1 / 202 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
NON-CARDIAC CHEST PAIN			
subjects affected / exposed	1 / 201 (0.50%)	0 / 202 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PYREXIA			
subjects affected / exposed	3 / 201 (1.49%)	7 / 202 (3.47%)	
occurrences causally related to treatment / all	1 / 3	1 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
ANAPHYLACTIC REACTION			
subjects affected / exposed	1 / 201 (0.50%)	0 / 202 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPERSENSITIVITY			
subjects affected / exposed	1 / 201 (0.50%)	1 / 202 (0.50%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Social circumstances			
DIET NONCOMPLIANCE			
subjects affected / exposed	0 / 201 (0.00%)	1 / 202 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
BREAST HAEMORRHAGE			
subjects affected / exposed	1 / 201 (0.50%)	0 / 202 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
BREAST ULCERATION			
subjects affected / exposed	1 / 201 (0.50%)	0 / 202 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Respiratory, thoracic and mediastinal disorders			
ASTHMA			
subjects affected / exposed	0 / 201 (0.00%)	1 / 202 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
DYSPNOEA			
subjects affected / exposed	2 / 201 (1.00%)	1 / 202 (0.50%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
DYSPNOEA EXERTIONAL			
subjects affected / exposed	0 / 201 (0.00%)	1 / 202 (0.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPOXIA			
subjects affected / exposed	0 / 201 (0.00%)	1 / 202 (0.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
INTERSTITIAL LUNG DISEASE			
subjects affected / exposed	0 / 201 (0.00%)	2 / 202 (0.99%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMONITIS			
subjects affected / exposed	1 / 201 (0.50%)	6 / 202 (2.97%)	
occurrences causally related to treatment / all	1 / 1	6 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMOTHORAX			
subjects affected / exposed	1 / 201 (0.50%)	1 / 202 (0.50%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PULMONARY EMBOLISM			
subjects affected / exposed	1 / 201 (0.50%)	1 / 202 (0.50%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Psychiatric disorders			
ACUTE PSYCHOSIS			
subjects affected / exposed	0 / 201 (0.00%)	1 / 202 (0.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ANXIETY			
subjects affected / exposed	0 / 201 (0.00%)	1 / 202 (0.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CONFUSIONAL STATE			
subjects affected / exposed	1 / 201 (0.50%)	2 / 202 (0.99%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
DELIRIUM			
subjects affected / exposed	0 / 201 (0.00%)	1 / 202 (0.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
DEPRESSION			
subjects affected / exposed	0 / 201 (0.00%)	1 / 202 (0.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
MENTAL DISORDER			
subjects affected / exposed	0 / 201 (0.00%)	2 / 202 (0.99%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
MENTAL STATUS CHANGES			
subjects affected / exposed	0 / 201 (0.00%)	2 / 202 (0.99%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
PSYCHOTIC DISORDER			
subjects affected / exposed	0 / 201 (0.00%)	1 / 202 (0.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			

EJECTION FRACTION DECREASED			
subjects affected / exposed	0 / 201 (0.00%)	1 / 202 (0.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
LYMPHOCYTE COUNT INCREASED			
subjects affected / exposed	0 / 201 (0.00%)	1 / 202 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
FALL			
subjects affected / exposed	0 / 201 (0.00%)	2 / 202 (0.99%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
FEMUR FRACTURE			
subjects affected / exposed	1 / 201 (0.50%)	1 / 202 (0.50%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HEAD INJURY			
subjects affected / exposed	0 / 201 (0.00%)	1 / 202 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
POST-TRAUMATIC PAIN			
subjects affected / exposed	0 / 201 (0.00%)	1 / 202 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SPINAL FRACTURE			
subjects affected / exposed	0 / 201 (0.00%)	1 / 202 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
TOXICITY TO VARIOUS AGENTS			
subjects affected / exposed	1 / 201 (0.50%)	0 / 202 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

ULNA FRACTURE			
subjects affected / exposed	0 / 201 (0.00%)	1 / 202 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
CARDIAC FAILURE CONGESTIVE			
subjects affected / exposed	1 / 201 (0.50%)	0 / 202 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
CARDIO-RESPIRATORY ARREST			
subjects affected / exposed	0 / 201 (0.00%)	1 / 202 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
PERICARDIAL EFFUSION			
subjects affected / exposed	0 / 201 (0.00%)	1 / 202 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
ALTERED STATE OF CONSCIOUSNESS			
subjects affected / exposed	0 / 201 (0.00%)	1 / 202 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
BRACHIAL PLEXOPATHY			
subjects affected / exposed	0 / 201 (0.00%)	1 / 202 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
BRAIN COMPRESSION			
subjects affected / exposed	1 / 201 (0.50%)	0 / 202 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
BRAIN OEDEMA			
subjects affected / exposed	0 / 201 (0.00%)	1 / 202 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	

CEREBRAL HAEMORRHAGE			
subjects affected / exposed	1 / 201 (0.50%)	0 / 202 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
ENCEPHALOPATHY			
subjects affected / exposed	0 / 201 (0.00%)	1 / 202 (0.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HEMIPARESIS			
subjects affected / exposed	0 / 201 (0.00%)	1 / 202 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
METABOLIC ENCEPHALOPATHY			
subjects affected / exposed	0 / 201 (0.00%)	1 / 202 (0.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PARAESTHESIA			
subjects affected / exposed	0 / 201 (0.00%)	1 / 202 (0.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SEIZURE			
subjects affected / exposed	0 / 201 (0.00%)	1 / 202 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SPINAL CORD COMPRESSION			
subjects affected / exposed	1 / 201 (0.50%)	0 / 202 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SYNCOPE			
subjects affected / exposed	2 / 201 (1.00%)	0 / 202 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			

FEBRILE NEUTROPENIA			
subjects affected / exposed	0 / 201 (0.00%)	1 / 202 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
LEUKOPENIA			
subjects affected / exposed	1 / 201 (0.50%)	0 / 202 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
NEUTROPENIA			
subjects affected / exposed	0 / 201 (0.00%)	2 / 202 (0.99%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
CATARACT			
subjects affected / exposed	1 / 201 (0.50%)	1 / 202 (0.50%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
OPTIC NEUROPATHY			
subjects affected / exposed	1 / 201 (0.50%)	0 / 202 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
ABDOMINAL PAIN			
subjects affected / exposed	1 / 201 (0.50%)	0 / 202 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CONSTIPATION			
subjects affected / exposed	1 / 201 (0.50%)	0 / 202 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DIARRHOEA			
subjects affected / exposed	3 / 201 (1.49%)	5 / 202 (2.48%)	
occurrences causally related to treatment / all	0 / 3	2 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	

NAUSEA			
subjects affected / exposed	1 / 201 (0.50%)	1 / 202 (0.50%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PANCREATITIS			
subjects affected / exposed	1 / 201 (0.50%)	0 / 202 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
VOMITING			
subjects affected / exposed	1 / 201 (0.50%)	2 / 202 (0.99%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
CHOLECYSTITIS			
subjects affected / exposed	1 / 201 (0.50%)	0 / 202 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
RASH			
subjects affected / exposed	0 / 201 (0.00%)	2 / 202 (0.99%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
RASH MACULAR			
subjects affected / exposed	0 / 201 (0.00%)	1 / 202 (0.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
RASH MACULO-PAPULAR			
subjects affected / exposed	0 / 201 (0.00%)	1 / 202 (0.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
RASH PRURITIC			
subjects affected / exposed	1 / 201 (0.50%)	0 / 202 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

SKIN MASS			
subjects affected / exposed	1 / 201 (0.50%)	0 / 202 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SKIN ULCER			
subjects affected / exposed	0 / 201 (0.00%)	2 / 202 (0.99%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
SWELLING FACE			
subjects affected / exposed	0 / 201 (0.00%)	1 / 202 (0.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
TOXIC SKIN ERUPTION			
subjects affected / exposed	0 / 201 (0.00%)	1 / 202 (0.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
URTICARIA			
subjects affected / exposed	0 / 201 (0.00%)	1 / 202 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
ACUTE KIDNEY INJURY			
subjects affected / exposed	0 / 201 (0.00%)	1 / 202 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
NEPHROLITHIASIS			
subjects affected / exposed	1 / 201 (0.50%)	0 / 202 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
RENAL FAILURE			
subjects affected / exposed	1 / 201 (0.50%)	0 / 202 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue			

disorders			
BACK PAIN			
subjects affected / exposed	1 / 201 (0.50%)	0 / 202 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
BONE PAIN			
subjects affected / exposed	2 / 201 (1.00%)	1 / 202 (0.50%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
MUSCULAR WEAKNESS			
subjects affected / exposed	0 / 201 (0.00%)	1 / 202 (0.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PAIN IN EXTREMITY			
subjects affected / exposed	1 / 201 (0.50%)	0 / 202 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PATHOLOGICAL FRACTURE			
subjects affected / exposed	1 / 201 (0.50%)	0 / 202 (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			
ABSCCESS LIMB			
subjects affected / exposed	1 / 201 (0.50%)	0 / 202 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CELLULITIS			
subjects affected / exposed	5 / 201 (2.49%)	1 / 202 (0.50%)	
occurrences causally related to treatment / all	1 / 8	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
DEVICE RELATED INFECTION			
subjects affected / exposed	2 / 201 (1.00%)	2 / 202 (0.99%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

GASTROENTERITIS			
subjects affected / exposed	1 / 201 (0.50%)	0 / 202 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTROINTESTINAL INFECTION			
subjects affected / exposed	1 / 201 (0.50%)	0 / 202 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HERPES ZOSTER			
subjects affected / exposed	0 / 201 (0.00%)	1 / 202 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
INFLUENZA			
subjects affected / exposed	1 / 201 (0.50%)	0 / 202 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
INFUSION SITE INFECTION			
subjects affected / exposed	0 / 201 (0.00%)	1 / 202 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
MENINGITIS			
subjects affected / exposed	1 / 201 (0.50%)	0 / 202 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
PNEUMOCYSTIS JIROVECI INFECTION			
subjects affected / exposed	0 / 201 (0.00%)	1 / 202 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMONIA			
subjects affected / exposed	0 / 201 (0.00%)	1 / 202 (0.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
PYELONEPHRITIS			

subjects affected / exposed	0 / 201 (0.00%)	1 / 202 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SEPSIS			
subjects affected / exposed	1 / 201 (0.50%)	3 / 202 (1.49%)	
occurrences causally related to treatment / all	1 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
STAPHYLOCOCCAL BACTERAEMIA			
subjects affected / exposed	0 / 201 (0.00%)	1 / 202 (0.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
URINARY TRACT INFECTION			
subjects affected / exposed	1 / 201 (0.50%)	4 / 202 (1.98%)	
occurrences causally related to treatment / all	0 / 1	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
DECREASED APPETITE			
subjects affected / exposed	1 / 201 (0.50%)	1 / 202 (0.50%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
DEHYDRATION			
subjects affected / exposed	3 / 201 (1.49%)	0 / 202 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPERGLYCAEMIA			
subjects affected / exposed	0 / 201 (0.00%)	2 / 202 (0.99%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPOCALCAEMIA			
subjects affected / exposed	0 / 201 (0.00%)	1 / 202 (0.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPOGLYCAEMIA			

subjects affected / exposed	0 / 201 (0.00%)	1 / 202 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPOKALAEMIA			
subjects affected / exposed	0 / 201 (0.00%)	1 / 202 (0.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPONATRAEMIA			
subjects affected / exposed	0 / 201 (0.00%)	1 / 202 (0.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo + Paclitaxel	Buparlisib + Paclitaxel	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	188 / 201 (93.53%)	196 / 202 (97.03%)	
Vascular disorders			
FLUSHING			
subjects affected / exposed	11 / 201 (5.47%)	7 / 202 (3.47%)	
occurrences (all)	19	8	
HYPERTENSION			
subjects affected / exposed	10 / 201 (4.98%)	17 / 202 (8.42%)	
occurrences (all)	13	21	
LYMPHOEDEMA			
subjects affected / exposed	16 / 201 (7.96%)	7 / 202 (3.47%)	
occurrences (all)	18	8	
General disorders and administration site conditions			
ASTHENIA			
subjects affected / exposed	45 / 201 (22.39%)	48 / 202 (23.76%)	
occurrences (all)	81	75	
FATIGUE			
subjects affected / exposed	64 / 201 (31.84%)	67 / 202 (33.17%)	
occurrences (all)	93	86	
NON-CARDIAC CHEST PAIN			

subjects affected / exposed occurrences (all)	11 / 201 (5.47%) 12	4 / 202 (1.98%) 5	
OEDEMA PERIPHERAL subjects affected / exposed occurrences (all)	50 / 201 (24.88%) 61	21 / 202 (10.40%) 25	
PAIN subjects affected / exposed occurrences (all)	11 / 201 (5.47%) 11	9 / 202 (4.46%) 10	
PYREXIA subjects affected / exposed occurrences (all)	19 / 201 (9.45%) 21	29 / 202 (14.36%) 31	
Respiratory, thoracic and mediastinal disorders COUGH subjects affected / exposed occurrences (all)	28 / 201 (13.93%) 37	40 / 202 (19.80%) 46	
DYSPNOEA subjects affected / exposed occurrences (all)	21 / 201 (10.45%) 24	26 / 202 (12.87%) 27	
EPISTAXIS subjects affected / exposed occurrences (all)	33 / 201 (16.42%) 35	29 / 202 (14.36%) 37	
OROPHARYNGEAL PAIN subjects affected / exposed occurrences (all)	16 / 201 (7.96%) 18	12 / 202 (5.94%) 12	
Psychiatric disorders ANXIETY subjects affected / exposed occurrences (all)	31 / 201 (15.42%) 43	41 / 202 (20.30%) 47	
DEPRESSION subjects affected / exposed occurrences (all)	17 / 201 (8.46%) 23	50 / 202 (24.75%) 58	
INSOMNIA subjects affected / exposed occurrences (all)	33 / 201 (16.42%) 36	31 / 202 (15.35%) 31	
MOOD ALTERED			

subjects affected / exposed occurrences (all)	5 / 201 (2.49%) 7	11 / 202 (5.45%) 13	
Investigations			
ALANINE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	12 / 201 (5.97%)	35 / 202 (17.33%)	
occurrences (all)	14	43	
ASPARTATE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	11 / 201 (5.47%)	30 / 202 (14.85%)	
occurrences (all)	13	44	
BLOOD GLUCOSE INCREASED			
subjects affected / exposed	10 / 201 (4.98%)	13 / 202 (6.44%)	
occurrences (all)	16	29	
GAMMA-GLUTAMYLTRANSFERASE INCREASED			
subjects affected / exposed	12 / 201 (5.97%)	7 / 202 (3.47%)	
occurrences (all)	14	7	
NEUTROPHIL COUNT DECREASED			
subjects affected / exposed	15 / 201 (7.46%)	15 / 202 (7.43%)	
occurrences (all)	35	39	
WEIGHT DECREASED			
subjects affected / exposed	14 / 201 (6.97%)	30 / 202 (14.85%)	
occurrences (all)	16	34	
WHITE BLOOD CELL COUNT DECREASED			
subjects affected / exposed	14 / 201 (6.97%)	10 / 202 (4.95%)	
occurrences (all)	43	29	
Nervous system disorders			
DIZZINESS			
subjects affected / exposed	21 / 201 (10.45%)	33 / 202 (16.34%)	
occurrences (all)	23	36	
DYSGEUSIA			
subjects affected / exposed	34 / 201 (16.92%)	39 / 202 (19.31%)	
occurrences (all)	38	40	
HEADACHE			
subjects affected / exposed	37 / 201 (18.41%)	35 / 202 (17.33%)	
occurrences (all)	48	51	

NEUROPATHY PERIPHERAL subjects affected / exposed occurrences (all)	48 / 201 (23.88%) 69	50 / 202 (24.75%) 59	
PARAESTHESIA subjects affected / exposed occurrences (all)	34 / 201 (16.92%) 46	25 / 202 (12.38%) 29	
PERIPHERAL SENSORY NEUROPATHY subjects affected / exposed occurrences (all)	31 / 201 (15.42%) 39	31 / 202 (15.35%) 36	
Blood and lymphatic system disorders ANAEMIA subjects affected / exposed occurrences (all)	51 / 201 (25.37%) 78	46 / 202 (22.77%) 64	
NEUTROPENIA subjects affected / exposed occurrences (all)	54 / 201 (26.87%) 147	64 / 202 (31.68%) 149	
Eye disorders LACRIMATION INCREASED subjects affected / exposed occurrences (all)	17 / 201 (8.46%) 18	12 / 202 (5.94%) 13	
VISION BLURRED subjects affected / exposed occurrences (all)	7 / 201 (3.48%) 7	19 / 202 (9.41%) 20	
Gastrointestinal disorders ABDOMINAL PAIN subjects affected / exposed occurrences (all)	22 / 201 (10.95%) 26	27 / 202 (13.37%) 32	
ABDOMINAL PAIN UPPER subjects affected / exposed occurrences (all)	14 / 201 (6.97%) 16	11 / 202 (5.45%) 12	
CONSTIPATION subjects affected / exposed occurrences (all)	38 / 201 (18.91%) 55	47 / 202 (23.27%) 58	
DIARRHOEA subjects affected / exposed occurrences (all)	68 / 201 (33.83%) 123	109 / 202 (53.96%) 191	
DRY MOUTH			

subjects affected / exposed	10 / 201 (4.98%)	12 / 202 (5.94%)	
occurrences (all)	11	12	
DYSPEPSIA			
subjects affected / exposed	15 / 201 (7.46%)	23 / 202 (11.39%)	
occurrences (all)	18	26	
NAUSEA			
subjects affected / exposed	51 / 201 (25.37%)	83 / 202 (41.09%)	
occurrences (all)	72	126	
STOMATITIS			
subjects affected / exposed	24 / 201 (11.94%)	56 / 202 (27.72%)	
occurrences (all)	31	77	
VOMITING			
subjects affected / exposed	30 / 201 (14.93%)	39 / 202 (19.31%)	
occurrences (all)	52	67	
Skin and subcutaneous tissue disorders			
ALOPECIA			
subjects affected / exposed	104 / 201 (51.74%)	103 / 202 (50.99%)	
occurrences (all)	105	106	
DRY SKIN			
subjects affected / exposed	13 / 201 (6.47%)	28 / 202 (13.86%)	
occurrences (all)	15	35	
ERYTHEMA			
subjects affected / exposed	17 / 201 (8.46%)	11 / 202 (5.45%)	
occurrences (all)	19	13	
NAIL DISCOLOURATION			
subjects affected / exposed	14 / 201 (6.97%)	7 / 202 (3.47%)	
occurrences (all)	14	7	
NAIL DISORDER			
subjects affected / exposed	19 / 201 (9.45%)	7 / 202 (3.47%)	
occurrences (all)	20	8	
ONYCHOMADESIS			
subjects affected / exposed	11 / 201 (5.47%)	7 / 202 (3.47%)	
occurrences (all)	11	8	
PRURITUS			
subjects affected / exposed	30 / 201 (14.93%)	32 / 202 (15.84%)	
occurrences (all)	35	42	

RASH			
subjects affected / exposed	43 / 201 (21.39%)	86 / 202 (42.57%)	
occurrences (all)	62	111	
RASH MACULO-PAPULAR			
subjects affected / exposed	8 / 201 (3.98%)	12 / 202 (5.94%)	
occurrences (all)	13	19	
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
subjects affected / exposed	32 / 201 (15.92%)	23 / 202 (11.39%)	
occurrences (all)	37	26	
BACK PAIN			
subjects affected / exposed	22 / 201 (10.95%)	21 / 202 (10.40%)	
occurrences (all)	25	24	
BONE PAIN			
subjects affected / exposed	14 / 201 (6.97%)	10 / 202 (4.95%)	
occurrences (all)	17	14	
MUSCULOSKELETAL PAIN			
subjects affected / exposed	12 / 201 (5.97%)	8 / 202 (3.96%)	
occurrences (all)	13	9	
MYALGIA			
subjects affected / exposed	27 / 201 (13.43%)	22 / 202 (10.89%)	
occurrences (all)	35	35	
PAIN IN EXTREMITY			
subjects affected / exposed	40 / 201 (19.90%)	27 / 202 (13.37%)	
occurrences (all)	51	37	
Infections and infestations			
RHINITIS			
subjects affected / exposed	9 / 201 (4.48%)	11 / 202 (5.45%)	
occurrences (all)	10	11	
UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	23 / 201 (11.44%)	11 / 202 (5.45%)	
occurrences (all)	31	12	
URINARY TRACT INFECTION			
subjects affected / exposed	18 / 201 (8.96%)	18 / 202 (8.91%)	
occurrences (all)	25	21	
Metabolism and nutrition disorders			

DECREASED APPETITE			
subjects affected / exposed	26 / 201 (12.94%)	64 / 202 (31.68%)	
occurrences (all)	32	71	
HYPERGLYCAEMIA			
subjects affected / exposed	22 / 201 (10.95%)	82 / 202 (40.59%)	
occurrences (all)	58	156	
HYPOKALAEMIA			
subjects affected / exposed	6 / 201 (2.99%)	19 / 202 (9.41%)	
occurrences (all)	7	34	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
31 July 2012	The purpose of this protocol amendment was to add contraceptive guidance in alignment with the local summary of product characteristics for contraception recommendations after discontinuation of paclitaxel study drug.
26 May 2013	The main purpose of this protocol amendment was to update and align the management of selected AEs across the buparlisib program, specifically psychiatric disorders, hyperglycemia, stomatitis and skin rash, and to increase the permitted treatment interruption period for buparlisib/placebo from 21 to 28 days. Moreover, due to the very low frequency of PI3KCA mutations in exon5 and PTEN mutations overall in breast cancer, the definition of the PI3K pathway activation status (one of the two stratification factors) was modified and no longer included the above mentioned mutations.
13 September 2013	The main purpose of this protocol amendment was to convert the existing Phase II trial into a Phase II/III study by implementing an adaptive Phase II/III seamless design with a Bayesian decision tool for targeted therapy in oncology as described by Brannath W, Zuber E, Branson M, et al. (2009), in accordance with the published FDA guidelines on adaptive designs and enrichment strategies (FDA Guidance 2010 and 2012), and the EU 2007 reflection paper (CHMP/EWP/2459/02). Prior to implementation, scientific advice was sought and the planned amendment discussed with the FDA, EMA and PMDA

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The safety set included all randomized patients who received at least one dose of the study treatment (either buparlisib + paclitaxel or matching placebo + paclitaxel) and had at least one post-baseline safety assessment.

Notes: