



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 2015

Results information

Result version number	v2 (current)
This version publication date	21 September 2019
First version publication date	29 July 2016
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	CBKM120F2203
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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, 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	18 February 2015
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	18 February 2015
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:

Planned: Minimum 128 patients (in case of early stopping of both cohorts), maximum: 220 patients (if both cohorts would have proceeded into stage 2), and 174 patients if one cohort would have stopped early.

Pre-assignment

Screening details:

Screened: 68 patients Randomized and analyzed (safety and efficacy): 50 patients

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	Trastuzumab + BKM120 + paclitaxel

Arm description:

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

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:

BKM120 was to be 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	paclitaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

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

Investigational medicinal product name	trastuzumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

trastuzumab was dosed at 4 mg/kg i.v. load followed by 2 mg/kg i.v. weekly for 6 weeks.

Arm title	Trastuzumab + BKM120 PBO + paclitaxel
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Arm description:

BKM120 placebo in combination with trastuzumab and paclitaxel

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

Dosage and administration details:

BKM120 placebo was to be 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	Injection
Routes of administration	Intravenous use

Dosage and administration details:

trastuzumab was dosed at 4 mg/kg i.v. load followed by 2 mg/kg i.v. weekly for 6 weeks.

Investigational medicinal product name	paclitaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

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

Number of subjects in period 1	Trastuzumab + BKM120 + paclitaxel	Trastuzumab + BKM120 PBO + paclitaxel
Started	25	25
Completed	14	23
Not completed	11	2
Consent withdrawn by subject	1	-
Physician decision	1	-
Adverse event, non-fatal	9	-
Local Progress	-	2

Baseline characteristics

Reporting groups

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

Reporting group values	Trastuzumab + BKM120 + paclitaxel	Trastuzumab + BKM120 PBO + paclitaxel	Total
Number of subjects	25	25	50
Age categorical Units: Subjects			
Adults (18-64 years)	21	22	43
From 65-84 years	4	3	7
Age Continuous Units: Years			
arithmetic mean	51.1	51.3	
standard deviation	± 11.5	± 11.2	-
Gender, Male/Female Units: Subjects			
Female	25	25	50
Male	0	0	0
Race/Ethnicity, Customized Units: Subjects			
Caucasian/white	21	24	45
Asian/Oriental	3	1	4
Other	1	0	1

End points

End points reporting groups

Reporting group title	Trastuzumab + BKM120 + paclitaxel
Reporting group description: BKM120 (oral, pan-class I PI3K inhibitor) in combination with trastuzumab and paclitaxel.	
Reporting group title	Trastuzumab + BKM120 PBO + paclitaxel
Reporting group description: BKM120 placebo in combination with trastuzumab and paclitaxel	
Subject analysis set title	Trastuzumab + BKM120 + paclitaxel (PIK3CA wild type)
Subject analysis set type	Sub-group analysis
Subject analysis set description: Subjects in the BKM120 in combination with trastuzumab and paclitaxel group with PIK3CA wild type.	
Subject analysis set title	Trastuzumab + BKM120 Placebo + paclitaxel (PIK3CA wild type)
Subject analysis set type	Sub-group analysis
Subject analysis set description: Subjects in the BKM120 Placebo in combination with trastuzumab and paclitaxel group with PIK3CA wild type.	
Subject analysis set title	Trastuzumab + BKM120 + paclitaxel (PIK3CA mutant)
Subject analysis set type	Sub-group analysis
Subject analysis set description: Subjects in the BKM120 in combination with trastuzumab and paclitaxel group with PIK3CA mutant.	
Subject analysis set title	Trastuzumab + BKM120 Placebo + paclitaxel (PIK3CA mutant)
Subject analysis set type	Sub-group analysis
Subject analysis set description: Subjects in the BKM120 Placebo in combination with trastuzumab and paclitaxel group with PIK3CA mutant.	
Subject analysis set title	ER+ subjects (Trastuzumab + BKM120 + paclitaxel)
Subject analysis set type	Sub-group analysis
Subject analysis set description: Subjects with a positive (+) Estrogen Receptor in the BKM120 group	
Subject analysis set title	ER + subjects (Trastuzumab + BKM120 PBO + paclitaxel)
Subject analysis set type	Sub-group analysis
Subject analysis set description: Subjects with a positive (+) Estrogen Receptor in the placebo group	
Subject analysis set title	ER- subjects (Trastuzumab + BKM120 + paclitaxel)
Subject analysis set type	Sub-group analysis
Subject analysis set description: Subjects with a negative (-) Estrogen Receptor in the BKM120 group	
Subject analysis set title	ER- subjects (Trastuzumab + BKM120 PBO + paclitaxel)
Subject analysis set type	Sub-group analysis
Subject analysis set description: Subjects with a negative (-) Estrogen Receptor in the BKM120 PBO group.	

Primary: Pathological complete response (pCR) rate at the time of surgery - All subjects

End point title	Pathological complete response (pCR) rate at the time of surgery - All subjects
End point description: Rate of pCR (as defined by NSABP criteria - absence of invasive disease in the breast [ypT0]) is the number of subjects with pathological complete response (pCR) at the time of surgery. Subjects were to	

be considered in pCR if there was no invasive cancer in the breast or only non-invasive in situ cancer in the breast specimen. NSABP guidelines do not take into account the histological nodal status to define the pCR.

End point type	Primary
End point timeframe:	
week 18	

End point values	Trastuzumab + BKM120 + paclitaxel	Trastuzumab + BKM120 PBO + paclitaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	25		
Units: Percentage of subjects				
number (confidence interval 95%)				
pCR yp T0/is - Yes (All subjects)	32.0 (14.9 to 53.5)	40.0 (21.1 to 61.3)		

Statistical analyses

Statistical analysis title	All subjects - pCR
Statistical analysis description:	
All subjects	
Comparison groups	Trastuzumab + BKM120 + paclitaxel v Trastuzumab + BKM120 PBO + paclitaxel
Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.811
Method	Fisher Exact (one-sided)

Primary: Pathological complete response (pCR) rate at the time of surgery - PIK3CA wild type (WT)

End point title	Pathological complete response (pCR) rate at the time of surgery - PIK3CA wild type (WT)
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End point description:

Rate of pCR (as defined by NSABP criteria - absence of invasive disease in the breast [ypT0]) is the number of subjects with pathological complete response (pCR) at the time of surgery. Participants in this group were to be considered in pCR if there was no invasive cancer in the breast or only non-invasive in situ cancer in the breast specimen. NSABP guidelines do not take into account the histological nodal status to define the pCR.

End point type	Primary
End point timeframe:	
week 18	

End point values	Trastuzumab + BKM120 + paclitaxel (PIK3CA wild type)	Trastuzumab + BKM120 Placebo + paclitaxel (PIK3CA wild type)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	21	21		
Units: Percentage of subjects				
number (confidence interval 95%)				
pCR yp T0/is - Yes (PIK3CA wild type (wt))	33.3 (14.6 to 57.0)	42.9 (21.8 to 66.0)		

Statistical analyses

Statistical analysis title	WT cohort- pCR
Statistical analysis description: wild type cohort	
Comparison groups	Trastuzumab + BKM120 + paclitaxel (PIK3CA wild type) v Trastuzumab + BKM120 Placebo + paclitaxel (PIK3CA wild type)
Number of subjects included in analysis	42
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.83
Method	Fisher Exact (one-sided)

Primary: Pathological complete response (pCR) rate at the time of surgery - PIK3CA mutant (MT)

End point title	Pathological complete response (pCR) rate at the time of surgery - PIK3CA mutant (MT)
End point description: Rate of pCR (as defined by NSABP criteria - absence of invasive disease in the breast [ypT0]) is the number of subjects with pathological complete response (pCR) at the time of surgery. Subjects in this group were to be considered in pCR if there was no invasive cancer in the breast or only non-invasive in situ cancer in the breast specimen. NSABP guidelines do not take into account the histological nodal status to define the pCR.	
End point type	Primary
End point timeframe: Week 18	

End point values	Trastuzumab + BKM120 + paclitaxel (PIK3CA mutant)	Trastuzumab + BKM120 Placebo + paclitaxel (PIK3CA mutant)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	4	4		

Units: Percentage of subjects				
number (confidence interval 95%)				
pCR yp T0/is - Yes (PIK3CA mutant (mt)) (n= 4, 4)	25.0 (0.6 to 80.6)	25.0 (0.6 to 80.6)		

Statistical analyses

Statistical analysis title	MT cohort- pCR
Statistical analysis description: mutant cohort	
Comparison groups	Trastuzumab + BKM120 + paclitaxel (PIK3CA mutant) v Trastuzumab + BKM120 Placebo + paclitaxel (PIK3CA mutant)
Number of subjects included in analysis	8
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.786
Method	Fisher Exact (one-sided)

Secondary: Overall objective clinical response rate at the end of the biologic window (after week 6) compared to baseline (Key Secondary) - All subjects

End point title	Overall objective clinical response rate at the end of the biologic window (after week 6) compared to baseline (Key Secondary) - All subjects
End point description: Percentage of Overall objective clinical response rate = Complete Response + Partial Response rate, measured by US bidimensional ultrasound (or MRI) and assessed by world health organization (WHO) criteria.	
End point type	Secondary
End point timeframe: end of biologic window (after week 6)	

End point values	Trastuzumab + BKM120 + paclitaxel	Trastuzumab + BKM120 PBO + paclitaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	25		
Units: Percentage of subjects with response				
number (confidence interval 95%)				
ORR (All subjects)	56.0 (34.9 to 75.6)	44.0 (24.4 to 65.1)		

Statistical analyses

Statistical analysis title	All subjects - ORR
Statistical analysis description: All subjects	
Comparison groups	Trastuzumab + BKM120 + paclitaxel v Trastuzumab + BKM120 PBO + paclitaxel
Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.286
Method	Fisher Exact (one-sided)

Secondary: Overall objective clinical response rate at the end of the biologic window (after week 6) compared to baseline (Key Secondary) - PIK3A wild type subjects

End point title	Overall objective clinical response rate at the end of the biologic window (after week 6) compared to baseline (Key Secondary) - PIK3A wild type subjects
End point description: Percentage of Overall objective clinical response rate = Complete Response + Partial Response rate, measured by US bidimensional ultrasound (or MRI) and assessed by world health organization (WHO) criteria for the PIK31 wild type subjects.	
End point type	Secondary
End point timeframe: end of biologic window (after week 6)	

End point values	Trastuzumab + BKM120 + paclitaxel (PIK3CA wild type)	Trastuzumab + BKM120 Placebo + paclitaxel (PIK3CA wild type)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	21	21		
Units: Percentage of subjects with response				
number (confidence interval 95%)				
ORR - WT subjects (n = 21, 21)	61.9 (38.4 to 81.9)	42.9 (21.8 to 66.0)		

Statistical analyses

Statistical analysis title	WT cohort - ORR
Statistical analysis description: wild type cohort	
Comparison groups	Trastuzumab + BKM120 + paclitaxel (PIK3CA wild type) v Trastuzumab + BKM120 Placebo + paclitaxel (PIK3CA wild type)

Number of subjects included in analysis	42
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.177
Method	Fisher Exact (one sided)

Secondary: Overall objective clinical response rate at the end of the biologic window (after week 6) compared to baseline (Key Secondary) - PIK3A mutant subjects

End point title	Overall objective clinical response rate at the end of the biologic window (after week 6) compared to baseline (Key Secondary) - PIK3A mutant subjects
End point description: Percentage of Overall objective clinical response rate = Complete Response + Partial Response rate, measured by US bidimensional ultrasound (or MRI) and assessed by world health organization (WHO) criteria for the mutant subjects.	
End point type	Secondary
End point timeframe: end of biologic window (after week 6)	

End point values	Trastuzumab + BKM120 + paclitaxel (PIK3CA mutant)	Trastuzumab + BKM120 Placebo + paclitaxel (PIK3CA mutant)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	4	4		
Units: Percentage of subjects with response				
number (confidence interval 95%)				
ORR - mt subjects (n = 4, 4)	25.0 (0.6 to 80.6)	50.0 (6.8 to 93.2)		

Statistical analyses

Statistical analysis title	MT cohort - ORR
Statistical analysis description: mutant cohort	
Comparison groups	Trastuzumab + BKM120 + paclitaxel (PIK3CA mutant) v Trastuzumab + BKM120 Placebo + paclitaxel (PIK3CA mutant)
Number of subjects included in analysis	8
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.929
Method	Fisher Exact (one sided)

Secondary: Rate of breast conserving surgery (most radical surgery)

End point title	Rate of breast conserving surgery (most radical surgery)
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End point description:

Rate of subjects with breast conserving surgery. No breast surgery was considered as breast conservation surgery (BCS)

End point type	Secondary
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End point timeframe:

18 weeks

End point values	Trastuzumab + BKM120 + paclitaxel	Trastuzumab + BKM120 PBO + paclitaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	25		
Units: Percentage of subjects				
number (confidence interval 95%)	60.0 (38.7 to 78.9)	68.0 (46.5 to 85.1)		

Statistical analyses

Statistical analysis title	Rate of BCS
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Statistical analysis description:

All subjects

Comparison groups	Trastuzumab + BKM120 + paclitaxel v Trastuzumab + BKM120 PBO + paclitaxel
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Number of subjects included in analysis	50
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Analysis specification	Pre-specified
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Analysis type	superiority
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P-value	= 0.811
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Method	Fisher Exact (one-sided)
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Secondary: pCR ypT0 ypN0 per GBG definition

End point title	pCR ypT0 ypN0 per GBG definition
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End point description:

pCR defined as no invasive and non-invasive (DCIS) residuals in breast and lymph nodes (ypT0, ypN0 [GBG definition]). If patient had a sentinel node biopsy before treatment which was negative and no axilla dissection was performed after treatment completion, such patient was considered to be pN0 for both secondary pCR definitions.

End point type	Secondary
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End point timeframe:

week 18

End point values	Trastuzumab + BKM120 + paclitaxel	Trastuzumab + BKM120 PBO + paclitaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	25		
Units: Percentage of subjects				
number (confidence interval 95%)	20.0 (6.8 to 40.7)	28.0 (12.1 to 49.4)		

Statistical analyses

Statistical analysis title	pCR - GBG
Statistical analysis description: All subjects	
Comparison groups	Trastuzumab + BKM120 + paclitaxel v Trastuzumab + BKM120 PBO + paclitaxel
Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.84
Method	Fisher Exact (one-sided)

Secondary: pCR ypT0/is ypN0 per MD Anderson definition

End point title	pCR ypT0/is ypN0 per MD Anderson definition
End point description: pCR defined as no invasive residuals in breast and lymph nodes (ypT0/Tis, ypN0 [MD Anderson definition]). If patient had a sentinel node biopsy before treatment which was negative and no axilla dissection was performed after treatment completion, such patient was considered to be pN0 for both secondary pCR definitions.	
End point type	Secondary
End point timeframe: week 18	

End point values	Trastuzumab + BKM120 + paclitaxel	Trastuzumab + BKM120 PBO + paclitaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	25		
Units: Percentage of subjects				
number (confidence interval 95%)	32.0 (14.9 to 53.5)	36.0 (18.0 to 57.5)		

Statistical analyses

Statistical analysis title	pCR - MD Anderson
Statistical analysis description: All subjects	
Comparison groups	Trastuzumab + BKM120 + paclitaxel v Trastuzumab + BKM120 PBO + paclitaxel
Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.724
Method	Fisher Exact (one-sided)

Secondary: Overall objective response rate (ORR) prior to surgery for all subjects

End point title	Overall objective response rate (ORR) prior to surgery for all subjects
End point description: Number of Overall objective response rate = Complete Response + Partial Response rate, measured by US bidimensional ultrasound (or MRI) and assessed by world health organization (WHO) criteria. CR: 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. PR: 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 subjects 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: prior to surgery	

End point values	Trastuzumab + BKM120 + paclitaxel	Trastuzumab + BKM120 PBO + paclitaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	25		
Units: Percentage of subjects with response				
number (confidence interval 95%)	56.0 (34.9 to 75.6)	76.0 (54.9 to 90.6)		

Statistical analyses

Statistical analysis title	ORR prior to surgery
Statistical analysis description: All subjects	
Comparison groups	Trastuzumab + BKM120 + paclitaxel v Trastuzumab + BKM120 PBO + paclitaxel
Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.964
Method	Fisher Exact (one-sided)

Secondary: Percentage of subjects with pCR rates by hormone receptor status - Positive Estrogen Receptor (ER+)

End point title	Percentage of subjects with pCR rates by hormone receptor status - Positive Estrogen Receptor (ER+)
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]). If a subject had a sentinel node biopsy before treatment which was negative and no axilla dissection was performed after treatment completion, such subject was considered to be pN0 for both secondary pCR definitions.	
End point type	Secondary
End point timeframe: baseline, week 18	

End point values	ER+ subjects (Trastuzumab + BKM120 + paclitaxel)	ER + subjects (Trastuzumab + BKM120 PBO + paclitaxel)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	16	15		
Units: Percentage of subjects				
number (confidence interval 95%)	31.3 (11.0 to 58.7)	26.7 (7.8 to 55.1)		

Statistical analyses

Statistical analysis title	ER+ subjects
Statistical analysis description: For ER+ subjects - pCR	
Comparison groups	ER+ subjects (Trastuzumab + BKM120 + paclitaxel) v ER + subjects (Trastuzumab + BKM120 PBO + paclitaxel)

Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.546
Method	Fisher Exact (one-sided)

Secondary: Percentage of subjects with pCR rates by hormone receptor status - Negative Estrogen Receptor (ER-)

End point title	Percentage of subjects with pCR rates by hormone receptor status - Negative Estrogen Receptor (ER-)
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]). If a subject had a sentinel node biopsy before treatment which was negative and no axilla dissection was performed after treatment completion, such subject was considered to be pN0 for both secondary pCR definitions.	
End point type	Secondary
End point timeframe: baseline, week 18	

End point values	ER- subjects (Trastuzumab + BKM120 + paclitaxel)	ER- subject (Trastuzumab + BKM120 PBO + paclitaxel)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	9	10		
Units: Percentage of subjects				
number (confidence interval 95%)				
ER- subjects with pCR (N = 9, 10)	33.3 (7.5 to 70.1)	60.0 (26.2 to 87.8)		

Statistical analyses

Statistical analysis title	ER- subjects
Statistical analysis description: For ER- subjects - pCR	
Comparison groups	ER- subjects (Trastuzumab + BKM120 + paclitaxel) v ER-subjecst (Trastuzumab + BKM120 PBO + paclitaxel)
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.949
Method	Fisher Exact (one-sided)

Secondary: Percentage of subjects with objective response rates by hormone receptor status - Positive Estrogen Receptor (ER+)

End point title	Percentage of subjects with objective response rates by hormone receptor status - Positive Estrogen Receptor (ER+)
End point description: Objective response rate = Complete Response + Partial Response rate, measured by US bidimensional ultrasound (or MRI) and assessed by world health organization (WHO) criteria. CR: 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. PR: 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 18	

End point values	ER+ subjects (Trastuzumab + BKM120 + paclitaxel)	ER + subjects (Trastuzumab + BKM120 PBO + paclitaxel)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	16	15		
Units: Percentage of subjects				
number (confidence interval 95%)				
ER+ subjects with ORR (N = 16, 15)	68.8 (41.3 to 89.0)	33.3 (11.8 to 61.6)		

Statistical analyses

Statistical analysis title	ER+ subjects
Statistical analysis description: For ER+ subjects - ORR	
Comparison groups	ER+ subjects (Trastuzumab + BKM120 + paclitaxel) v ER + subjects (Trastuzumab + BKM120 PBO + paclitaxel)
Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.053
Method	Fisher Exact (one-sided)

Secondary: Percentage of subjects with objective response rates by hormone receptor status - Negative Estrogen Receptor (ER-)

End point title	Percentage of subjects with objective response rates by hormone receptor status - Negative Estrogen Receptor (ER-)
End point description: Objective response rate = Complete Response + Partial Response rate, measured by US bidimensional ultrasound (or MRI) and assessed by world health organization (WHO) criteria. CR: 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. PR: 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 subjects 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 18	

End point values	ER- subjects (Trastuzumab + BKM120 + paclitaxel)	ER- subject (Trastuzumab + BKM120 PBO + paclitaxel)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	9	10		
Units: Percentage of subjects				
number (confidence interval 95%)				
ER- subjects with ORR (N = 9, 10)	33.3 (7.5 to 70.1)	60.0 (26.2 to 87.8)		

Statistical analyses

Statistical analysis title	ER- subjects
Statistical analysis description:	
For ER- subjects - ORR	
Comparison groups	ER- subjects (Trastuzumab + BKM120 + paclitaxel) v ER- subject (Trastuzumab + BKM120 PBO + paclitaxel)
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.949
Method	Fisher Exact (one-sided)

Secondary: Percentage of subjects with Remaining Ductal carcinoma in situ (DCIS) (ypTis)

End point title	Percentage of subjects with Remaining Ductal carcinoma in situ (DCIS) (ypTis)
End point description:	
This included subjects at definitive surgery irrespective of lymph node status	
End point type	Secondary
End point timeframe:	
18 weeks	

End point values	Trastuzumab + BKM120 + paclitaxel	Trastuzumab + BKM120 PBO + paclitaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	25		
Units: Percentage of subjects				
number (confidence interval 95%)	12.0 (2.5 to 31.2)	12.0 (2.5 to 31.2)		

Statistical analyses

Statistical analysis title	For DCIS
Statistical analysis description:	
All subjects	
Comparison groups	Trastuzumab + BKM120 + paclitaxel v Trastuzumab + BKM120 PBO + paclitaxel
Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.666
Method	Fisher Exact (one -sided)

Secondary: Percentage of subjects with node-negative disease at definitive surgery (ypN0)

End point title	Percentage of subjects 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	Trastuzumab + BKM120 + paclitaxel	Trastuzumab + BKM120 PBO + paclitaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	25		
Units: Percentage of subjects				
number (confidence interval 95%)	52.0 (31.3 to 72.2)	60.0 (38.7 to 78.9)		

Statistical analyses

Statistical analysis title	For Node-negative disease
Statistical analysis description:	
All subjects	
Comparison groups	Trastuzumab + BKM120 + paclitaxel v Trastuzumab + BKM120 PBO + paclitaxel
Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.803
Method	Fisher Exact (one-sided)

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events and serious adverse events were collected for the maximum actual duration of treatment exposure and follow up for a participant per the protocol for approximately 19.1 weeks.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	18.1
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Reporting groups

Reporting group title	BKM120
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Reporting group description:

BKM120

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

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

Leukopenia subjects affected / exposed occurrences (all)	11 / 25 (44.00%) 11	15 / 25 (60.00%) 15	
Lymphopenia subjects affected / exposed occurrences (all)	11 / 25 (44.00%) 11	8 / 25 (32.00%) 8	
Neutropenia subjects affected / exposed occurrences (all)	6 / 25 (24.00%) 6	9 / 25 (36.00%) 9	
Thrombopenia subjects affected / exposed occurrences (all)	4 / 25 (16.00%) 4	0 / 25 (0.00%) 0	
Ear and labyrinth disorders Ear and labyrinth disorders subjects affected / exposed occurrences (all)	1 / 25 (4.00%) 1	2 / 25 (8.00%) 2	
Eye disorders Eye disorders subjects affected / exposed occurrences (all)	5 / 25 (20.00%) 5	3 / 25 (12.00%) 3	
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all)	2 / 25 (8.00%) 2	4 / 25 (16.00%) 4	
Constipation subjects affected / exposed occurrences (all)	4 / 25 (16.00%) 4	7 / 25 (28.00%) 7	
Diarrhea subjects affected / exposed occurrences (all)	15 / 25 (60.00%) 15	10 / 25 (40.00%) 10	
Dysgeusia subjects affected / exposed occurrences (all)	4 / 25 (16.00%) 4	5 / 25 (20.00%) 5	
Dyspepsia subjects affected / exposed occurrences (all)	4 / 25 (16.00%) 4	4 / 25 (16.00%) 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 occurrences (all)	15 / 25 (60.00%) 15	12 / 25 (48.00%) 12	
Rash other than macular-papular or NOS subjects affected / exposed occurrences (all)	8 / 25 (32.00%) 8	8 / 25 (32.00%) 8	
Renal and urinary disorders Renal and urinary disorders subjects affected / exposed occurrences (all)	2 / 25 (8.00%) 2	0 / 25 (0.00%) 0	
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	7 / 25 (28.00%) 7	10 / 25 (40.00%) 10	
Bone pain subjects affected / exposed occurrences (all)	3 / 25 (12.00%) 3	5 / 25 (20.00%) 5	
Myalgia subjects affected / exposed occurrences (all)	3 / 25 (12.00%) 3	5 / 25 (20.00%) 5	
Other musculo-skeletal and connective tissue disorders subjects affected / exposed occurrences (all)	2 / 25 (8.00%) 2	1 / 25 (4.00%) 1	
Infections and infestations Fever without neutropenia subjects affected / exposed occurrences (all)	7 / 25 (28.00%) 7	3 / 25 (12.00%) 3	
Infection subjects affected / exposed occurrences (all)	12 / 25 (48.00%) 12	19 / 25 (76.00%) 19	
Metabolism and nutrition disorders Anorexia subjects affected / exposed occurrences (all)	5 / 25 (20.00%) 5	1 / 25 (4.00%) 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