



Clinical trial results:

Phase II multicenter randomized, double blind, placebo controlled study assessing the efficacy of buparlisib (BKM120) plus paclitaxel vs. placebo plus paclitaxel in patients with platinum pre-treated recurrent or metastatic head and neck squamous cell carcinoma

Summary

EudraCT number	2013-000744-26
Trial protocol	HU ES IT GB DE IE PL FR
Global end of trial date	30 March 2017

Results information

Result version number	v1 (current)
This version publication date	15 April 2018
First version publication date	15 April 2018

Trial information

Trial identification

Sponsor protocol code	CBKM120H2201
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01852292
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 613241111, novartis.email@novartis.com
Scientific contact	Clinical Disclosure Office, Novartis Pharma, AG, 41 613241111, novartis.email@novartis.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	30 March 2017
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	30 March 2017
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To estimate the efficacy of buparlisib in combination with paclitaxel in terms of progression-free survival (PFS) according to local radiological assessment and Response Evaluation Criteria In Solid Tumors (RECIST) 1.1.

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	01 October 2013
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: 2
Country: Number of subjects enrolled	Canada: 10
Country: Number of subjects enrolled	France: 2
Country: Number of subjects enrolled	Germany: 13
Country: Number of subjects enrolled	Hungary: 20
Country: Number of subjects enrolled	India: 14
Country: Number of subjects enrolled	Ireland: 1
Country: Number of subjects enrolled	Italy: 21
Country: Number of subjects enrolled	Japan: 3
Country: Number of subjects enrolled	Korea, Republic of: 5
Country: Number of subjects enrolled	Poland: 2
Country: Number of subjects enrolled	Russian Federation: 11
Country: Number of subjects enrolled	Spain: 11
Country: Number of subjects enrolled	Switzerland: 4
Country: Number of subjects enrolled	United Kingdom: 6
Country: Number of subjects enrolled	United States: 11
Country: Number of subjects enrolled	Taiwan: 14
Country: Number of subjects enrolled	Thailand: 8

Worldwide total number of subjects	158
EEA total number of subjects	76

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)	117
From 65 to 84 years	41
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Planned: 150; Analyzed: 158. Patients were randomized to receive treatment with buparlisib 100 mg daily (n=79) or placebo (n=79) in combination with paclitaxel.

Pre-assignment

Screening details:

One hundred and fifty-eight patients were randomized in a 1:1 ratio to treatment with buparlisib plus paclitaxel or placebo plus paclitaxel, with stratification according to number of prior lines of treatment in the recurrent/metastatic setting (1 vs.2) and the region of Investigator site (North America vs. Rest of the World).

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	Buparlisib + Paclitaxel

Arm description:

Patients who were randomized to this arm on a 1:1 randomization, took buparlisib 100 mg daily and paclitaxel 80 mg/m² weekly.

Arm type	Experimental
Investigational medicinal product name	Buparlisib
Investigational medicinal product code	BKM120
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Buparlisib was supplied as 10-mg, and 50-mg hard gelatin capsules. Buparlisib was administered orally once daily on a continuous dosing schedule starting on Day 1.

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

Dosage and administration details:

Paclitaxel was administered weekly (Days 1, 8, 15 and 22 of a 28-day cycle) as an intravenous infusion at a dose of 80 mg/m² on a continuous dosing schedule.

Arm title	Buparlisib matching placebo + Paclitaxel
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Arm description:

Patients who were randomized to this arm on a 1:1 randomization, took buparlisib matching placebo 100 mg daily and paclitaxel 80 mg/m² weekly.

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

Dosage and administration details:

Buparlisib matching placebo was supplied as 10-mg, and 50-mg hard gelatin capsules. Buparlisib matching placebo was administered orally once daily on a continuous dosing schedule starting on Day 1.

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

Dosage and administration details:

Paclitaxel was administered weekly (Days 1, 8, 15 and 22 of a 28-day cycle) as an intravenous infusion at a dose of 80 mg/m² on a continuous dosing schedule.

Number of subjects in period 1	Buparlisib + Paclitaxel	Buparlisib matching placebo + Paclitaxel
Started	79	79
Completed	0	0
Not completed	79	79
Adverse event, serious fatal	9	8
Physician decision	6	2
Study terminated by Sponsor	-	1
Adverse event, non-fatal	8	11
Non-compliance with study treatment	1	-
Patient/guardian decision	8	4
Progressive disease	42	52
Protocol deviation	2	-
Untreated - did not receive study drug	3	1

Baseline characteristics

Reporting groups

Reporting group title	Buparlisib + Paclitaxel
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Reporting group description:

Patients who were randomized to this arm on a 1:1 randomization, took buparlisib 100 mg daily and paclitaxel 80 mg/m² weekly.

Reporting group title	Buparlisib matching placebo + Paclitaxel
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Reporting group description:

Patients who were randomized to this arm on a 1:1 randomization, took buparlisib matching placebo 100 mg daily and paclitaxel 80 mg/m² weekly.

Reporting group values	Buparlisib + Paclitaxel	Buparlisib matching placebo + Paclitaxel	Total
Number of subjects	79	79	158
Age categorical			
Units: Subjects			
Adults (18-64 years)	59	58	117
From 65-84 years	20	21	41
85 years and over	0	0	0
Age Continuous			
Units: Years			
arithmetic mean	58.0	58.2	
standard deviation	± 9.44	± 9.44	-
Sex: Female, Male			
Units: Subjects			
Female	14	11	25
Male	65	68	133
Race/Ethnicity, Customized			
Units: Subjects			
Hispanic or Latino	3	0	3
East Asian	12	9	21
Southeast Asian	4	9	13
South Asian	6	5	11
Russian	7	4	11
Mixed ethnicity	1	2	3
Not reported	13	10	23
Unknown	3	6	9
Other	30	34	64

End points

End points reporting groups

Reporting group title	Buparlisib + Paclitaxel
Reporting group description: Patients who were randomized to this arm on a 1:1 randomization, took buparlisib 100 mg daily and paclitaxel 80 mg/m ² weekly.	
Reporting group title	Buparlisib matching placebo + Paclitaxel
Reporting group description: Patients who were randomized to this arm on a 1:1 randomization, took buparlisib matching placebo 100 mg daily and paclitaxel 80 mg/m ² weekly.	

Primary: Progression Free Survival (PFS) per Investigator assessment

End point title	Progression Free Survival (PFS) per Investigator 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 per RECIST v 1.1 or death due to any cause. If a patient has not progressed or died at the analysis cut-off date or when the patient receives further anti-neoplastic therapy, PFS was censored on the date of the last adequate tumor assessment before the earlier of the cut-off date or start of the further anti-neoplastic therapy date.	
End point type	Primary
End point timeframe: 4 weeks and thereafter every 6 weeks until disease progression or death up to 3.5 years	

End point values	Buparlisib + Paclitaxel	Buparlisib matching placebo + Paclitaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	79	79		
Units: months				
median (confidence interval 95%)	4.63 (3.52 to 5.32)	3.45 (2.17 to 3.71)		

Statistical analyses

Statistical analysis title	Analysis of Double Criteria for PFS
Comparison groups	Buparlisib + Paclitaxel v Buparlisib matching placebo + Paclitaxel

Number of subjects included in analysis	158
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Cox proportional hazard
Point estimate	0.646
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.44
upper limit	0.94

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)
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
End point timeframe:	
4 weeks and thereafter every 6 weeks until disease progression or death up to 3.5 years	

End point values	Buparlisib + Paclitaxel	Buparlisib matching placebo + Paclitaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	79	79		
Units: months				
median (confidence interval 95%)	10.41 (7.29 to 12.78)	6.54 (5.26 to 8.77)		

Statistical analyses

Statistical analysis title	Analysis of Double Criteria for Overall survival
Comparison groups	Buparlisib + Paclitaxel v Buparlisib matching placebo + Paclitaxel
Number of subjects included in analysis	158
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Cox proportional hazard
Point estimate	0.72

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.49
upper limit	1.04

Secondary: Overall Response Rate (ORR) as per local radiological assessment

End point title	Overall Response Rate (ORR) as per local radiological assessment
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End point description:

ORR: Percentage of patients with best overall response of complete response (CR) or partial response (PR) according to RECIST v1.1.

End point type	Secondary
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End point timeframe:

4 weeks and thereafter every 6 weeks until disease progression or death up to 3.5 years

End point values	Buparlisib + Paclitaxel	Buparlisib matching placebo + Paclitaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	79	79		
Units: Percentage of participants				
median (confidence interval 95%)	39.2 (28.4 to 50.9)	13.9 (7.2 to 23.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Response (TTR) as per local radiological assessment

End point title	Time to Response (TTR) as per local radiological assessment
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End point description:

TTR is the time from date of randomization until first documented response (CR or PR, which has to be confirmed subsequently) according to RECIST v1.1.

End point type	Secondary
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End point timeframe:

4 weeks and thereafter every 6 weeks until disease progression or death up to 3.5 years

End point values	Buparlisib + Paclitaxel	Buparlisib matching placebo + Paclitaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	79 ^[1]	79 ^[2]		
Units: months				
median (full range (min-max))	1.02 (0.8 to 9.2)	0.99 (0.8 to 5.1)		

Notes:

[1] - n for responders = 31

[2] - n for responders = 11

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Control Rate (DCR) as per local radiological assessment

End point title	Disease Control Rate (DCR) as per local radiological assessment
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End point description:

DCR is the the proportion of patients with a best overall response of CR, PR or stable disease (SD), according to RECIST v1.1.

End point type	Secondary
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End point timeframe:

4 weeks and thereafter every 6 weeks until disease progression or death up to 3.5 years

End point values	Buparlisib + Paclitaxel	Buparlisib matching placebo + Paclitaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	79	79		
Units: Percentage of participants				
number (confidence interval 95%)	72.2 (60.9 to 81.7)	69.6 (58.2 to 79.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DoR) as per local investigator

End point title	Duration of Response (DoR) as per local investigator
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End point description:

DoR is the 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 according to RECIST v1.1 .

End point type	Secondary
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End point timeframe:

4 weeks and thereafter every 6 weeks until disease progression or death up to 3.5 years

End point values	Buparlisib + Paclitaxel	Buparlisib matching placebo + Paclitaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	79 ^[3]	79 ^[4]		
Units: months				
median (full range (min-max))	3.06 (2.1 to 9.6)	4.17 (2.7 to 5.6)		

Notes:

[3] - n for responders = 17

[4] - n for responders = 4

Statistical analyses

No statistical analyses for this end point

Secondary: Health-related quality of life (HRQoL):Time to 10% definitive deterioration in the global health status/Quality of life per EORTC-QLQ-C30

End point title	Health-related quality of life (HRQoL):Time to 10% definitive deterioration in the global health status/Quality of life per EORTC-QLQ-C30
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End point description:

A summary of EORTC-QLQ-C30 scores by time window. Time to deterioration is the number of days between the date of randomization and the date of the assessment at which definitive deterioration is seen. Definitive Deterioration in global health status and symptoms was defined as a decrease in the subscale score by at least 10% compared to baseline, with no later increase above this threshold observed during the course of the study. If a patient had not had an event prior to analysis cut-off or start of another anticancer therapy, time to deterioration was censored at the date of the last quality of life (QoL) evaluation.

End point type	Secondary
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End point timeframe:

Baseline, every 6 weeks starting from cycle 2 day 15 up to 3.5 years

End point values	Buparlisib + Paclitaxel	Buparlisib matching placebo + Paclitaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	79	79		
Units: months				

median (confidence interval 95%)	3.0 (1.6 to 4.9)	3.5 (2.1 to 4.3)		
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Statistical analyses

No statistical analyses for this end point

Secondary: Health-related quality of life (HRQoL):Time to 10% definitive deterioration in the head and neck cancer symptoms scales for pain, speech problems, swallowing and sense problems per EORTC-QLQ-HN35

End point title	Health-related quality of life (HRQoL):Time to 10% definitive deterioration in the head and neck cancer symptoms scales for pain, speech problems, swallowing and sense problems per EORTC-QLQ-HN35
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End point description:

A summary of EORTC-QLQ-HN35 scores by time window. Time to deterioration is the number of days between the date of randomization and the date of the assessment at which definitive deterioration is seen. Definitive Deterioration in global health status and symptoms was defined as an increase in the subscale score of at least 10% compared to baseline, with no later decrease above this threshold observed during the course of the study. If a patient had not had an event prior to analysis cut-off or start of another anticancer therapy, time to deterioration was censored at the date of the last quality of life (QoL) evaluation.

End point type	Secondary
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End point timeframe:

Baseline, every 6 weeks starting from cycle 2 day 15 up to 3.5 years

End point values	Buparlisib + Paclitaxel	Buparlisib matching placebo + Paclitaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	79	79		
Units: Months				
median (confidence interval 95%)				
Pain Subscale	5.8 (4.2 to 7.3)	5.3 (3.2 to 6.8)		
Speech problems	5.6 (4.1 to 6.9)	4.2 (2.2 to 5.4)		
Swallowing	5.1 (3.7 to 7.2)	4.6 (2.8 to 6.7)		
Sense Problems	5.1 (3.1 to 7.3)	4.6 (2.9 to 6.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Concentration-time profiles of BKM120 Pharmacokinetics (PK) for AUC0-24 and AUClast

End point title	Plasma Concentration-time profiles of BKM120 Pharmacokinetics (PK) for AUC0-24 and AUClast ^[5]
End point description: To characterize the pharmacokinetics of buparlisib given in combination with paclitaxel for AUC0-24 and AUClast. At a 100 mg QD dose these primary PK parameters were determined for buparlisib.	
End point type	Secondary
End point timeframe: 6 Full PK samples over 24hrs at Day 15 of Cycle 1 (steady state)	

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: There was no statistical analysis planned for this endpoint.

End point values	Buparlisib + Paclitaxel			
Subject group type	Reporting group			
Number of subjects analysed	79 ^[6]			
Units: ng*hr/mL				
median (full range (min-max))				
AUC0-24	25628.56 (13651.75 to 33375.10)			
AUClast	25734.33 (13651.75 to 33306.37)			

Notes:

[6] - n = 4

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Concentration-time profiles of BKM120 Pharmacokinetics (PK) for Cmax

End point title	Plasma Concentration-time profiles of BKM120 Pharmacokinetics (PK) for Cmax ^[7]
End point description: To characterize the pharmacokinetics of buparlisib given in combination with paclitaxel for Cmax.	
End point type	Secondary
End point timeframe: At a 100 mg QD dose this primary PK parameter was determined for buparlisib.	

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: There was no statistical analysis planned for this endpoint.

End point values	Buparlisib + Paclitaxel			
Subject group type	Reporting group			
Number of subjects analysed	79 ^[8]			
Units: ng/mL				
median (full range (min-max))	1775.00 (834.00 to			

Notes:

[8] - n = 4

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Concentration-time profiles of BKM120 Pharmacokinetics (PK) for Tmax

End point title	Plasma Concentration-time profiles of BKM120 Pharmacokinetics (PK) for Tmax ^[9]
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End point description:

To characterize the pharmacokinetics of buparlisib given in combination with paclitaxel for Tmax.

End point type	Secondary
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End point timeframe:

At a 100 mg QD dose this primary PK parameter was determined for buparlisib.

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: There was no statistical analysis planned for this endpoint.

End point values	Buparlisib + Paclitaxel			
Subject group type	Reporting group			
Number of subjects analysed	79 ^[10]			
Units: hour (hr)				
median (full range (min-max))	2.42 (1.00 to 4.00)			

Notes:

[10] - n = 4

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Concentration-time profiles of BKM120 Pharmacokinetics (PK) for CL/F

End point title	Plasma Concentration-time profiles of BKM120 Pharmacokinetics (PK) for CL/F ^[11]
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End point description:

To characterize the pharmacokinetics of buparlisib given in combination with paclitaxel for CL/F.

End point type	Secondary
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End point timeframe:

At a 100 mg QD dose this primary PK parameter was determined for buparlisib.

Notes:

[11] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: There was no statistical analysis planned for this endpoint.

End point values	Buparlisib + Paclitaxel			
Subject group type	Reporting group			
Number of subjects analysed	79 ^[12]			
Units: L/hr				
median (full range (min-max))	4.14 (3.00 to 7.33)			

Notes:

[12] - n = 4

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 up to approximately 3.5 yrs.

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
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Dictionary version	19.1
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Reporting groups

Reporting group title	Buparlisib + Paclitaxel
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Reporting group description:

Patients who were randomized to this arm on a 1:1 randomization, took buparlisib 100 mg daily and paclitaxel 80 mg/m² weekly.

Reporting group title	Buparlisib matching placebo + Paclitaxel
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Reporting group description:

Patients who were randomized to this arm on a 1:1 randomization, took buparlisib matching placebo 100 mg daily and paclitaxel 80 mg/m² weekly.

Serious adverse events	Buparlisib + Paclitaxel	Buparlisib matching placebo + Paclitaxel	
Total subjects affected by serious adverse events			
subjects affected / exposed	43 / 76 (56.58%)	37 / 78 (47.44%)	
number of deaths (all causes)	16	17	
number of deaths resulting from adverse events	2	2	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			
subjects affected / exposed	0 / 76 (0.00%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant neoplasm progression			
subjects affected / exposed	0 / 76 (0.00%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Tumour haemorrhage			

subjects affected / exposed	3 / 76 (3.95%)	5 / 78 (6.41%)	
occurrences causally related to treatment / all	0 / 3	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 3	
Tumour invasion			
subjects affected / exposed	0 / 76 (0.00%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Arterial rupture			
subjects affected / exposed	1 / 76 (1.32%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	1 / 76 (1.32%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Phlebitis			
subjects affected / exposed	1 / 76 (1.32%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	2 / 76 (2.63%)	2 / 78 (2.56%)	
occurrences causally related to treatment / all	2 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Face oedema			
subjects affected / exposed	0 / 76 (0.00%)	2 / 78 (2.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	1 / 76 (1.32%)	4 / 78 (5.13%)	
occurrences causally related to treatment / all	1 / 1	3 / 4	
deaths causally related to treatment / all	0 / 0	1 / 1	

General physical health deterioration subjects affected / exposed	3 / 76 (3.95%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Non-cardiac chest pain subjects affected / exposed	1 / 76 (1.32%)	2 / 78 (2.56%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain subjects affected / exposed	0 / 76 (0.00%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia subjects affected / exposed	0 / 76 (0.00%)	2 / 78 (2.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Systemic inflammatory response syndrome subjects affected / exposed	0 / 76 (0.00%)	1 / 78 (1.28%)	
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			
Acute respiratory failure subjects affected / exposed	0 / 76 (0.00%)	2 / 78 (2.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Dyspnoea subjects affected / exposed	2 / 76 (2.63%)	2 / 78 (2.56%)	
occurrences causally related to treatment / all	2 / 2	1 / 2	
deaths causally related to treatment / all	1 / 1	0 / 1	
Haemoptysis subjects affected / exposed	1 / 76 (1.32%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pneumonia aspiration			
subjects affected / exposed	1 / 76 (1.32%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pneumonitis			
subjects affected / exposed	1 / 76 (1.32%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	1 / 76 (1.32%)	2 / 78 (2.56%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	1 / 76 (1.32%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory arrest			
subjects affected / exposed	1 / 76 (1.32%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Respiratory failure			
subjects affected / exposed	1 / 76 (1.32%)	2 / 78 (2.56%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Upper airway obstruction			
subjects affected / exposed	1 / 76 (1.32%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Psychiatric disorders			
Acute psychosis			
subjects affected / exposed	0 / 76 (0.00%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aggression			

subjects affected / exposed	1 / 76 (1.32%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Completed suicide			
subjects affected / exposed	1 / 76 (1.32%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Mental status changes			
subjects affected / exposed	1 / 76 (1.32%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Device connection issue			
subjects affected / exposed	1 / 76 (1.32%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood creatinine increased			
subjects affected / exposed	1 / 76 (1.32%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutrophil count decreased			
subjects affected / exposed	1 / 76 (1.32%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	0 / 76 (0.00%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural discharge			
subjects affected / exposed	1 / 76 (1.32%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Post procedural fistula subjects affected / exposed	0 / 76 (0.00%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haemorrhage subjects affected / exposed	0 / 76 (0.00%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal compression fracture subjects affected / exposed	0 / 76 (0.00%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac arrest subjects affected / exposed	1 / 76 (1.32%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	1 / 1	0 / 1	
Sinus bradycardia subjects affected / exposed	0 / 76 (0.00%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Nervous system disorders			
Dizziness subjects affected / exposed	0 / 76 (0.00%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoaesthesia subjects affected / exposed	1 / 76 (1.32%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intracranial pressure increased subjects affected / exposed	0 / 76 (0.00%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Ischaemic cerebral infarction			
subjects affected / exposed	1 / 76 (1.32%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuralgia			
subjects affected / exposed	1 / 76 (1.32%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraplegia			
subjects affected / exposed	1 / 76 (1.32%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Somnolence			
subjects affected / exposed	1 / 76 (1.32%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Spinal cord compression			
subjects affected / exposed	1 / 76 (1.32%)	0 / 78 (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	1 / 76 (1.32%)	2 / 78 (2.56%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 76 (3.95%)	3 / 78 (3.85%)	
occurrences causally related to treatment / all	3 / 3	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	1 / 76 (1.32%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			

subjects affected / exposed	1 / 76 (1.32%)	0 / 78 (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	2 / 76 (2.63%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	1 / 76 (1.32%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Blindness			
subjects affected / exposed	0 / 76 (0.00%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 76 (2.63%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	1 / 2	0 / 0	
Aorto-oesophageal fistula			
subjects affected / exposed	1 / 76 (1.32%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Diarrhoea			
subjects affected / exposed	4 / 76 (5.26%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	4 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	2 / 76 (2.63%)	3 / 78 (3.85%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			

subjects affected / exposed	1 / 76 (1.32%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mouth haemorrhage			
subjects affected / exposed	0 / 76 (0.00%)	2 / 78 (2.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	1 / 76 (1.32%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal obstruction			
subjects affected / exposed	0 / 76 (0.00%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophagitis			
subjects affected / exposed	1 / 76 (1.32%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oral cavity fistula			
subjects affected / exposed	1 / 76 (1.32%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			
subjects affected / exposed	1 / 76 (1.32%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	1 / 76 (1.32%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			

subjects affected / exposed	2 / 76 (2.63%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatic failure			
subjects affected / exposed	1 / 76 (1.32%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Jaundice			
subjects affected / exposed	1 / 76 (1.32%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Skin and subcutaneous tissue disorders			
Erythema			
subjects affected / exposed	1 / 76 (1.32%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	1 / 76 (1.32%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Hypercalcaemia of malignancy			
subjects affected / exposed	0 / 76 (0.00%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Spinal pain			
subjects affected / exposed	1 / 76 (1.32%)	0 / 78 (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			
Anal abscess			

subjects affected / exposed	2 / 76 (2.63%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	1 / 76 (1.32%)	2 / 78 (2.56%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Candida sepsis			
subjects affected / exposed	1 / 76 (1.32%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest wall abscess			
subjects affected / exposed	0 / 76 (0.00%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	1 / 76 (1.32%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	0 / 76 (0.00%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	1 / 76 (1.32%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	0 / 76 (0.00%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Lung abscess			

subjects affected / exposed	1 / 76 (1.32%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Lung infection			
subjects affected / exposed	2 / 76 (2.63%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	6 / 76 (7.89%)	6 / 78 (7.69%)	
occurrences causally related to treatment / all	2 / 6	1 / 6	
deaths causally related to treatment / all	0 / 0	0 / 1	
Post procedural infection			
subjects affected / exposed	1 / 76 (1.32%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary tuberculosis			
subjects affected / exposed	1 / 76 (1.32%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	1 / 76 (1.32%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 76 (0.00%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Septic shock			
subjects affected / exposed	3 / 76 (3.95%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	0 / 2	0 / 0	
Urinary tract infection			

subjects affected / exposed	1 / 76 (1.32%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			
subjects affected / exposed	2 / 76 (2.63%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Cachexia			
subjects affected / exposed	1 / 76 (1.32%)	3 / 78 (3.85%)	
occurrences causally related to treatment / all	0 / 1	1 / 3	
deaths causally related to treatment / all	0 / 1	1 / 3	
Decreased appetite			
subjects affected / exposed	3 / 76 (3.95%)	2 / 78 (2.56%)	
occurrences causally related to treatment / all	2 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	2 / 76 (2.63%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia			
subjects affected / exposed	1 / 76 (1.32%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	3 / 76 (3.95%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypocalcaemia			
subjects affected / exposed	1 / 76 (1.32%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			

subjects affected / exposed	1 / 76 (1.32%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	1 / 76 (1.32%)	2 / 78 (2.56%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypomagnesaemia			
subjects affected / exposed	1 / 76 (1.32%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Buparlisib + Paclitaxel	Buparlisib matching placebo + Paclitaxel	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	76 / 76 (100.00%)	75 / 78 (96.15%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour pain			
subjects affected / exposed	5 / 76 (6.58%)	2 / 78 (2.56%)	
occurrences (all)	5	2	
Vascular disorders			
Hypertension			
subjects affected / exposed	11 / 76 (14.47%)	6 / 78 (7.69%)	
occurrences (all)	13	8	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	20 / 76 (26.32%)	15 / 78 (19.23%)	
occurrences (all)	27	19	
Face oedema			
subjects affected / exposed	2 / 76 (2.63%)	4 / 78 (5.13%)	
occurrences (all)	2	4	
Fatigue			

subjects affected / exposed	31 / 76 (40.79%)	16 / 78 (20.51%)	
occurrences (all)	45	19	
Non-cardiac chest pain			
subjects affected / exposed	2 / 76 (2.63%)	4 / 78 (5.13%)	
occurrences (all)	2	4	
Oedema peripheral			
subjects affected / exposed	5 / 76 (6.58%)	10 / 78 (12.82%)	
occurrences (all)	5	12	
Pyrexia			
subjects affected / exposed	12 / 76 (15.79%)	16 / 78 (20.51%)	
occurrences (all)	16	23	
Respiratory, thoracic and mediastinal disorders			
Catarrh			
subjects affected / exposed	1 / 76 (1.32%)	4 / 78 (5.13%)	
occurrences (all)	1	4	
Cough			
subjects affected / exposed	17 / 76 (22.37%)	18 / 78 (23.08%)	
occurrences (all)	18	20	
Dysphonia			
subjects affected / exposed	3 / 76 (3.95%)	4 / 78 (5.13%)	
occurrences (all)	3	4	
Dyspnoea			
subjects affected / exposed	8 / 76 (10.53%)	13 / 78 (16.67%)	
occurrences (all)	10	17	
Epistaxis			
subjects affected / exposed	7 / 76 (9.21%)	4 / 78 (5.13%)	
occurrences (all)	7	5	
Haemoptysis			
subjects affected / exposed	1 / 76 (1.32%)	7 / 78 (8.97%)	
occurrences (all)	1	7	
Hiccups			
subjects affected / exposed	5 / 76 (6.58%)	3 / 78 (3.85%)	
occurrences (all)	9	3	
Oropharyngeal pain			

subjects affected / exposed occurrences (all)	5 / 76 (6.58%) 5	6 / 78 (7.69%) 6	
Pneumonitis subjects affected / exposed occurrences (all)	4 / 76 (5.26%) 4	3 / 78 (3.85%) 3	
Productive cough subjects affected / exposed occurrences (all)	4 / 76 (5.26%) 5	3 / 78 (3.85%) 3	
Psychiatric disorders Anxiety subjects affected / exposed occurrences (all)	13 / 76 (17.11%) 17	9 / 78 (11.54%) 10	
Depression subjects affected / exposed occurrences (all)	13 / 76 (17.11%) 16	7 / 78 (8.97%) 7	
Insomnia subjects affected / exposed occurrences (all)	10 / 76 (13.16%) 13	6 / 78 (7.69%) 6	
Mood altered subjects affected / exposed occurrences (all)	4 / 76 (5.26%) 4	5 / 78 (6.41%) 5	
Investigations Alanine aminotransferase increased subjects affected / exposed occurrences (all)	6 / 76 (7.89%) 6	4 / 78 (5.13%) 4	
Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	6 / 76 (7.89%) 8	7 / 78 (8.97%) 8	
Blood alkaline phosphatase increased subjects affected / exposed occurrences (all)	6 / 76 (7.89%) 6	1 / 78 (1.28%) 1	
Blood creatinine increased subjects affected / exposed occurrences (all)	4 / 76 (5.26%) 6	1 / 78 (1.28%) 1	
Blood glucose increased			

subjects affected / exposed	3 / 76 (3.95%)	4 / 78 (5.13%)	
occurrences (all)	4	5	
Blood lactate dehydrogenase increased			
subjects affected / exposed	5 / 76 (6.58%)	5 / 78 (6.41%)	
occurrences (all)	5	5	
Gamma-glutamyltransferase increased			
subjects affected / exposed	8 / 76 (10.53%)	7 / 78 (8.97%)	
occurrences (all)	9	8	
Neutrophil count decreased			
subjects affected / exposed	5 / 76 (6.58%)	4 / 78 (5.13%)	
occurrences (all)	5	7	
Weight decreased			
subjects affected / exposed	19 / 76 (25.00%)	9 / 78 (11.54%)	
occurrences (all)	27	11	
White blood cell count decreased			
subjects affected / exposed	7 / 76 (9.21%)	3 / 78 (3.85%)	
occurrences (all)	18	3	
Nervous system disorders			
Dizziness			
subjects affected / exposed	6 / 76 (7.89%)	6 / 78 (7.69%)	
occurrences (all)	6	7	
Dysgeusia			
subjects affected / exposed	4 / 76 (5.26%)	1 / 78 (1.28%)	
occurrences (all)	4	1	
Headache			
subjects affected / exposed	14 / 76 (18.42%)	6 / 78 (7.69%)	
occurrences (all)	17	6	
Neuropathy peripheral			
subjects affected / exposed	6 / 76 (7.89%)	18 / 78 (23.08%)	
occurrences (all)	7	21	
Paraesthesia			
subjects affected / exposed	8 / 76 (10.53%)	9 / 78 (11.54%)	
occurrences (all)	11	12	
Peripheral sensory neuropathy			

subjects affected / exposed occurrences (all)	6 / 76 (7.89%) 6	3 / 78 (3.85%) 3	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	29 / 76 (38.16%)	32 / 78 (41.03%)	
occurrences (all)	39	42	
Leukopenia			
subjects affected / exposed	7 / 76 (9.21%)	13 / 78 (16.67%)	
occurrences (all)	15	28	
Neutropenia			
subjects affected / exposed	23 / 76 (30.26%)	10 / 78 (12.82%)	
occurrences (all)	49	21	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	7 / 76 (9.21%)	2 / 78 (2.56%)	
occurrences (all)	7	2	
Constipation			
subjects affected / exposed	14 / 76 (18.42%)	8 / 78 (10.26%)	
occurrences (all)	15	9	
Diarrhoea			
subjects affected / exposed	26 / 76 (34.21%)	13 / 78 (16.67%)	
occurrences (all)	50	23	
Dyspepsia			
subjects affected / exposed	4 / 76 (5.26%)	2 / 78 (2.56%)	
occurrences (all)	4	2	
Dysphagia			
subjects affected / exposed	9 / 76 (11.84%)	5 / 78 (6.41%)	
occurrences (all)	10	5	
Nausea			
subjects affected / exposed	19 / 76 (25.00%)	13 / 78 (16.67%)	
occurrences (all)	22	19	
Odynophagia			
subjects affected / exposed	4 / 76 (5.26%)	1 / 78 (1.28%)	
occurrences (all)	5	1	
Oral pain			

subjects affected / exposed	4 / 76 (5.26%)	1 / 78 (1.28%)	
occurrences (all)	4	1	
Stomatitis			
subjects affected / exposed	23 / 76 (30.26%)	10 / 78 (12.82%)	
occurrences (all)	30	13	
Vomiting			
subjects affected / exposed	19 / 76 (25.00%)	11 / 78 (14.10%)	
occurrences (all)	25	15	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	24 / 76 (31.58%)	15 / 78 (19.23%)	
occurrences (all)	25	15	
Dry skin			
subjects affected / exposed	8 / 76 (10.53%)	2 / 78 (2.56%)	
occurrences (all)	8	2	
Dermatitis acneiform			
subjects affected / exposed	5 / 76 (6.58%)	1 / 78 (1.28%)	
occurrences (all)	9	1	
Erythema			
subjects affected / exposed	8 / 76 (10.53%)	2 / 78 (2.56%)	
occurrences (all)	8	3	
Onycholysis			
subjects affected / exposed	0 / 76 (0.00%)	4 / 78 (5.13%)	
occurrences (all)	0	4	
Palmar-plantar erythrodysesthesia syndrome			
subjects affected / exposed	4 / 76 (5.26%)	0 / 78 (0.00%)	
occurrences (all)	4	0	
Pruritus			
subjects affected / exposed	8 / 76 (10.53%)	3 / 78 (3.85%)	
occurrences (all)	10	4	
Rash			
subjects affected / exposed	14 / 76 (18.42%)	11 / 78 (14.10%)	
occurrences (all)	18	14	
Rash maculo-papular			

subjects affected / exposed occurrences (all)	5 / 76 (6.58%) 8	3 / 78 (3.85%) 3	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 76 (0.00%)	6 / 78 (7.69%)	
occurrences (all)	0	7	
Muscle spasms			
subjects affected / exposed	4 / 76 (5.26%)	3 / 78 (3.85%)	
occurrences (all)	4	3	
Muscular weakness			
subjects affected / exposed	0 / 76 (0.00%)	5 / 78 (6.41%)	
occurrences (all)	0	5	
Musculoskeletal pain			
subjects affected / exposed	5 / 76 (6.58%)	2 / 78 (2.56%)	
occurrences (all)	5	2	
Myalgia			
subjects affected / exposed	4 / 76 (5.26%)	1 / 78 (1.28%)	
occurrences (all)	4	2	
Neck pain			
subjects affected / exposed	6 / 76 (7.89%)	7 / 78 (8.97%)	
occurrences (all)	7	7	
Pain in extremity			
subjects affected / exposed	1 / 76 (1.32%)	5 / 78 (6.41%)	
occurrences (all)	1	5	
Pain in jaw			
subjects affected / exposed	5 / 76 (6.58%)	1 / 78 (1.28%)	
occurrences (all)	5	1	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	4 / 76 (5.26%)	4 / 78 (5.13%)	
occurrences (all)	5	4	
Pneumonia			
subjects affected / exposed	2 / 76 (2.63%)	6 / 78 (7.69%)	
occurrences (all)	2	6	
Respiratory tract infection			

subjects affected / exposed occurrences (all)	5 / 76 (6.58%) 5	2 / 78 (2.56%) 4	
Upper respiratory tract infection subjects affected / exposed occurrences (all)	1 / 76 (1.32%) 1	4 / 78 (5.13%) 4	
Metabolism and nutrition disorders			
Decreased appetite subjects affected / exposed occurrences (all)	23 / 76 (30.26%) 34	14 / 78 (17.95%) 15	
Hyperglycaemia subjects affected / exposed occurrences (all)	47 / 76 (61.84%) 95	27 / 78 (34.62%) 46	
Hyperkalaemia subjects affected / exposed occurrences (all)	2 / 76 (2.63%) 2	8 / 78 (10.26%) 10	
Hypoalbuminaemia subjects affected / exposed occurrences (all)	4 / 76 (5.26%) 5	3 / 78 (3.85%) 3	
Hypocalcaemia subjects affected / exposed occurrences (all)	5 / 76 (6.58%) 7	4 / 78 (5.13%) 5	
Hypokalaemia subjects affected / exposed occurrences (all)	7 / 76 (9.21%) 9	3 / 78 (3.85%) 3	
Hypomagnesaemia subjects affected / exposed occurrences (all)	4 / 76 (5.26%) 12	6 / 78 (7.69%) 7	
Hyponatraemia subjects affected / exposed occurrences (all)	5 / 76 (6.58%) 8	6 / 78 (7.69%) 8	
Hypophosphataemia subjects affected / exposed occurrences (all)	3 / 76 (3.95%) 3	5 / 78 (6.41%) 7	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 December 2013	Amendment 1 introduced the following changes: • Added pharmacokinetics (PK) sampling collection in a subset of patients in order to characterize the PK of buparlisib given in combination with paclitaxel. Aim: to assess if patients treated with buparlisib are exposed to the drug within the targeted range. The inclusion of this assessment was based on findings that emerged from Study CBEZ235A2118, which investigated the use of the same combination. The collection of additional PK data was to provide more information in support of this study indication and also to obtain a more robust population PK model based on several indications currently in clinical development using the same regimen. Objectives and statistical plan were updated accordingly. • Reduced the amount of tumor tissue required at Baseline for HPV and PI3K pathway determination. Novartis had adopted the use of a more sensitive platform requiring smaller amount of DNA compared to the one previously used. The list of biomarkers being assessed was not changed. • Allowed confirmation of an adequate amount of tumor tissue for enrollment by central or local pathologist in order to accelerate the turnaround time for eligibility decision making process and eventually to start the study treatment earlier. • Mild and asymptomatic transaminase elevations at Baseline are a common finding in this patient population even in the absence of liver metastasis (e.g. related to concomitant medications, prior treatment/surgery, underlying disease, fatty liver, etc.). Therefore, the upper limit for aspartate aminotransferase (AST)/alanine aminotransferase (ALT) in patients without liver metastases was slightly increased to allow 1.5x upper limit of normal (ULN) for study inclusion. The ULN for bilirubin remained unchanged
02 July 2015	Amendment 2 issued when recruitment was 100% complete, introduced the following change(s): • Provided additional guidance to Investigators regarding management of liver toxicities: - o Clarification of the management of AST or ALT side effects - o New section added "Management of hepatotoxicity (ALT and/or AST >3.0x ULN and total bilirubin >2.0x ULN) in patients receiving buparlisib/placebo" including detailed liver event follow-up assessments and close monitoring measures • Addition of hepatotoxicity follow-up testing/procedures • Clarification provided in the data analysis to reflect the change in wording for number of events needed for final PFS and final OS analyses • Update of the clinical background section on liver toxicity to align with the protocol amendment rationale. • Clarification of laboratory parameters collection plan and viral hepatitis testing. • Clarification of the wording for the number of PFS events required for the PFS analysis and for the number of deaths to be observed for the planned final Overall Survival analyses.

30 August 2016	The main purposes of this protocol amendment 3 were to: • Provide a clarification on the measures to follow when a patient exhibits suicidal ideation regardless of the response to question 9 of the Patient Health Questionnaire-9 (PHQ-9) questionnaire (as has been described in the BKM120 Investigator's Brochure Ed. 8.0). • Unblind patients' treatment considering that all planned analyses (final PFS analysis & final OS analysis) have been completed. The study was to be closed after LPLV. • Reduce assessment schedule for patients still on study treatment. Tumor assessment will be performed per local clinical practices & safety evaluation will be done per revised visit schedule. • For patients who are still on study treatment & are considered benefiting from study drug (s), study treatment will continue to be provided on or off this study. Treatment for these patients can also be managed according to local clinical practices per Investigator discretion.
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Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported