Clinical trial results:
A Phase III randomized, double blind, placebo-controlled study of BKM120 with fulvestrant, in postmenopausal women with hormone receptor-positive HER2-negative AI-treated, locally advanced or metastatic breast cancer who progressed on or after mTOR inhibitor based treatment

Summary

EudraCT number	2012-002571-34
Trial protocol	AT GB DE ES NO IT SE NL GR FI HU PL BE BG
Global end of trial date	21 September 2017

Results information

Result version number	v1
This version publication date	06 October 2018
First version publication date	06 October 2018

Trial information

Trial identification

Sponsor protocol code	CBKM120F2303

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01633060
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	21 September 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	21 September 2017
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to determine whether treatment with buparlisib plus fulvestrant prolongs PFS based on local Investigator assessment compared to treatment with placebo plus fulvestrant.

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.nov for complete trial results.

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	03 October 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	Argentina: 9
Country: Number of subjects enrolled	Austria: 13
Country: Number of subjects enrolled	Belgium: 10
Country: Number of subjects enrolled	Bulgaria: 18
Country: Number of subjects enrolled	Canada: 3
Country: Number of subjects enrolled	Colombia: 7
Country: Number of subjects enrolled	Finland: 1
Country: Number of subjects enrolled	France: 31
Country: Number of subjects enrolled	Germany: 48
Country: Number of subjects enrolled	Greece: 12
Country: Number of subjects enrolled	Hungary: 9
Country: Number of subjects enrolled	Italy: 90
Country: Number of subjects enrolled	Korea, Republic of: 21
Country: Number of subjects enrolled	Lebanon: 5
Country: Number of subjects enrolled	Netherlands: 22
Country: Number of subjects enrolled	Norway: 11
Country: Number of subjects enrolled	Poland: 1

Country: Number of subjects enrolled	Spain: 41
Country: Number of subjects enrolled	Sweden: 7
Country: Number of subjects enrolled	Thailand: 3
Country: Number of subjects enrolled	United Kingdom: 18
Country: Number of subjects enrolled	United States: 52
Worldwide total number of subjects	432
EEA total number of subjects	332

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)	274
From 65 to 84 years	158
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study was conducted at 201 centers in 22 countries worldwide (Argentina, Austria, Belgium, Bulgaria, Canada, Colombia, Finland, France, Germany, Greece, Hungary, Italy, Republic of Korea, Lebanon, The Netherlands, Norway, Poland, Spain, Sweden, Thailand, UK and USA).

Pre-assignment

Screening details:

At least 420 patients were planned to be enrolled, randomized in a 2:1 ratio (two buparlisib, one placebo). A total of 432 patients were actually enrolled and analyzed (buparlisib arm: N=289; placebo arm: N=143). Not completed: in Randomization Phase=Randomized and not Treated; in Treatment Phase=Discontinued study treatment per Protocol.

Period 1

Period 1 title	Randomization Phase
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer, Data analyst, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	BKM120 100mg + Fulvestrant

Arm description:

BKM120 100 mg per day and fulvestrant given until progression or as described in the protocol.

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

Dosage and administration details:

100 mg once daily starting Cycle 1 Day 1

Investigational medicinal product name	Fulvestrant
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

500 mg (Day 1 and Day 15 of Cycle 1 and Day 1 of every cycle thereafter)

Arm title	Placebo + Fulvestrant

Arm description:

BKM120 matching placebo daily and fulvestrant given until progression or as described in the protocol.

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

Dosage and administration details:

100 mg once daily starting Cycle 1 Day 1

Investigational medicinal product name	Fulvestrant
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:
500 mg (Day 1 and Day 15 of Cycle 1 and Day 1 of every cycle thereafter)

Number of subjects in period 1	BKM120 100mg + Fulvestrant	Placebo + Fulvestrant
Started	289	143
Completed	288	140
Not completed	1	3
Technical problem	-	1
Protocol Deviation	1	2

Period 2	
Period 2 title	Treatment Phase
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer, Data analyst, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	BKM120 100mg + Fulvestrant

Arm description:
BKM120 100 mg per day and fulvestrant given until progression or as described in the protocol.

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

Dosage and administration details:
100 mg once daily starting Cycle 1 Day 1

Investigational medicinal product name	Fulvestrant
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:
500 mg (Day 1 and Day 15 of Cycle 1 and Day 1 of every cycle thereafter)

Arm title	Placebo + Fulvestrant

Arm description:	
BKM120 matching placebo daily and fulvestrant given until progression or as described in the protocol.	
Arm type	Placebo
Investigational medicinal product name	Buparlisib
Investigational medicinal product code	BKM120
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use
Dosage and administration details:	
100 mg once daily starting Cycle 1 Day 1	
Investigational medicinal product name	Fulvestrant
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use
Dosage and administration details:	
500 mg (Day 1 and Day 15 of Cycle 1 and Day 1 of every cycle thereafter)	

Number of subjects in period 2	BKM120 100mg + Fulvestrant	Placebo + Fulvestrant
Started	288	140
FAS - ctDNA PIK3CA Mutant	100	35
FAS - ctDNA PIK3CA Non-mutant	132	81
Safety Set (SS)	288	140
Pharmacokinetic Analysis Set (PAS)	63	0
Completed	0	0
Not completed	288	140
Adverse event, serious fatal	4	3
Physician decision	16	7
Adverse event, non-fatal	24	3
Protocol Deviation	1	-
Progressive Disease	210	120
Study terminated by sponsor	7	3
Subject/Guardian Decision	25	4
Lost to follow-up	1	-

Period 3	
Period 3 title	Post-Treatment Efficacy Follow-Up Phase
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind

Roles blinded	Subject, Investigator, Monitor, Carer, Data analyst, Assessor

Arms

Are arms mutually exclusive?	No
Arm title	BKM120 100mg + Fulvestrant

Arm description:

BKM120 100 mg per day and fulvestrant given until progression or as described in the protocol.

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

Dosage and administration details:

100 mg once daily starting Cycle 1 Day 1

Investigational medicinal product name	Fulvestrant
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

500 mg (Day 1 and Day 15 of Cycle 1 and Day 1 of every cycle thereafter)

Arm title	Placebo + Fulvestrant

Arm description:

BKM120 matching placebo daily and fulvestrant given until progression or as described in the protocol.

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

Dosage and administration details:

100 mg once daily starting Cycle 1 Day 1

Investigational medicinal product name	Fulvestrant
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

500 mg (Day 1 and Day 15 of Cycle 1 and Day 1 of every cycle thereafter)

Number of subjects in period 3	BKM120 100mg + Fulvestrant	Placebo + Fulvestrant
Started	16	2
Completed	0	0
Not completed	16	2
Adverse event, serious fatal	1	-
Physician decision	1	-

Adverse event, non-fatal	2	-
Progressive Disease	10	1
Study terminated by sponsor	1	-
Subject/Guardian Decision	1	1

Baseline characteristics

Reporting groups	
Reporting group title	BKM120 100mg + Fulvestrant
Reporting group description:	
BKM120 100 mg per day and fulvestrant given until progression or as described in the protocol.	
Reporting group title	Placebo + Fulvestrant
Reporting group description:	
BKM120 matching placebo daily and fulvestrant given until progression or as described in the protocol.	

Reporting group values	BKM120 100mg + Fulvestrant	Placebo + Fulvestrant	Total
Number of subjects	289	143	432
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)	191	83	274
From 65-84 years	98	60	158
85 years and over	0	0	0
Age Continuous Units: Years			
arithmetic mean	60.5	61.5	
standard deviation	± 9.76	± 9.23	-
Sex: Female, Male Units: Subjects			
Female	289	143	432
Male	0	0	0
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	4	1	5
Asian	20	9	29
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	4	4	8
White	249	121	370
More than one race	0	0	0
Unknown or Not Reported	12	8	20

End points

End points reporting groups

Reporting group title	BKM120 100mg + Fulvestrant
Reporting group description:	
BKM120 100 mg per day and fulvestrant given until progression or as described in the protocol.	
Reporting group title	Placebo + Fulvestrant
Reporting group description:	
BKM120 matching placebo daily and fulvestrant given until progression or as described in the protocol.	
Reporting group title	BKM120 100mg + Fulvestrant
Reporting group description:	
BKM120 100 mg per day and fulvestrant given until progression or as described in the protocol.	
Reporting group title	Placebo + Fulvestrant
Reporting group description:	
BKM120 matching placebo daily and fulvestrant given until progression or as described in the protocol.	
Reporting group title	BKM120 100mg + Fulvestrant
Reporting group description:	
BKM120 100 mg per day and fulvestrant given until progression or as described in the protocol.	
Reporting group title	Placebo + Fulvestrant
Reporting group description:	
BKM120 matching placebo daily and fulvestrant given until progression or as described in the protocol.	

Primary: Progression Free Survival (PFS) based on Local Investigator assessment - Full Analysis Set (FAS)

End point title	Progression Free Survival (PFS) based on Local Investigator assessment - Full Analysis Set (FAS)
End point description:	
Progression Free Survival (PFS) is defined as the time from date of randomization to the date of first radiologically documented progression or death due to any cause. If a patient did not progress or die at the time of the analysis data cut-off or start of new anti-neoplastic therapy, PFS was censored at the date of the last adequate tumor assessment before the earliest of the cut-off date or the start date of additional anti-neoplastic therapy. PFS was assessed via a local radiology assessment according to RECIST 1.1.Patients were followed up for approximately every 6 weeks after randomization.	
End point type	Primary
End point timeframe:	
Every 6 weeks after randomization up to a maximum of 4 years	

End point values	BKM120 100mg + Fulvestrant	Placebo + Fulvestrant		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	289	143		
Units: Months				
median (confidence interval 95%)	3.9 (2.8 to 4.2)	1.8 (1.5 to 2.8)		

Statistical analyses

Statistical analysis title	Progression-Free survival (PFS)
Comparison groups	BKM120 100mg + Fulvestrant v Placebo + Fulvestrant
Number of subjects included in analysis	432
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.67
Confidence interval	
level	95 %
sides	1-sided
lower limit	0.53

Secondary: Overall Survival (OS) - Full Analysis Set (FAS)

End point title	Overall Survival (OS) - Full Analysis Set (FAS)

End point description:

Overall Survival (OS) is 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 known date patient alive. Patients were followed up approximately every 6 weeks after randomization and every 3 months during survival follow-up.

End point type	Secondary

End point timeframe:

Every 6 weeks after randomization up to a maximum of 5 years

End point values	BKM120 100mg + Fulvestrant	Placebo + Fulvestrant		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	289	143		
Units: Months				
median (confidence interval 95%)	21.2 (18.2 to 23.4)	22.1 (17.3 to 999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival (PFS) by PIK3CA mutational status

End point title	Progression Free Survival (PFS) by PIK3CA mutational status

End point description:

Progression Free Survival (PFS) by PIK3CA mutational status based on ctDNA is defined as the time from date of randomization to the date of first radiologically documented progression or death due to any cause. If a patient did not progress or die at the time of the analysis data cut-off or start of new anti-neoplastic therapy, PFS was censored at the date of the last adequate tumor assessment before the

earliest of the cut-off date or the start date of additional anti-neoplastic therapy. PFS was assessed via a local radiology assessment according to RECIST 1.1.Patients were followed up for approximately every 6 weeks after randomization.

End point type	Secondary

End point timeframe:

Every 6 weeks after randomization up to a maximum of 5 years

End point values	BKM120 100mg + Fulvestrant	Placebo + Fulvestrant		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	289	143		
Units: Months				
median (confidence interval 95%)				
FAS ctDNA PIK3CA mutant|	4.2 (2.8 to 6.7)	1.6 (1.4 to 2.8)		
FAS ctDNA PIK3CA non-mutant|	3.9 (2.8 to 4.3)	2.7 (1.5 to 3.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS) by PIK3CA mutational status

End point title	Overall Survival (OS) by PIK3CA mutational status

End point description:

Overall Survival (OS) by PIK3CA mutational status based on ctDNA is 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 known date patient alive. Patients were followed up approximately every 6 weeks after randomization and every 3 months during survival follow-up.

End point type	Secondary

End point timeframe:

Every 6 weeks after randomization up to a maximum of 5 years

End point values	BKM120 100mg + Fulvestrant	Placebo + Fulvestrant		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	289	143		
Units: Months				
median (confidence interval 95%)				
FAS ctDNA PIK3CA mutant|	21.8 (14.7 to 25.8)	999 (14.5 to 999)		
FAS ctDNA PIK3CA non-mutant|	21.4 (17.3 to 999)	21.4 (17.3 to 999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Response Rate (ORR) by PIK3CA mutational status

End point title	Overall Response Rate (ORR) by PIK3CA mutational status

End point description:

Overall Response Rate (ORR) is defined as the proportion of participants with best overall response of complete response (CR) or partial response (PR) based on local investigator's assessment according to RECIST 1.1. ORR was analyzed in the full population and by PIK3CA mutational status based on ctDNA. Patients were followed up for the duration of the study and for approximately every 6 weeks after randomization.

End point type	Secondary

End point timeframe:

Every 6 weeks after randomization up to a maximum of 5 years

End point values	BKM120 100mg + Fulvestrant	Placebo + Fulvestrant		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	289	143		
Units: Percentage of Participants				
number (confidence interval 95%)				
Full Analysis Set (FAS)|	7.6 (4.8 to 11.3)	2.1 (0.4 to 6.0)		
FAS ctDNA PIK3CA mutant|	10.0 (4.9 to 17.6)	0 (0.0 to 10.0)		
FAS ctDNA PIK3CA non-mutant|	7.6 (3.7 to 13.5)	3.7 (0.8 to 10.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Benefit Rate (CBR) by PIK3CA mutational status

End point title	Clinical Benefit Rate (CBR) by PIK3CA mutational status

End point description:

Clinical Benefit Rate (CBR) is defined as the proportion of participants with a best overall response of complete response (CR) or partial response (PR) or stable disease (SD) or Non-CR/non-PD lasting more than 14 or 24 weeks based on local investigator's assessment according to RECIST 1.1. CBR was analyzed in the full population and by PIK3CA mutational status based on ctDNA. Patients were followed up for the duration of the study and approximately every 6 weeks after randomization.

End point type	Secondary

End point timeframe:

Every 6 weeks after randomization up to a maximum of 5 years

End point values	BKM120 100mg + Fulvestrant	Placebo + Fulvestrant		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	289	143		
Units: Percentage of Participants				
number (confidence interval 95%)				
CBR >= 14 weeks (FAS)|	33.2 (27.8 to 39.0)	20.3 (14.0 to 27.8)		
CBR >= 24 weeks (FAS)|	24.6 (19.7 to 29.9)	15.4 (9.9 to 22.4)		
CBR >= 14 weeks (FAS ctDNA PIK3CA mutant)|	38.0 (28.5 to 48.3)	14.3 (4.8 to 30.3)		
CBR >= 24 weeks (FAS ctDNA PIK3CA mutant)|	30.0 (21.2 to 40.0)	11.4 (3.2 to 26.7)		
CBR >= 14 weeks (FAS ctDNA PIK3CA non-mutant)|	36.4 (28.2 to 45.2)	21.0 (12.7 to 31.5)		
CBR >= 24 weeks (FAS ctDNA PIK3CA non-mutant)|	25.8 (18.5 to 34.1)	14.8 (7.9 to 24.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Long-term safety and tolerability in the two treatment arms - Safety Set (SS)

End point title	Long-term safety and tolerability in the two treatment arms - Safety Set (SS)

End point description:

Analysis of frequencies for treatment emergent Adverse Event (AE), Serious Adverse Event (SAE) and Deaths.

End point type	Secondary

End point timeframe:

From first dose of study treatment to 30 days after last dose of study treatment

End point values	BKM120 100mg + Fulvestrant	Placebo + Fulvestrant		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	288	140		
Units: Percentage of participants				
number (not applicable)				
AEs|	97.9	92.9		
SAEs|	25.7	18.6		
Deaths|	42.7	48.6		

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma concentration-time profiles of BKM120 in combination with fulvestrant at Cycle 1 Day 1 - Pharmacokinetic Analysis Set (PAS)

End point title	Plasma concentration-time profiles of BKM120 in combination with fulvestrant at Cycle 1 Day 1 - Pharmacokinetic Analysis Set (PAS)

End point description:

Plasma samples were collected from the first 100 BKM120-treated patients on Cycle 1 Day 1 (at 1h, 2h, and 6h post-dose and a recommended 9h post-dose sample).

End point type	Secondary

End point timeframe:

C1D1 1 hour post dose, C1D1 2 hour post dose, C1D1 6 hour post dose and C1D1 9 hour post dose

End point values	BKM120 100mg + Fulvestrant	Placebo + Fulvestrant		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	63	0[1]		
Units: nanogram per milliliter (ng/mL)				
geometric mean (geometric coefficient of variation)				
C1D1 - 1 hour post dose|	425.178 (± 149.6)	()		
C1D1 - 2 hour post dose|	615.441 (± 70.9)	()		
C1D1 - 6 hour post dose|	314.094 (± 41.9)	()		
C1D1 - 9 hour post dose|	302.899 (± 58.3)	()		

Notes:

[1] - Only collected in BKM120 100mg + Fulvestrant arm

Statistical analyses

No statistical analyses for this end point

Secondary: Predose trough concentration-time profile of BKM120 in combination with fulvestrant over time - Pharmacokinetic Analysis Set (PAS)

End point title	Predose trough concentration-time profile of BKM120 in combination with fulvestrant over time - Pharmacokinetic Analysis Set (PAS)

End point description:

Pre-dose samples were collected for trough concentrations at Cycle 1 Day 15, Cycle 2 Day 1, Cycle 3 Day 1 and Cycle 4 Day 1.

End point type	Secondary

End point timeframe:

C1D15, C2D1, C3D1 and C4D1

End point values	BKM120 100mg + Fulvestrant	Placebo + Fulvestrant		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	63	0[2]		
Units: nanogram per milliliter (ng/mL)				
geometric mean (geometric coefficient of variation)				
C1D15|	939.978 (± 36.8)	()		
C2D1|	880.074 (± 38.4)	()		
C3D1|	777.026 (± 131.0)	()		
C4D1|	1088.074 (± 27.0)	()		

Notes:

[2] - Only collected in BKM120 100mg + Fulvestrant arm

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 - Full Analysis Set (FAS)

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 - Full Analysis Set (FAS)

End point description:

The global health status/QoL scale score of the QLQ-C30 is identified as the primary PRO variable of interest. Physical Functioning (PF), Emotional Functioning (EF) and Social Functioning (SF) scale scores of the QLQ-C30. The time to definitive 10% deterioration is defined as the time from the randomization date to the date of an event, which is defined as a worsening (decrease) in score by at least 10% compared to baseline, with no later increase above this threshold observed during the course of the study or death due to any cause.

End point type	Secondary

End point timeframe:

Baseline, Week 6 (C2D15), Week 12 (C4D1), then every 8 weeks until discontinuation (a cycle [C] = 4 weeks).

End point values	BKM120 100mg + Fulvestrant	Placebo + Fulvestrant		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	289	143		
Units: Months				
median (confidence interval 95%)				
EORTC QLQ-30 - Global QoL score|	5.3 (4.4 to 8.1)	6.3 (3.0 to 9.9)		
EORTC QLQ-30 - PF scale score|	11.8 (8.1 to 999)	10.1 (7.5 to 14.6)		
EORTC QLQ-30 - EF scale score|	10.0 (6.2 to 999)	10.0 (4.9 to 999)		
EORTC QLQ-30 - SF scale score|	10.0 (6.2 to 20.2)	11.5 (6.4 to 14.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Definitive deterioration of ECOG Performance Status from Baseline - Full Analysis Set (FAS)

End point title	Time to Definitive deterioration of ECOG Performance Status from Baseline - Full Analysis Set (FAS)

End point description:

The Eastern Cooperative Oncology Group (ECOG) Performance Status is a scale used to assess how a patient's disease is progressing, assess how the disease affects the daily living abilities of the patient, and determine appropriate treatment and prognosis. The ECOG Performance Scores has 5 grades: 0 = fully active, able to carry on all pre-disease performance without restriction, 1 = restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work, 2 = ambulatory and capable of all self-care but unable to carry out any work activities, up and about more than 50% of waking hours, 3 = capable of only limited self-care, confined to bed or chair more than 50% of waking hours, 4 = completely disabled, cannot carry on any self-care, totally confined to bed or chair and 5 = dead.

End point type	Secondary

End point timeframe:

Screening, Baseline (Cycle 1 Day 1) and then at day 1 of each cycle and at the EOT visit

End point values	BKM120 100mg + Fulvestrant	Placebo + Fulvestrant		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	289	143		
Units: Months				
median (confidence interval 95%)	18.3 (6.9 to 999)	12.0 (6.4 to 14.2)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Adverse Events (AEs) are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All AEs reported in this record are from date of First Patient First Treatment (FPFT) until LPLV up to approximately 5 years.	
Adverse event reporting additional description:	
Consistent with EudraCT disclosure specifications, Novartis has reported under the Serious adverse events fields "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

Dictionary used	
Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups	
Reporting group title	BKM120 100 mg@+ fulvestrant
Reporting group description: BKM120 100 mg@+ fulvestrant	
Reporting group title	Placebo@+ fulvestrant
Reporting group description: Placebo@+ fulvestrant	
Reporting group title	All@Patients
Reporting group description: All@Patients	

Serious adverse events	BKM120 100 mg@+ fulvestrant	Placebo@+ fulvestrant	All@Patients
Total subjects affected by serious adverse events			
subjects affected / exposed	74 / 288 (25.69%)	26 / 140 (18.57%)	100 / 428 (23.36%)
number of deaths (all causes)	123	68	191
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			
subjects affected / exposed	1 / 288 (0.35%)	0 / 140 (0.00%)	1 / 428 (0.23%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant pleural effusion			
subjects affected / exposed	1 / 288 (0.35%)	1 / 140 (0.71%)	2 / 428 (0.47%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			

Circulatory collapse			
subjects affected / exposed	2 / 288 (0.69%)	0 / 140 (0.00%)	2 / 428 (0.47%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 2
Hypertension			
subjects affected / exposed	2 / 288 (0.69%)	0 / 140 (0.00%)	2 / 428 (0.47%)
occurrences causally related to treatment / all	1 / 2	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			
subjects affected / exposed	1 / 288 (0.35%)	0 / 140 (0.00%)	1 / 428 (0.23%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Venous thrombosis			
subjects affected / exposed	1 / 288 (0.35%)	0 / 140 (0.00%)	1 / 428 (0.23%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 288 (0.35%)	0 / 140 (0.00%)	1 / 428 (0.23%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Death			
subjects affected / exposed	0 / 288 (0.00%)	1 / 140 (0.71%)	1 / 428 (0.23%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	1 / 1	1 / 1
Facial pain			
subjects affected / exposed	1 / 288 (0.35%)	0 / 140 (0.00%)	1 / 428 (0.23%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fatigue			
subjects affected / exposed	1 / 288 (0.35%)	1 / 140 (0.71%)	2 / 428 (0.47%)
occurrences causally related to treatment / all	1 / 1	1 / 1	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

General physical health deterioration			
subjects affected / exposed	1 / 288 (0.35%)	0 / 140 (0.00%)	1 / 428 (0.23%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Malaise			
subjects affected / exposed	1 / 288 (0.35%)	0 / 140 (0.00%)	1 / 428 (0.23%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-cardiac chest pain			
subjects affected / exposed	1 / 288 (0.35%)	0 / 140 (0.00%)	1 / 428 (0.23%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	0 / 288 (0.00%)	2 / 140 (1.43%)	2 / 428 (0.47%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Social circumstances			
Homicide			
subjects affected / exposed	1 / 288 (0.35%)	0 / 140 (0.00%)	1 / 428 (0.23%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	1 / 288 (0.35%)	0 / 140 (0.00%)	1 / 428 (0.23%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	1 / 1	0 / 0	1 / 1
Atelectasis			
subjects affected / exposed	1 / 288 (0.35%)	0 / 140 (0.00%)	1 / 428 (0.23%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	7 / 288 (2.43%)	1 / 140 (0.71%)	8 / 428 (1.87%)
occurrences causally related to treatment / all	1 / 7	0 / 1	1 / 8
deaths causally related to treatment / all	1 / 2	0 / 0	1 / 2

Pleural effusion			
subjects affected / exposed	6 / 288 (2.08%)	0 / 140 (0.00%)	6 / 428 (1.40%)
occurrences causally related to treatment / all	0 / 6	0 / 0	0 / 6
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3
Respiratory failure			
subjects affected / exposed	1 / 288 (0.35%)	0 / 140 (0.00%)	1 / 428 (0.23%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Confusional state			
subjects affected / exposed	4 / 288 (1.39%)	1 / 140 (0.71%)	5 / 428 (1.17%)
occurrences causally related to treatment / all	3 / 4	0 / 1	3 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Disorientation			
subjects affected / exposed	2 / 288 (0.69%)	0 / 140 (0.00%)	2 / 428 (0.47%)
occurrences causally related to treatment / all	1 / 2	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mania			
subjects affected / exposed	1 / 288 (0.35%)	0 / 140 (0.00%)	1 / 428 (0.23%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mental disorder			
subjects affected / exposed	1 / 288 (0.35%)	0 / 140 (0.00%)	1 / 428 (0.23%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mood altered			
subjects affected / exposed	1 / 288 (0.35%)	0 / 140 (0.00%)	1 / 428 (0.23%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicide attempt			
subjects affected / exposed	3 / 288 (1.04%)	0 / 140 (0.00%)	3 / 428 (0.70%)
occurrences causally related to treatment / all	2 / 3	0 / 0	2 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			

Alanine aminotransferase increased			
subjects affected / exposed	5 / 288 (1.74%)	0 / 140 (0.00%)	5 / 428 (1.17%)
occurrences causally related to treatment / all	5 / 5	0 / 0	5 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase increased			
subjects affected / exposed	6 / 288 (2.08%)	0 / 140 (0.00%)	6 / 428 (1.40%)
occurrences causally related to treatment / all	5 / 6	0 / 0	5 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 288 (0.35%)	0 / 140 (0.00%)	1 / 428 (0.23%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transaminases increased			
subjects affected / exposed	1 / 288 (0.35%)	0 / 140 (0.00%)	1 / 428 (0.23%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Weight decreased			
subjects affected / exposed	2 / 288 (0.69%)	0 / 140 (0.00%)	2 / 428 (0.47%)
occurrences causally related to treatment / all	2 / 2	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	0 / 288 (0.00%)	1 / 140 (0.71%)	1 / 428 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Electric injury			
subjects affected / exposed	0 / 288 (0.00%)	1 / 140 (0.71%)	1 / 428 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femur fracture			

subjects affected / exposed	0 / 288 (0.00%)	1 / 140 (0.71%)	1 / 428 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Head injury			
subjects affected / exposed	0 / 288 (0.00%)	1 / 140 (0.71%)	1 / 428 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal cord injury thoracic			
subjects affected / exposed	0 / 288 (0.00%)	1 / 140 (0.71%)	1 / 428 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wrist fracture			
subjects affected / exposed	1 / 288 (0.35%)	0 / 140 (0.00%)	1 / 428 (0.23%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	2 / 288 (0.69%)	0 / 140 (0.00%)	2 / 428 (0.47%)
occurrences causally related to treatment / all	1 / 2	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	0 / 288 (0.00%)	1 / 140 (0.71%)	1 / 428 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			
subjects affected / exposed	1 / 288 (0.35%)	0 / 140 (0.00%)	1 / 428 (0.23%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Cardiac failure acute			
subjects affected / exposed	1 / 288 (0.35%)	0 / 140 (0.00%)	1 / 428 (0.23%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	1 / 1	0 / 0	1 / 1
Cardiac tamponade			

subjects affected / exposed	0 / 288 (0.00%)	1 / 140 (0.71%)	1 / 428 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intracardiac mass			
subjects affected / exposed	0 / 288 (0.00%)	1 / 140 (0.71%)	1 / 428 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericardial effusion			
subjects affected / exposed	1 / 288 (0.35%)	0 / 140 (0.00%)	1 / 428 (0.23%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebral haemorrhage			
subjects affected / exposed	1 / 288 (0.35%)	0 / 140 (0.00%)	1 / 428 (0.23%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular accident			
subjects affected / exposed	0 / 288 (0.00%)	1 / 140 (0.71%)	1 / 428 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dizziness			
subjects affected / exposed	1 / 288 (0.35%)	0 / 140 (0.00%)	1 / 428 (0.23%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epilepsy			
subjects affected / exposed	1 / 288 (0.35%)	0 / 140 (0.00%)	1 / 428 (0.23%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Horner's syndrome			
subjects affected / exposed	1 / 288 (0.35%)	0 / 140 (0.00%)	1 / 428 (0.23%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hydrocephalus			

subjects affected / exposed	1 / 288 (0.35%)	0 / 140 (0.00%)	1 / 428 (0.23%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Loss of consciousness			
subjects affected / exposed	1 / 288 (0.35%)	0 / 140 (0.00%)	1 / 428 (0.23%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Migraine			
subjects affected / exposed	1 / 288 (0.35%)	0 / 140 (0.00%)	1 / 428 (0.23%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neuralgia			
subjects affected / exposed	1 / 288 (0.35%)	0 / 140 (0.00%)	1 / 428 (0.23%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neurological symptom			
subjects affected / exposed	0 / 288 (0.00%)	1 / 140 (0.71%)	1 / 428 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Posterior reversible encephalopathy syndrome			
subjects affected / exposed	1 / 288 (0.35%)	0 / 140 (0.00%)	1 / 428 (0.23%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Presyncope			
subjects affected / exposed	0 / 288 (0.00%)	1 / 140 (0.71%)	1 / 428 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Resting tremor			
subjects affected / exposed	1 / 288 (0.35%)	0 / 140 (0.00%)	1 / 428 (0.23%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			

subjects affected / exposed	2 / 288 (0.69%)	0 / 140 (0.00%)	2 / 428 (0.47%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	2 / 288 (0.69%)	1 / 140 (0.71%)	3 / 428 (0.70%)
occurrences causally related to treatment / all	1 / 2	0 / 1	1 / 3
deaths causally related to treatment / all	1 / 1	0 / 0	1 / 1
Transient ischaemic attack			
subjects affected / exposed	1 / 288 (0.35%)	0 / 140 (0.00%)	1 / 428 (0.23%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vith nerve paralysis			
subjects affected / exposed	1 / 288 (0.35%)	0 / 140 (0.00%)	1 / 428 (0.23%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vocal cord paralysis			
subjects affected / exposed	1 / 288 (0.35%)	0 / 140 (0.00%)	1 / 428 (0.23%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 288 (0.35%)	1 / 140 (0.71%)	2 / 428 (0.47%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			
subjects affected / exposed	2 / 288 (0.69%)	0 / 140 (0.00%)	2 / 428 (0.47%)
occurrences causally related to treatment / all	1 / 2	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemolytic anaemia			
subjects affected / exposed	1 / 288 (0.35%)	0 / 140 (0.00%)	1 / 428 (0.23%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			

Vertigo			
subjects affected / exposed	1 / 288 (0.35%)	0 / 140 (0.00%)	1 / 428 (0.23%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Amaurosis			
subjects affected / exposed	1 / 288 (0.35%)	0 / 140 (0.00%)	1 / 428 (0.23%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diplopia			
subjects affected / exposed	0 / 288 (0.00%)	1 / 140 (0.71%)	1 / 428 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eyelid ptosis			
subjects affected / exposed	0 / 288 (0.00%)	1 / 140 (0.71%)	1 / 428 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Optic atrophy			
subjects affected / exposed	1 / 288 (0.35%)	0 / 140 (0.00%)	1 / 428 (0.23%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vision blurred			
subjects affected / exposed	0 / 288 (0.00%)	1 / 140 (0.71%)	1 / 428 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 288 (0.35%)	1 / 140 (0.71%)	2 / 428 (0.47%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ascites			
subjects affected / exposed	1 / 288 (0.35%)	0 / 140 (0.00%)	1 / 428 (0.23%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Diarrhoea			
subjects affected / exposed	3 / 288 (1.04%)	1 / 140 (0.71%)	4 / 428 (0.93%)
occurrences causally related to treatment / all	1 / 3	0 / 1	1 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 288 (0.35%)	0 / 140 (0.00%)	1 / 428 (0.23%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematemesis			
subjects affected / exposed	0 / 288 (0.00%)	1 / 140 (0.71%)	1 / 428 (0.23%)
occurrences causally related to treatment / all	0 / 0	2 / 2	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus			
subjects affected / exposed	1 / 288 (0.35%)	0 / 140 (0.00%)	1 / 428 (0.23%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal perforation			
subjects affected / exposed	0 / 288 (0.00%)	1 / 140 (0.71%)	1 / 428 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Nausea			
subjects affected / exposed	1 / 288 (0.35%)	2 / 140 (1.43%)	3 / 428 (0.70%)
occurrences causally related to treatment / all	1 / 1	2 / 3	3 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal haemorrhage			
subjects affected / exposed	1 / 288 (0.35%)	0 / 140 (0.00%)	1 / 428 (0.23%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Vomiting			
subjects affected / exposed	4 / 288 (1.39%)	1 / 140 (0.71%)	5 / 428 (1.17%)
occurrences causally related to treatment / all	1 / 4	1 / 2	2 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			

Bile duct obstruction			
subjects affected / exposed	0 / 288 (0.00%)	1 / 140 (0.71%)	1 / 428 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bile duct stenosis			
subjects affected / exposed	1 / 288 (0.35%)	0 / 140 (0.00%)	1 / 428 (0.23%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic function abnormal			
subjects affected / exposed	1 / 288 (0.35%)	0 / 140 (0.00%)	1 / 428 (0.23%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatotoxicity			
subjects affected / exposed	2 / 288 (0.69%)	0 / 140 (0.00%)	2 / 428 (0.47%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Jaundice			
subjects affected / exposed	1 / 288 (0.35%)	0 / 140 (0.00%)	1 / 428 (0.23%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	1 / 288 (0.35%)	0 / 140 (0.00%)	1 / 428 (0.23%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary retention			
subjects affected / exposed	1 / 288 (0.35%)	0 / 140 (0.00%)	1 / 428 (0.23%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 288 (0.35%)	0 / 140 (0.00%)	1 / 428 (0.23%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Back pain			
subjects affected / exposed	1 / 288 (0.35%)	2 / 140 (1.43%)	3 / 428 (0.70%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Flank pain			
subjects affected / exposed	0 / 288 (0.00%)	1 / 140 (0.71%)	1 / 428 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Muscular weakness			
subjects affected / exposed	0 / 288 (0.00%)	1 / 140 (0.71%)	1 / 428 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal chest pain			
subjects affected / exposed	0 / 288 (0.00%)	1 / 140 (0.71%)	1 / 428 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal pain			
subjects affected / exposed	1 / 288 (0.35%)	0 / 140 (0.00%)	1 / 428 (0.23%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteonecrosis of jaw			
subjects affected / exposed	1 / 288 (0.35%)	0 / 140 (0.00%)	1 / 428 (0.23%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain in extremity			
subjects affected / exposed	1 / 288 (0.35%)	0 / 140 (0.00%)	1 / 428 (0.23%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Clostridial infection			
subjects affected / exposed	1 / 288 (0.35%)	0 / 140 (0.00%)	1 / 428 (0.23%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridium difficile infection			

subjects affected / exposed	1 / 288 (0.35%)	0 / 140 (0.00%)	1 / 428 (0.23%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cystitis			
subjects affected / exposed	1 / 288 (0.35%)	0 / 140 (0.00%)	1 / 428 (0.23%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infective thrombosis			
subjects affected / exposed	0 / 288 (0.00%)	1 / 140 (0.71%)	1 / 428 (0.23%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritonitis			
subjects affected / exposed	0 / 288 (0.00%)	1 / 140 (0.71%)	1 / 428 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Pneumonia			
subjects affected / exposed	4 / 288 (1.39%)	0 / 140 (0.00%)	4 / 428 (0.93%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection			
subjects affected / exposed	1 / 288 (0.35%)	0 / 140 (0.00%)	1 / 428 (0.23%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 288 (0.00%)	1 / 140 (0.71%)	1 / 428 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral infection			
subjects affected / exposed	1 / 288 (0.35%)	0 / 140 (0.00%)	1 / 428 (0.23%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Decreased appetite			

subjects affected / exposed	1 / 288 (0.35%)	1 / 140 (0.71%)	2 / 428 (0.47%)
occurrences causally related to treatment / all	1 / 1	1 / 1	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dehydration			
subjects affected / exposed	0 / 288 (0.00%)	1 / 140 (0.71%)	1 / 428 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetes mellitus inadequate control			
subjects affected / exposed	1 / 288 (0.35%)	0 / 140 (0.00%)	1 / 428 (0.23%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypercalcaemia			
subjects affected / exposed	1 / 288 (0.35%)	1 / 140 (0.71%)	2 / 428 (0.47%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Hyperglycaemia			
subjects affected / exposed	3 / 288 (1.04%)	0 / 140 (0.00%)	3 / 428 (0.70%)
occurrences causally related to treatment / all	3 / 3	0 / 0	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperuricaemia			
subjects affected / exposed	1 / 288 (0.35%)	0 / 140 (0.00%)	1 / 428 (0.23%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	2 / 288 (0.69%)	0 / 140 (0.00%)	2 / 428 (0.47%)
occurrences causally related to treatment / all	1 / 2	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	BKM120 100 mg@+ fulvestrant	Placebo@+ fulvestrant	All@Patients
Total subjects affected by non-serious adverse events			
subjects affected / exposed	271 / 288 (94.10%)	113 / 140 (80.71%)	384 / 428 (89.72%)
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	113 / 288 (39.24%)	10 / 140 (7.14%)	123 / 428 (28.74%)
occurrences (all)	142	12	154
Aspartate aminotransferase increased			
subjects affected / exposed	108 / 288 (37.50%)	14 / 140 (10.00%)	122 / 428 (28.50%)
occurrences (all)	141	21	162
Gamma-glutamyltransferase increased			
subjects affected / exposed	26 / 288 (9.03%)	5 / 140 (3.57%)	31 / 428 (7.24%)
occurrences (all)	31	7	38
Weight decreased			
subjects affected / exposed	27 / 288 (9.38%)	7 / 140 (5.00%)	34 / 428 (7.94%)
occurrences (all)	30	8	38
Vascular disorders			
Hot flush			
subjects affected / exposed	10 / 288 (3.47%)	11 / 140 (7.86%)	21 / 428 (4.91%)
occurrences (all)	11	14	25
Hypertension			
subjects affected / exposed	33 / 288 (11.46%)	8 / 140 (5.71%)	41 / 428 (9.58%)
occurrences (all)	37	8	45
Nervous system disorders			
Dizziness			
subjects affected / exposed	35 / 288 (12.15%)	10 / 140 (7.14%)	45 / 428 (10.51%)
occurrences (all)	44	11	55
Dysgeusia			
subjects affected / exposed	19 / 288 (6.60%)	4 / 140 (2.86%)	23 / 428 (5.37%)
occurrences (all)	21	4	25
Headache			
subjects affected / exposed	27 / 288 (9.38%)	15 / 140 (10.71%)	42 / 428 (9.81%)
occurrences (all)	33	16	49
Tremor			
subjects affected / exposed	18 / 288 (6.25%)	0 / 140 (0.00%)	18 / 428 (4.21%)
occurrences (all)	19	0	19

General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	52 / 288 (18.06%)	15 / 140 (10.71%)	67 / 428 (15.65%)
occurrences (all)	67	16	83
Fatigue			
subjects affected / exposed	69 / 288 (23.96%)	25 / 140 (17.86%)	94 / 428 (21.96%)
occurrences (all)	78	27	105
Oedema peripheral			
subjects affected / exposed	18 / 288 (6.25%)	2 / 140 (1.43%)	20 / 428 (4.67%)
occurrences (all)	18	2	20
Pyrexia			
subjects affected / exposed	20 / 288 (6.94%)	8 / 140 (5.71%)	28 / 428 (6.54%)
occurrences (all)	21	8	29
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	16 / 288 (5.56%)	6 / 140 (4.29%)	22 / 428 (5.14%)
occurrences (all)	18	6	24
Abdominal pain upper			
subjects affected / exposed	23 / 288 (7.99%)	4 / 140 (2.86%)	27 / 428 (6.31%)
occurrences (all)	27	4	31
Constipation			
subjects affected / exposed	29 / 288 (10.07%)	13 / 140 (9.29%)	42 / 428 (9.81%)
occurrences (all)	30	14	44
Diarrhoea			
subjects affected / exposed	76 / 288 (26.39%)	13 / 140 (9.29%)	89 / 428 (20.79%)
occurrences (all)	111	15	126
Dry mouth			
subjects affected / exposed	23 / 288 (7.99%)	5 / 140 (3.57%)	28 / 428 (6.54%)
occurrences (all)	26	5	31
Dyspepsia			
subjects affected / exposed	29 / 288 (10.07%)	2 / 140 (1.43%)	31 / 428 (7.24%)
occurrences (all)	30	2	32
Nausea			
subjects affected / exposed	100 / 288 (34.72%)	24 / 140 (17.14%)	124 / 428 (28.97%)
occurrences (all)	123	35	158
Stomatitis			

subjects affected / exposed	32 / 288 (11.11%)	6 / 140 (4.29%)	38 / 428 (8.88%)
occurrences (all)	36	6	42
Vomiting			
subjects affected / exposed	27 / 288 (9.38%)	13 / 140 (9.29%)	40 / 428 (9.35%)
occurrences (all)	43	14	57
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	27 / 288 (9.38%)	9 / 140 (6.43%)	36 / 428 (8.41%)
occurrences (all)	30	9	39
Dyspnoea			
subjects affected / exposed	22 / 288 (7.64%)	12 / 140 (8.57%)	34 / 428 (7.94%)
occurrences (all)	28	13	41
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	22 / 288 (7.64%)	3 / 140 (2.14%)	25 / 428 (5.84%)
occurrences (all)	23	3	26
Pruritus			
subjects affected / exposed	25 / 288 (8.68%)	4 / 140 (2.86%)	29 / 428 (6.78%)
occurrences (all)	37	4	41
Rash			
subjects affected / exposed	37 / 288 (12.85%)	3 / 140 (2.14%)	40 / 428 (9.35%)
occurrences (all)	49	3	52
Psychiatric disorders			
Anxiety			
subjects affected / exposed	51 / 288 (17.71%)	15 / 140 (10.71%)	66 / 428 (15.42%)
occurrences (all)	62	15	77
Depression			
subjects affected / exposed	60 / 288 (20.83%)	11 / 140 (7.86%)	71 / 428 (16.59%)
occurrences (all)	72	12	84
Insomnia			
subjects affected / exposed	26 / 288 (9.03%)	11 / 140 (7.86%)	37 / 428 (8.64%)
occurrences (all)	26	11	37
Mood altered			
subjects affected / exposed	15 / 288 (5.21%)	2 / 140 (1.43%)	17 / 428 (3.97%)
occurrences (all)	16	3	19
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	21 / 288 (7.29%)	12 / 140 (8.57%)	33 / 428 (7.71%)
occurrences (all)	25	12	37
Back pain			
subjects affected / exposed	27 / 288 (9.38%)	11 / 140 (7.86%)	38 / 428 (8.88%)
occurrences (all)	32	13	45
Bone pain			
subjects affected / exposed	9 / 288 (3.13%)	11 / 140 (7.86%)	20 / 428 (4.67%)
occurrences (all)	13	13	26
Muscle spasms			
subjects affected / exposed	21 / 288 (7.29%)	5 / 140 (3.57%)	26 / 428 (6.07%)
occurrences (all)	24	6	30
Pain in extremity			
subjects affected / exposed	19 / 288 (6.60%)	10 / 140 (7.14%)	29 / 428 (6.78%)
occurrences (all)	24	12	36
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	15 / 288 (5.21%)	3 / 140 (2.14%)	18 / 428 (4.21%)
occurrences (all)	21	3	24
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	47 / 288 (16.32%)	9 / 140 (6.43%)	56 / 428 (13.08%)
occurrences (all)	53	9	62
Hyperglycaemia			
subjects affected / exposed	104 / 288 (36.11%)	4 / 140 (2.86%)	108 / 428 (25.23%)
occurrences (all)	172	5	177

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 July 2013	Amendment 1 issued after randomization of seven patients, introduced the following key changes: • Discontinuation of enrollment of patients with unknown PI3K pathway activation status • Modification of the definition of PI3K pathway activation status to no longer include PIK3CA mutation in exon 5 and phosphatase and tensin homolog mutation overall • Modification of the guidelines for management of selected AEs, including psychiatric disorders, hyperglycemia grade 2, transaminases, stomatitis and skin rash • Extension of the buparlisib/placebo interruption period to recover from an AE from 21 to 28 days before the patient had to be permanently discontinued from study treatment
19 December 2013	Amendment 2 issued after randomization of 34 patients, introduced the following key changes: • Removal of the co-primary endpoint of PFS in the PI3K pathway activated subpopulation • Removal of stratification of randomization by molecular PI3K status • Modification of guideline for management of skin rash • Addition of clarification of the definition of a light breakfast
07 May 2015	Amendment 3 issued after randomization of 260 patients, introduced the following key changes: • Addition of guidance to Investigators regarding management of liver toxicities • Additional clarification regarding the use of validated translations for patient-reported outcome measures in the study • Additional clarification regarding withdrawal of consent • Implementation of tumor assessments and collection of scans until disease progression irrespective of start of new anti-neoplastic therapy • Exclusion criteria number 27 was added to exclude enrollment of patients with an acute viral hepatitis or with a history of chronic or active Hepatitis B Virus or Hepatitis C Virus infection
20 August 2015	Amendment 4 issued after randomization of 315 patients, introduced the following key changes: • Addition of a secondary objective to assess efficacy of buparlisib plus fulvestrant vs. placebo plus fulvestrant in PIK3CA mutant and non-mutant patients based on ctDNA • Simplification of the dose reduction schedule for buparlisib/placebo. Prior to introduction of Amendment 4, the first dose reduction (i.e., dose level −1) was to a dose of 80 mg/day continuously. Subsequent to introduction of Amendment 4, dose level −1 was 100 mg/day 5 days out of 7
07 June 2016	Amendment 5 issued after randomization of 432 patients, introduced the following key changes: • Addition of clarification on the measures to follow when a patient exhibits suicidal ideation regardless of the response to question 9 of the PHQ-9 questionnaire • Addition of clarification that buparlisib/placebo can be administered with or without food

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 LPLV date was 21-Sep-2017, however efficacy analysis were only conducted on data through 08-Sep-2017.

Notes: