Clinical trial results:
NeoPHOEBE: Pi3k inhibition in Her2 OverExpressing Breast cancEr: A phase II, randomized, parallel cohort, two stage, double-blind, placebo-controlled study of neoadjuvant trastuzumab versus trastuzumab + BKM120 in combination with weekly paclitaxel in HER2-positive, PIK3CA wild-type and PIK3CA mutant primary breast cancer

Summary

EudraCT number	2012-000738-21
Trial protocol	AT ES
Global end of trial date	18 February 2016

Results information

Result version number	v1
This version publication date	29 July 2016
First version publication date	29 July 2016

Trial information

Trial identification

Sponsor protocol code	CBKM120F2203

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01816594
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,
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111,

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	18 February 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	18 February 2016
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was to evaluate efficacy, in terms of pathological complete response (pCR) rate, at the time of surgery in patients with HER2 overexpressing or amplified (HER2+) operable breast cancer randomized to trastuzumab plus BKM120 placebo (followed by trastuzumab plus BKM120 placebo and paclitaxel) OR trastuzumab plus BKM120 (followed by trastuzumab plus BKM120 and paclitaxel) separately for PIK3CA mutant and wild-type cohorts.

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 September 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: 1
Country: Number of subjects enrolled	Germany: 37
Country: Number of subjects enrolled	Singapore: 3
Country: Number of subjects enrolled	Spain: 9
Worldwide total number of subjects	50
EEA total number of subjects	46

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)	43
From 65 to 84 years	7
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Study enrolled patients with newly-diagnosed HER2-+ breast cancers, larger than 2 cm by clinical examination &/or larger than 1.5 cm by ultrasound or MRI. Randomization established accurately the efficacy of the combination of agents compared to standard of care "control" arm was stratified by ER status.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer

Arms

Are arms mutually exclusive?	Yes
Arm title	BKM120 + Trastuzumab + paclitaxel

Arm description:

BKM120 (oral, pan-class I PI3K inhibitor) in combination with trastuzumab and paclitaxel.

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

Dosage and administration details:

Oral 100 mg qd BKM120 was supplied in 10 mg and 50 mg hard gelatin capsules, administered on a once daily continuous dosing schedule and was dosed on a flat scale of mg/day and not adjusted to weight or body surface area.

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

Dosage and administration details:

4 mg/kg i.v. load over 90 minutes followed by weekly doses of 2 mg/kg i.v. for 30 minutes for 6 weeks and then for an additioal 12 weeks

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

Dosage and administration details:

administered weekly paclitaxel (80 mg/m2 i.v.) for 12 weeks

Arm title	BKM120 PBO + Trastuzumab +paclitaxel

Arm description:

BKM120 placebo in combination with trastuzumab and paclitaxel

Arm type	Placebo

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

Dosage and administration details:

Oral 100 mg qd BKM120 placebo was supplied in 10 mg and 50 mg hard gelatin capsules, administered on a once daily continuous dosing schedule and was dosed on a flat scale of mg/day and not adjusted to weight or body surface area.

Number of subjects in period 1	BKM120 + Trastuzumab + paclitaxel	BKM120 PBO + Trastuzumab +paclitaxel
Started	25	25
Randomized to the wt cohort	21	21 [1]
Randomized to the mt cohort	4 [2]	4 [3]
Completed	14	23
Not completed	11	2
Consent withdrawn by subject	1	-
Physician decision	1	-
Adverse event, non-fatal	9	-
Local Progress	-	2

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Per our results disclosure process, the study was not powered enough (50 patients) to support the hypothesis. Therefore statistical analysis are not provided.

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Per our results disclosure process, the study was not powered enough (50 patients) to support the hypothesis. Therefore statistical analysis are not provided.

[3] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Per our results disclosure process, the study was not powered enough (50 patients) to support the hypothesis. Therefore statistical analysis are not provided.

Baseline characteristics

Reporting groups	
Reporting group title	BKM120 + Trastuzumab + paclitaxel
Reporting group description:	
BKM120 (oral, pan-class I PI3K inhibitor) in combination with trastuzumab and paclitaxel.	
Reporting group title	BKM120 PBO + Trastuzumab +paclitaxel
Reporting group description:	
BKM120 placebo in combination with trastuzumab and paclitaxel	

Reporting group values	BKM120 + Trastuzumab + paclitaxel	BKM120 PBO + Trastuzumab +paclitaxel	Total
Number of subjects	25	25	50
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)	21	22	43
From 65-84 years	4	3	7
85 years and over	0	0	0
Age Continuous Units: Years			
arithmetic mean	51.1	51.3	
standard deviation	± 11.5	± 11.2	-
Gender, Male/Female Units: Participants			
Female	25	25	50
Male	0	0	0

End points

End points reporting groups

Reporting group title	BKM120 + Trastuzumab + paclitaxel
Reporting group description:	
BKM120 (oral, pan-class I PI3K inhibitor) in combination with trastuzumab and paclitaxel.	
Reporting group title	BKM120 PBO + Trastuzumab +paclitaxel
Reporting group description:	
BKM120 placebo in combination with trastuzumab and paclitaxel	

Primary: Number of patients with pathological complete response (pCR) at the time of surgery for all patients

End point title	Number of patients with pathological complete response (pCR) at the time of surgery for all patients[1]
End point description:	
Rate of pCR, as defined by NSABP criteria, is the absence of invasive disease in the breast [ypT0]) at the time of surgery.No statistical analysis was planned for this endpoint.	
End point type	Primary
End point timeframe:	
week 18	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Per our results disclosure process, the study was not powered enough (50 patients) to support the hypothesis. Therefore statistical analysis are not provided.

End point values	BKM120 + Trastuzumab + paclitaxel	BKM120 PBO + Trastuzumab +paclitaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[2]	0[3]		
Units: Participants				

Notes:

[2] - Termination: challenges enrolling PIK3CA mt cohort. Enrolled 50 of planned 220. No data for analysis
[3] - Termination: challenges enrolling PIK3CA mt cohort. Enrolled 50 of planned 220. No data for analysis

Statistical analyses

No statistical analyses for this end point

Secondary: Objective response rate (ORR) at the end of the biologic window and prior to surgery

End point title	Objective response rate (ORR) at the end of the biologic window and prior to surgery
End point description:	

Objective response rate = number of participants with clinical complete response (cCR) or clinical partial response (cPR) assessed using world health organization (WHO) criteria. OR was defined as decrease in area by 50% or more of the primary tumor; the response of the axillary nodes was not to be considered. cCR = Complete disappearance of all tumor signs in the breast as assessed by ultrasound or MRI. The response of the axillary nodes was not to be considered. cPR = Reduction in the product of the two largest perpendicular diameters of the primary tumor size by 50% or more assessed by ultrasound or MRI. In patients with multifocal or multicentric disease, the lesion with the largest diameters should

be chosen for follow-up. The response of the axillary nodes was not to be considered.

End point type	Secondary

End point timeframe:

baseline, week 6

End point values	BKM120 + Trastuzumab + paclitaxel	BKM120 PBO + Trastuzumab +paclitaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[4]	0[5]		
Units: Participants				

Notes:

[4] - Termination: challenges enrolling PIK3CA mt cohort. Enrolled 50 of planned 220. No data for analysis

[5] - Termination: challenges enrolling PIK3CA mt cohort. Enrolled 50 of planned 220. No data for analysis

Statistical analyses

No statistical analyses for this end point

Secondary: pCR ypT0 ypN0 (GBG definition) and pCR ypT0/is ypN0 (MD Anderson definition)

End point title	pCR ypT0 ypN0 (GBG definition) and pCR ypT0/is ypN0 (MD Anderson definition)

End point description:

pCR defined as no invasive and non-invasive (DCIS) residuals in breast and lymph nodes (ypT0, ypN0 [GBG definition]); pCR defined as no invasive residuals in breast and lymph nodes (ypT0/Tis, ypN0 [MD Anderson definition]); Percent of patients with remaining DCIS in breast at definitive surgery irrespective of lymph node status

End point type	Secondary

End point timeframe:

baseline, week 18

End point values	BKM120 + Trastuzumab + paclitaxel	BKM120 PBO + Trastuzumab +paclitaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[6]	0[7]		
Units: Participants				

Notes:

[6] - Termination: challenges enrolling PIK3CA mt cohort. Enrolled 50 of planned 220. No data for analysis

[7] - Termination: challenges enrolling PIK3CA mt cohort. Enrolled 50 of planned 220. No data for analysis

Statistical analyses

No statistical analyses for this end point

Secondary: Number of patients with node-negative disease at definitive surgery

(ypN0)

End point title	Number of patients with node-negative disease at definitive surgery (ypN0)

End point description:

Node-negative disease at definitive surgery (ypN0) were considered as binary variables of 'response' versus 'non response'.

End point type	Secondary

End point timeframe:

18 weeks

End point values	BKM120 + Trastuzumab + paclitaxel	BKM120 PBO + Trastuzumab +paclitaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[8]	0[9]		
Units: Participants				

Notes:

[8] - Termination: challenges enrolling PIK3CA mt cohort. Enrolled 50 of planned 220. No data for analysis
[9] - Termination: challenges enrolling PIK3CA mt cohort. Enrolled 50 of planned 220. No data for analysis

Statistical analyses

No statistical analyses for this end point

Secondary: Breast conservation rate (most radical surgery)

End point title	Breast conservation rate (most radical surgery)

End point description:

End point type	Secondary

End point timeframe:

18 weeks

End point values	BKM120 + Trastuzumab + paclitaxel	BKM120 PBO + Trastuzumab +paclitaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[10]	0[11]		
Units: Percentage of participants				
number (not applicable)				

Notes:

[10] - Termination: challenges enrolling PIK3CA mt cohort. Enrolled 50 of planned 220. No data for analysis
[11] - Termination: challenges enrolling PIK3CA mt cohort. Enrolled 50 of planned 220. No data for analysis

Statistical analyses

No statistical analyses for this end point

Secondary: Remaining Ductal carcinoma in situ (DCIS) (yp Tis)

End point title	Remaining Ductal carcinoma in situ (DCIS) (yp Tis)

End point description:

Percentage of participants with remaining DCIS in breast at definitive surgery irrespective of lymph node status

End point type	Secondary

End point timeframe:

18 weeks

End point values	BKM120 + Trastuzumab + paclitaxel	BKM120 PBO + Trastuzumab +paclitaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[12]	0[13]		
Units: percentage of particpants				
number (not applicable)				

Notes:

[12] - Termination: challenges enrolling PIK3CA mt cohort. Enrolled 50 of planned 220. No data for analysis

[13] - Termination: challenges enrolling PIK3CA mt cohort. Enrolled 50 of planned 220. No data for analysis

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.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	BKM120

Reporting group description:

BKM120

Reporting group title	Placebo

Reporting group description:

Placebo

Serious adverse events	BKM120	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 25 (32.00%)	2 / 25 (8.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Investigations			
Hepatic enzyme increased			
subjects affected / exposed	2 / 25 (8.00%)	0 / 25 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 25 (0.00%)	1 / 25 (4.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Catheter site pain			
subjects affected / exposed	1 / 25 (4.00%)	0 / 25 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pyrexia			
subjects affected / exposed	1 / 25 (4.00%)	0 / 25 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombosis in device			
subjects affected / exposed	0 / 25 (0.00%)	1 / 25 (4.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 25 (4.00%)	0 / 25 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 25 (4.00%)	0 / 25 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatotoxicity			
subjects affected / exposed	1 / 25 (4.00%)	0 / 25 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pulmonary oedema			
subjects affected / exposed	1 / 25 (4.00%)	0 / 25 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Mental disorder			
subjects affected / exposed	1 / 25 (4.00%)	0 / 25 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Acute sinusitis			

subjects affected / exposed	0 / 25 (0.00%)	1 / 25 (4.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 25 (4.00%)	0 / 25 (0.00%)	
occurrences causally related to treatment / all	0 / 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	BKM120	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	21 / 25 (84.00%)	19 / 25 (76.00%)	
Vascular disorders			
Hot flushes			
subjects affected / exposed	5 / 25 (20.00%)	7 / 25 (28.00%)	
occurrences (all)	5	7	
Vascular disorders			
subjects affected / exposed	1 / 25 (4.00%)	3 / 25 (12.00%)	
occurrences (all)	1	3	
General disorders and administration site conditions			
Chills			
subjects affected / exposed	1 / 25 (4.00%)	4 / 25 (16.00%)	
occurrences (all)	1	4	
Fatigue			
subjects affected / exposed	13 / 25 (52.00%)	14 / 25 (56.00%)	
occurrences (all)	13	14	
Oedema			
subjects affected / exposed	3 / 25 (12.00%)	8 / 25 (32.00%)	
occurrences (all)	3	8	
Other general disorders and administration site conditions			
subjects affected / exposed	2 / 25 (8.00%)	1 / 25 (4.00%)	
occurrences (all)	2	1	
Immune system disorders			

Allergic reactions			
subjects affected / exposed	3 / 25 (12.00%)	1 / 25 (4.00%)	
occurrences (all)	3	1	
Reproductive system and breast disorders			
Reproductive system and breast disorders			
subjects affected / exposed	1 / 25 (4.00%)	3 / 25 (12.00%)	
occurrences (all)	1	3	
Respiratory, thoracic and mediastinal disorders			
Dyspnea			
subjects affected / exposed	2 / 25 (8.00%)	6 / 25 (24.00%)	
occurrences (all)	2	6	
Epistaxis			
subjects affected / exposed	0 / 25 (0.00%)	5 / 25 (20.00%)	
occurrences (all)	0	5	
Other respiratory and mediastinal disorders			
subjects affected / exposed	5 / 25 (20.00%)	6 / 25 (24.00%)	
occurrences (all)	5	6	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	5 / 25 (20.00%)	3 / 25 (12.00%)	
occurrences (all)	5	3	
Depression			
subjects affected / exposed	6 / 25 (24.00%)	8 / 25 (32.00%)	
occurrences (all)	6	8	
Insomnia			
subjects affected / exposed	3 / 25 (12.00%)	4 / 25 (16.00%)	
occurrences (all)	3	4	
Psychiatric disorders			
subjects affected / exposed	2 / 25 (8.00%)	0 / 25 (0.00%)	
occurrences (all)	2	0	
Investigations			
Decreased calcium			
subjects affected / exposed	9 / 25 (36.00%)	11 / 25 (44.00%)	
occurrences (all)	9	11	
Decreased potassium			

subjects affected / exposed	6 / 25 (24.00%)	2 / 25 (8.00%)		
occurrences (all)	6	2		
Decreased serum albumin				
subjects affected / exposed	5 / 25 (20.00%)	2 / 25 (8.00%)		
occurrences (all)	5	2		
Decreased sodium				
subjects affected / exposed	9 / 25 (36.00%)	7 / 25 (28.00%)		
occurrences (all)	9	7		
Increased ALT				
subjects affected / exposed	21 / 25 (84.00%)	18 / 25 (72.00%)		
occurrences (all)	21	18		
Increased AP				
subjects affected / exposed	6 / 25 (24.00%)	6 / 25 (24.00%)		
occurrences (all)	6	6		
Increased AST				
subjects affected / exposed	19 / 25 (76.00%)	9 / 25 (36.00%)		
occurrences (all)	19	9		
Increased FPG				
subjects affected / exposed	13 / 25 (52.00%)	8 / 25 (32.00%)		
occurrences (all)	13	8		
Increased GGT				
subjects affected / exposed	8 / 25 (32.00%)	7 / 25 (28.00%)		
occurrences (all)	8	7		
Increased aPTT				
subjects affected / exposed	5 / 25 (20.00%)	6 / 25 (24.00%)		
occurrences (all)	5	6		
Increased potassium				
subjects affected / exposed	3 / 25 (12.00%)	11 / 25 (44.00%)		
occurrences (all)	3	11		
Increased serum creatinine				
subjects affected / exposed	1 / 25 (4.00%)	2 / 25 (8.00%)		
occurrences (all)	1	2		
Increased sodium				
subjects affected / exposed	4 / 25 (16.00%)	2 / 25 (8.00%)		
occurrences (all)	4	2		
Increased total bilirubin				

subjects affected / exposed	2 / 25 (8.00%)	0 / 25 (0.00%)	
occurrences (all)	2	0	
Increased total cholesterol			
subjects affected / exposed	14 / 25 (56.00%)	14 / 25 (56.00%)	
occurrences (all)	14	14	
Increased triglycerides			
subjects affected / exposed	5 / 25 (20.00%)	6 / 25 (24.00%)	
occurrences (all)	5	6	
Increased uric acid			
subjects affected / exposed	6 / 25 (24.00%)	10 / 25 (40.00%)	
occurrences (all)	6	10	
Injury, poisoning and procedural complications			
Injury and poisoning and procedural complications			
subjects affected / exposed	1 / 25 (4.00%)	2 / 25 (8.00%)	
occurrences (all)	1	2	
Cardiac disorders			
Cardiac disorders not yet listed			
subjects affected / exposed	1 / 25 (4.00%)	3 / 25 (12.00%)	
occurrences (all)	1	3	
Nervous system disorders			
Dizziness			
subjects affected / exposed	9 / 25 (36.00%)	4 / 25 (16.00%)	
occurrences (all)	9	4	
Headache			
subjects affected / exposed	2 / 25 (8.00%)	8 / 25 (32.00%)	
occurrences (all)	2	8	
Other neurological disorder			
subjects affected / exposed	3 / 25 (12.00%)	2 / 25 (8.00%)	
occurrences (all)	3	2	
Peripheral sensory neuropathy			
subjects affected / exposed	14 / 25 (56.00%)	16 / 25 (64.00%)	
occurrences (all)	14	16	
Blood and lymphatic system disorders			
Anemia			
subjects affected / exposed	17 / 25 (68.00%)	18 / 25 (72.00%)	
occurrences (all)	17	18	

Leukopenia			
subjects affected / exposed	11 / 25 (44.00%)	15 / 25 (60.00%)	
occurrences (all)	11	15	
Lymphopenia			
subjects affected / exposed	11 / 25 (44.00%)	8 / 25 (32.00%)	
occurrences (all)	11	8	
Neutropenia			
subjects affected / exposed	6 / 25 (24.00%)	9 / 25 (36.00%)	
occurrences (all)	6	9	
Thrombopenia			
subjects affected / exposed	4 / 25 (16.00%)	0 / 25 (0.00%)	
occurrences (all)	4	0	
Ear and labyrinth disorders			
Ear and labyrinth disorders			
subjects affected / exposed	1 / 25 (4.00%)	2 / 25 (8.00%)	
occurrences (all)	1	2	
Eye disorders			
Eye disorders			
subjects affected / exposed	5 / 25 (20.00%)	3 / 25 (12.00%)	
occurrences (all)	5	3	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 25 (8.00%)	4 / 25 (16.00%)	
occurrences (all)	2	4	
Constipation			
subjects affected / exposed	4 / 25 (16.00%)	7 / 25 (28.00%)	
occurrences (all)	4	7	
Diarrhea			
subjects affected / exposed	15 / 25 (60.00%)	10 / 25 (40.00%)	
occurrences (all)	15	10	
Dysgeusia			
subjects affected / exposed	4 / 25 (16.00%)	5 / 25 (20.00%)	
occurrences (all)	4	5	
Dyspepsia			
subjects affected / exposed	4 / 25 (16.00%)	4 / 25 (16.00%)	
occurrences (all)	4	4	
Mucositis			

subjects affected / exposed	19 / 25 (76.00%)	12 / 25 (48.00%)	
occurrences (all)	19	12	
Nausea			
subjects affected / exposed	11 / 25 (44.00%)	8 / 25 (32.00%)	
occurrences (all)	11	8	
Other gastrointestinal disorders			
subjects affected / exposed	7 / 25 (28.00%)	7 / 25 (28.00%)	
occurrences (all)	7	7	
Upper abdominal pain			
subjects affected / exposed	5 / 25 (20.00%)	1 / 25 (4.00%)	
occurrences (all)	5	1	
Vomiting			
subjects affected / exposed	3 / 25 (12.00%)	2 / 25 (8.00%)	
occurrences (all)	3	2	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	18 / 25 (72.00%)	17 / 25 (68.00%)	
occurrences (all)	18	17	
Dry skin			
subjects affected / exposed	5 / 25 (20.00%)	4 / 25 (16.00%)	
occurrences (all)	5	4	
Erythema			
subjects affected / exposed	3 / 25 (12.00%)	5 / 25 (20.00%)	
occurrences (all)	3	5	
Nail disorder			
subjects affected / exposed	5 / 25 (20.00%)	5 / 25 (20.00%)	
occurrences (all)	5	5	
Other skin and subcutaneous tissue disorders			
subjects affected / exposed	5 / 25 (20.00%)	7 / 25 (28.00%)	
occurrences (all)	5	7	
Pruritus			
subjects affected / exposed	10 / 25 (40.00%)	5 / 25 (20.00%)	
occurrences (all)	10	5	
Rash maculo-papular			

subjects affected / exposed	15 / 25 (60.00%)	12 / 25 (48.00%)	
occurrences (all)	15	12	
Rash other than macular-papular or NOS			
subjects affected / exposed	8 / 25 (32.00%)	8 / 25 (32.00%)	
occurrences (all)	8	8	
Renal and urinary disorders			
Renal and urinary disorders			
subjects affected / exposed	2 / 25 (8.00%)	0 / 25 (0.00%)	
occurrences (all)	2	0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	7 / 25 (28.00%)	10 / 25 (40.00%)	
occurrences (all)	7	10	
Bone pain			
subjects affected / exposed	3 / 25 (12.00%)	5 / 25 (20.00%)	
occurrences (all)	3	5	
Myalgia			
subjects affected / exposed	3 / 25 (12.00%)	5 / 25 (20.00%)	
occurrences (all)	3	5	
Other musculo-skeletal and connective tissue disorders			
subjects affected / exposed	2 / 25 (8.00%)	1 / 25 (4.00%)	
occurrences (all)	2	1	
Infections and infestations			
Fever without neutropenia			
subjects affected / exposed	7 / 25 (28.00%)	3 / 25 (12.00%)	
occurrences (all)	7	3	
Infection			
subjects affected / exposed	12 / 25 (48.00%)	19 / 25 (76.00%)	
occurrences (all)	12	19	
Metabolism and nutrition disorders			
Anorexia			
subjects affected / exposed	5 / 25 (20.00%)	1 / 25 (4.00%)	
occurrences (all)	5	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 February 2014	The main purpose of the protocol amendment was to update and align the management of selected adverse events across the BKM120 program, specifically psychiatric disorders, hyperglycemia, stomatitis, skin rash and Posterior Reversible Encephalopathy Syndrome (PRES). In addition, changes for clarification purposes had been implemented to the inclusion/ exclusion criteria, definition of post-menopausal status and pregnancy testing requirements, visit evaluation schedule, and tumor tissue samples collected at baseline. Furthermore, the sections on clinical and pharmacokinetic experience with BKM120, and in combination with paclitaxel and trastuzumab as well as concomitant medication use had been updated to align with the latest Investigators Brochure (IB) Update (Version 6) and recently published data. Finally, the timepoints of the interim safety analyses reviews by the IDMC had been updated and a section describing the TRC had been added.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
01 October 2014	Study enrollment was suspended due to safety concerns (high rate of increased liver enzymes and high number of treatment discontinuations). Until then 50 patients were recruited. Patients who were under therapy were allowed to continue.	29 October 2014

Notes:

Limitations and caveats

None reported