Sponsor

Novartis

Generic Drug Name

Not determined for BEZ235 and Buparlisib for BKM120

Trial Indication(s)

Metastatic and advanced solid tumor for dual agent dose escalation and HER2+ metastatic breast cancer for triple combination

Protocol Number

CBEZ235A2118

Protocol Title

A Phase Ib multi-center, open-label, 4-arm dose-escalation study of oral BEZ235 and BKM120 in combination with weekly paclitaxel in patients with advanced solid tumors and weekly paclitaxel/trastuzumab in patients with HER2+ metastatic breast cancer

Clinical Trial Phase

Ib

Phase of Drug Development

Ib

Study Start/End Dates

13-Jan-2011 to 24-Oct- 2014

Reason for Termination (If applicable)

Not applicable

Study Design/Methodology

- This was a Phase Ib, multicenter, open-label, four-arm dose finding study of oral BEZ235 or oral BKM120 with intravenous paclitaxel with or without trastuzumab to determine the maximum tolerated doses (MTD) of these regimens. This study included dual-agent dose escalation part followed by a safety expansion and a triple-agent dose combination part. Once MTD was established for a dual combination, a triple combination dose escalation was started and a safety expansion part was initiated at the dual combination MTD. Specific molecular screening of patients for PI3K activation and HER2+ amplification was required for the enrolment of patients in respectively the safety expansion part and the triple agent combination part. Dose escalation was guided by a Bayesian logistic regression model with overdose control.

Centers

10 centers in 5 countries: Netherlands (1), Belgium (3), Germany (2), Spain (2), Switzerland (2)

Objectives:

Primary objective(s):

Dual-agent dose escalation part

- To determine the maximum tolerated dose (MTD) of oral BEZ235, daily (qd) in combination with paclitaxel, weekly (qw) in patients with advanced solid tumors (MTD1, Arm 1).
- To determine the MTD of oral BKM120, qd in combination with paclitaxel, qw in patients with advanced solid tumors (MTD2, Arm 2).

Triple-agent dose combination part

- To determine the MTD of oral BEZ235, qd in combination with paclitaxel/trastuzumab, qw in patients with HER2+ metastatic breast cancer (MTD3, Arm 3).
- To determine the MTD of oral BKM120, qd in combination with paclitaxel/trastuzumab, qw in patients with HER2+ metastatic breast cancer (MTD4, Arm 4).

Secondary objectives

- To assess the safety and tolerability of the dual and triple combinations administered in both parts of the study, including acute and chronic toxicities.
- To characterize the single dose pharmacokinetics (PK) of paclitaxel as single agent on Day 1.

- To characterize the steady-state PK of BEZ235/BKM120 qd and paclitaxel qw given in combination (Day 8 and 22).
- To characterize exposure to trastuzumab (trough levels).
- To assess the preliminary anti-tumor activity associated with these combination treatments.

Test Product (s), Dose(s), and Mode(s) of Administration

- BEZ235 and BKM120 were the investigational study drugs. A dual-agent dose escalation phase with BEZ235 and BKM120 doses representing 40% of the highest doses was administered as a single agent and a reduced paclitaxel dose of 70 mg/m2 was also administered based on the single-agent data obtained in CBEZ235A2101 and CBKM120X2101 trials.
- These doses met the BLRM overdose control requirements.
- In the triple-agent dose combination part, trastuzumab was administered at the standard dose of 2 mg/kg/w.
- The starting doses for BEZ235, BKM120 and paclitaxel in combination with trastuzumab were to be determined by the BLRM on the basis of the data obtained during the dual-agent dose escalation part of the study. Both study drugs were orally administered.
- BKM120 was provided as hard gelatin capsules (10 and 50 mg) and BEZ235 were provided as sachets (200 and 400 mg).

Statistical Methods

- The patient's background and demographic characteristics including age, gender, race, ethnicity, height, weight, body mass index, body surface area, WHO performance status, tumor type, medical conditions, etc. were listed by patient, and summarized using descriptive statistics (mean, median, standard deviation, minimum and maximum for continuous data) or contingency tables (categorical data).
- For categorical variables, the number and percentage of patients with missing data was provided. Relevant medical history, current medical conditions, prior anti-neoplastic therapy, and diagnosis and extent of cancer were listed and summarized.
- Estimation of the MTDs in the dose escalation part of the study was based upon the estimation of the probability of DLT in Cycle 1 in patients of the dose determining set.
- For each combination (BEZ235+paclitaxel, BKM120+paclitaxel) an adaptive five-parameter Bayesian logistic regression model (BLRM) using the EWOC principle was used to guide the dose-escalation of the combination treatment.
- The BLRM was also used to evaluate the impact of the addition of trastuzumab. The BLRMs were fitted on the Cycle 1 DLT data, accumulated throughout the dose-escalation

to model the dose-toxicity relationship of paclitaxel and each of the PI3K-inhibitors, when given in combination

- The assessment of safety was based mainly on the frequency of adverse events and on the number of lab evaluations outside of pre-defined ranges of common toxicity criteria (CTC) grading limits or normal ranges as appropriate).
- The tolerability of the study drug treatment was also assessed by summarizing the number of drug interruptions, dose reduction and drug intensity. The efficacy analysis was based on full analysis set (FAS).
- Best overall response (BOR) by RECIST v1.0 was summarized using objective response rate (ORR) and disease control rate (DCR). The DCR and ORR were presented by treatment group with exact 90% confidence intervals and summarized with counts and percentages. The analyses of DCR and ORR were performed using the overall lesion responses reported by the Investigator (local radiology).
- The percentage changes from baseline of the sum of the longest diameters (SLD) across target lesions were listed and the best percentage change from baseline displayed graphically.
- Basic PK parameters for BEZ235 and BKM120, paclitaxel (and its metabolites) were calculated including but not limited to, AUC0-tlast, AUC0-inf, AUC0-24, Cmax, tmax, terminal t1/2. Analyses of covariance (ANCOVA) was performed on log-transformed AUCs and Cmax for BKM120 (Day 8 and 22 of Cycle 1), BEZ235 (Day 8 and 22 of Cycle 1) and paclitaxel (Day 1, Day 8 and 22 of Cycle 1) using linear mixed effect models. Trastuzumab concentrations were only measured at trough concentrations in order to insure a sufficient level of exposure
- All biomarker sample results were listed by dose cohort and study arm as appropriate. For selected biomarkers with results pre- and post-baseline (p-S6 and p-4EBP1) individual values as well as change from baseline were summarized by means of descriptive statistics and graphs.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion criteria

- Male or female patients ≥18 years
- Adequate bone marrow function, renal and hepatic function, adequate coagulation and cardiovascular function.

Dual-agent dose escalation part

- Patients with metastatic or locally advanced solid tumors eligible for weekly paclitaxel

Dual-agent safety expansion part

- Adult patients with locally advanced or metastatic advanced solid tumors carrying an activation of the PI3K pathway for whom weekly paclitaxel treatment is indicated.

Triple-agent dose combination part

- HER2+ locally advanced or metastatic breast cancer patients eligible for weekly paclitaxel and trastuzumab.
- Availaibility of a representative tumor specimen (primary or metastatic, archival or fresh).

Exclusion criteria

- Patients with primary central nervous system (CNS) tumor or CNS tumor involvement.
- Patients who have received prior systemic anticancer therapy within ≤ 3-4 weeks before study treatment.
- Patients who have undergone major surgery ≤ 4 weeks before study treatment
- Patients receiving chronic treatment with corticosteroids or other immunosuppressive agents.
- Patients with uncontrolled and unmanageable treatment-refractory diabetes mellitus
- Impaired gastrointestinal (GI) function or GI disease that may significantly alter the absorption of study drug
- Patients who are currently receiving treatment with agents that are metabolized solely by CYP3A, and/or have a narrow therapeutic window or are strong inhibitors or inducers of CYP3A or CYP2C8.
- Patients who are receiving treatment withQT-prolonging medication known to have a risk to induce Torsades de Pointes.
- Patients who have received radiotherapy ≤4 weeks before starting study drug
- Patients who previously received PI3K inhibitors.
- Patients with known human immunodeficiency virus (HIV)
- Women of child-bearing potential (WCBP) who are pregnant or breastfeeding

Participant Flow Table

BEZ235 dual combination:

Patient disposition, by treatment group (Full Analysis Set- BEZ235/paclitaxel)

	BEZ235 400 mg/ Ptx 70mg N=2 n (%)	BEZ235 400 mg/ Ptx 80mg N=3 n (%)	BEZ235 600 mg/ Ptx 80mg N=4 n (%)	BEZ235 800 mg/ Ptx 80mg N=26 n (%)	All BEZ235/ Ptx N=35 n (%)
Patients treated					
Treatment discontinued	2 (100.0%)	3 (100.0%)	4 (100.0%)	26 (100.0%)	35 (100.0%)
Primary reason for treatment discontinuation					
Adverse Event(s)	0	0	1 (25.0%)	9 (34.6%)	10 (28.6%)
Death	0	0	0	1 (3.8%)	1 (2.9%)
Disease progression	1 (50.0%)	3 (100.0%)	3 (75.0%)	15 (57.7%)	22 (62.9%)
Subject withdrew consent	1 (50.0%)	0	0	1 (3.8%)	2 (5.7%)

BEZ235 triple-agent combination:

Patient disposition, by treatment group BEZ235/paclitaxel/trastuzumab (Full Analysis Set)

	BEZ235 400 mg/ Ptx 80mg/ Tz N=6 n (%)	BEZ235 600 mg/ Ptx 80mg/ Tz N=5 n (%)	All BEZ235/ Ptx/Tz N=11 n (%)
Patients treated			
Treatment discontinued	6 (100.0)	5 (100.0)	11 (100.0)
Primary reason for treatment discontinuation			
Adverse Event(s)	1 (16.7)	0	1 (9.1)
Disease progression	4 (66.7)	4 (80.0)	8 (72.7)
Protocol deviation	1 (16.7)	0	1 (9.1)
Subject withdrew consent	0	1 (20.0)	1 (9.1)

BKM120 dual combination:

Patient disposition, by treatment group BKM120/paclitaxel (Full Analysis Set)

	BKM120 40 mg/ Ptx 70mg N=1 n (%)	BKM120 40 mg/ Ptx 80mg N=5 n (%)	BKM120 60 mg/ Ptx 80mg N=3 n (%)	BKM120 80 mg/ Ptx 80mg N=4 n (%)	BKM120 100 mg/ Ptx 80mg N=36 n (%)	BKM120 120 mg/ Ptx 80mg N=4 n (%)	All BKM120/ Ptx N=53 n (%)
Patients treated							
Treatment discontinued	1 (100.0)	5 (100.0)	3 (100.0)	4 (100.0)	36 (100.0)	4 (100.0)	53 (100.0)
Primary reason for treatment discontinuation							
Adverse Event(s)	0	0	0	1 (25.0)	7 (19.4)	0	8 (15.1)
Death	0	0	0	0	1 (2.8)	0	1 (1.9)
Disease progression	1 (100.0)	5 (100.0)	2 (66.7)	2 (50.0)	26 (72.2)	3 (75.0)	39 (73.6)
Subject withdrew consent	0	0	1 (33.3)	1 (25.0)	2 (5.6)	1 (25.0)	5 (9.4)

BKM120 triple agent combination:

Patient disposition, by treatment group BKM120/paclitaxel/trastuzumab (Full Analysis Set)

	BKM120 100 mg/ Ptx 80mg/ Tz N=11	All BKM120/ Ptx/Tz N=11
Patients treated		
Treatment discontinued	11 (100.0%)	11 (100.0%)
Primary reason for treatment discontinuation		
Adverse Event(s)	2 (18.2%)	2 (18.2%)
Disease progression	9 (81.8%)	9 (81.8%)

Baseline Characteristics

BEZ235 dual combination:

Demographics at baseline, by treatment group BEZ235/paclitaxel dual combination (Full analysis set)

Demographic Variable	BEZ235 400 mg/ Ptx 70mg N=2	BEZ235 400 mg/ Ptx 80mg N=3	BEZ235 600 mg/ Ptx 80mg N=4	BEZ235 800 mg/ Ptx 80mg N=26	All BEZ235/ Ptx N=35

Demographic Variable	BEZ235 400 mg/ Ptx 70mg N=2	BEZ235 400 mg/ Ptx 80mg N=3	BEZ235 600 mg/ Ptx 80mg N=4	BEZ235 800 mg/ Ptx 80mg N=26	All BEZ235/ Ptx N=35
Age (Years)					
n	2	3	4	26	35
Mean	72.5	62.7	48.3	53.6	54.8
SD	10.61	11.06	6.34	11.98	12.24
Median	72.5	64.0	47.0	54.5	55.0
Min	65.0	51.0	42.0	29.0	29.0
Max	80.0	73.0	57.0	80.0	80.0
Age category (Years)					
< 65	0	2 (66.7%)	4 (100.0%)	21 (80.8%)	27 (77.1%)
≥ 65	2 (100.0%)	1 (33.3%)	0	5 (19.2%)	8 (22.9%)
Sex					
Male	1 (50.0%)	2 (66.7%)	1 (25.0%)	18 (69.2%)	22 (62.9%)
Female	1 (50.0%)	1 (33.3%)	3 (75.0%)	8 (30.8%)	13 (37.1%)
If female- child bearing potential					
Able to bear children	0	0	2 (50.0%)	0	2 (5.7%)
Post-menopausal	1 (50.0%)	1 (33.3%)	1 (25.0%)	5 (19.2%)	8 (22.9%)
Sterile - of child bearing age	0	0	0	3 (11.5%)	3 (8.6%)
Race					
Caucasian	2 (100.0%)	3 (100.0%)	4 (100.0%)	25 (96.2%)	34 (97.1%)
Asian	0	0	0	1 (3.8%)	1 (2.9%)
Ethnicity					
Hispanic/Latino	0	1 (33.3%)	1 (25.0%)	11 (42.3%)	13 (37.1%)
Chinese	0	0	0	1 (3.8%)	1 (2.9%)
Other	2 (100.0%)	2 (66.7%)	3 (75.0%)	14 (53.8%)	21 (60.0%)
Weight (kg)					
n	2	3	4	26	35
Mean	79.2	76.1	63.2	71.4	71.3
SD	23.83	19.86	7.18	14.54	14.60
Median	79.2	70.9	64.2	70.6	70.0
Min	62.3	59.3	54.0	48.0	48.0
Max	96.0	98.0	70.4	100.0	100.0
Weight category (kg)					
< 55	0	0	1 (25.0%)	4 (15.4%)	5 (14.3%)
55 - 75	1 (50.0%)	2 (66.7%)	3 (75.0%)	13 (50.0%)	19 (54.3%)
≥ 75	1 (50.0%)	1 (33.3%)	0	9 (34.6%)	11 (31.4%)

Demographic Variable	BEZ235 400 mg/ Ptx 70mg N=2	BEZ235 400 mg/ Ptx 80mg N=3	BEZ235 600 mg/ Ptx 80mg N=4	BEZ235 800 mg/ Ptx 80mg N=26	All BEZ235/ Ptx N=35
Height (cm)					
n	2	3	4	26	35
Mean	162.5	176.3	162.0	169.3	168.7
SD	13.44	7.51	6.38	8.71	9.00
Median	162.5	172.0	160.0	171.5	171.0
Min	153.0	172.0	157.0	151.0	151.0
Max	172.0	185.0	171.0	183.0	185.0
Body surface area (m^2)					
n	2	3	4	26	35
Mean	1.9	2.0	1.7	1.8	1.8
SD	0.42	0.31	0.08	0.23	0.23
Median	1.9	1.9	1.7	1.9	1.8
Min	1.6	1.7	1.6	1.5	1.5
Max	2.2	2.3	1.8	2.2	2.3
Body Mass Index (kg/m^2)					
n	2	3	4	26	35
Mean	29.5	24.2	24.2	24.8	25.0
SD	4.10	4.30	3.30	4.28	4.16
Median	29.5	24.0	24.2	25.2	25.4
Min	26.6	20.0	21.0	17.4	17.4
Max	32.4	28.6	27.2	34.2	34.2
WHO Performance Status					
0	1 (50.0%)	3 (100.0%)	2 (50.0%)	12 (46.2%)	18 (51.4%)
1	1 (50.0%)	0	2 (50.0%)	14 (53.8%)	17 (48.6%)

Body Mass Index: BMI [kg/m^2] = weight[kg] / (height[m]**2).

Body Surface Area (Gehan and George): BSA [m^2] = 234.94*(height[cm]**0.422)*(weight[kg]**0.515)/10000.

WHO performance status: 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 house work, office work; 2 - Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours; 3 - Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours; 4 - Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.

BEZ235 triple-agent combination:

Demographics at baseline, by treatment group BEZ235/paclitaxel/Trastuzumab triple agent combination. (Full Analysis Set)

Demographic Variable	BEZ235 400 mg/ Ptx 80mg/ Tz N=6	BEZ235 600 mg/ Ptx 80mg/ Tz N=5	All BEZ235/ Ptx/Tz N=11
Age (Years)			
n	6	5	11
Mean	49.5	43.8	46.9
SD	15.67	11.43	13.56
Median	55.0	43.0	49.0
Min	25.0	28.0	25.0
Max	63.0	59.0	63.0
Age category (Years)			
< 65	6 (100.0%)	5 (100.0%)	11 (100.0%)
Sex			
Female			
If Female- child bearing potential	6 (100.0%)	5 (100.0%)	11 (100.0%)
Able to bear children	2 (33.3%)	2 (40.0%)	4 (36.4%)
Premenarche	0	1 (20.0%)	1 (9.1%)
Post-menopausal	3 (50.0%)	2 (40.0%)	5 (45.5%)
Sterile - of child bearing age	1 (16.7%)	0	1 (9.1%)
Race			
Caucasian	6 (100.0%)	5 (100.0%)	11 (100.0%)
Ethnicity			
Hispanic/Latino	3 (50.0%)	0	3 (27.3%)
Other	3 (50.0%)	5 (100.0%)	8 (72.7%)
Weight (kg)			
n	6	5	11
Mean	60.8	57.7	59.4
SD	7.87	10.98	9.05
Median	65.1	59.0	65.0
Min	49.0	45.0	45.0
Max	67.0	69.4	69.4
Weight category (kg)			
< 55	2 (33.3%)	2 (40.0%)	4 (36.4%)

Demographic Variable	BEZ235 400 mg/ Ptx 80mg/ Tz N=6	BEZ235 600 mg/ Ptx 80mg/ Tz N=5	All BEZ235/ Ptx/Tz N=11
55 - 75	4 (66.7%)	3 (60.0%)	7 (63.6%)
Height (cm)			
n	6	5	11
Mean	163.2	163.0	163.1
SD	3.31	6.86	4.93
Median	163.5	163.5	163.5
Min	157.0	155.0	155.0
Max	166.0	173.0	173.0
Body surface area (m^2)			
n	6	5	11
Mean	1.7	1.6	1.6
SD	0.08	0.20	0.14
Median	1.7	1.7	1.7
Min	1.5	1.4	1.4
Max	1.7	1.8	1.8
Body Mass Index (kg/m^2)			
n	6	5	11
Mean	22.9	21.6	22.3
SD	3.43	3.02	3.17
Median	23.9	21.7	22.4
Min	18.4	17.9	17.9
Max	27.2	26.0	27.2
WHO Performance Status			
0	5 (83.3%)	1 (20.0%)	6 (54.5%)
1	1 (16.7%)	4 (80.0%)	5 (45.5%)

Body Mass Index: BMI [kg/m^2] = weight[kg] / (height[m]**2).

Body Surface Area (Gehan and George):
BSA[m^2]=234.94*(height[cm]**0.422)*(weight[kg]**0.515)/10000.

WHO performance status: 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 house work, office work; 2 - Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours; 3 - Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours; 4 - Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.

BKM120 dual combination:

Demographics at baseline, by treatment group BKM120/paclitaxel (Full analysis set)

Demographic Variable	BKM120 40 mg/ Ptx 70mg N=1	BKM120 40 mg/ Ptx 80mg N=5	BKM120 60 mg/ Ptx 80mg N=3	BKM120 80 mg/ Ptx 80mg N=4	BKM120 100 mg/ Ptx 80mg N=36	BKM120 120 mg/ Ptx 80mg N=4	All BKM120/ Ptx N=53
Age (Years)							
n	1	5	3	4	36	4	53
Mean	66.0	55.6	57.3	59.3	54.9	49.3	55.2
SD		18.39	14.57	7.41	12.18	14.36	12.48
Median	66.0	58.0	62.0	60.0	56.0	50.5	56.0
Min	66.0	32.0	41.0	50.0	30.0	34.0	30.0
Max	66.0	78.0	69.0	67.0	80.0	62.0	80.0
Age category (Years)							
< 65	0 (0.0%)	3 (60.0%)	2 (66.7%)	3 (75.0%)	28 (77.8%)	4 (100.0%)	40 (75.5%)
≥ 65	1 (100.0%)	2 (40.0%)	1 (33.3%)	1 (25.0%)	8 (22.2%)	0	13 (24.5%)
Sex							
Male	0	1 (20.0%)	3 (100.0%)	0	18 (50.0%)	3 (75.0%)	25 (47.2%)
Female	1 (100.0%)	4 (80.0%)	0	4 (100.0%)	18 (50.0%)	1 (25.0%)	28 (52.8%)
If Female- child bearing potential							
Able to bear children	0	0	0	1 (25.0%)	2 (5.6%)	0	3 (5.7%)
Post menopausal	1 (100.0%)	3 (60.0%)	0	1 (25.0%)	10 (27.8%)	1 (25.0%)	16 (30.2%)
Sterile - of child bearing age	0	1 (20.0%)	0	2 (50.0%)	6 (16.7%)	0	9 (17.0%)
Race							
Caucasian	1 (100.0%)	4 (80.0%)	3 (100.0%)	4 (100.0%)	36 (100.0%)	4 (100.0%)	52 (98.1%)
Asian	0	1 (20.0%)	0	0	0	0	1 (1.9%)
Ethnicity							
Hispanic/Latino	0	0	1 (33.3%)	0	15 (41.7%)	1 (25.0%)	17 (32.1%)

Demographic Variable	BKM120 40 mg/ Ptx 70mg N=1	BKM120 40 mg/ Ptx 80mg N=5	BKM120 60 mg/ Ptx 80mg N=3	BKM120 80 mg/ Ptx 80mg N=4	BKM120 100 mg/ Ptx 80mg N=36	BKM120 120 mg/ Ptx 80mg N=4	All BKM120/ Ptx N=53
Chinese	0	1 (20.0%)	0	0	0	0	1 (1.9%)
Other	1 (100.0%)	4 (80.0%)	2 (66.7%)	4 (100.0%)	21 (58.3%)	3 (75.0%)	35 (66.0%)
Weight (kg)							
n	1	5	3	4	36	4	53
Mean	68.6	67.7	88.3	59.6	74.4	79.5	73.7
SD		17.09	27.39	13.99	17.55	20.74	18.14
Median	68.6	64.0	83.0	54.9	71.3	79.0	70.7
Min	68.6	53.4	64.0	48.8	47.0	55.0	47.0
Max	68.6	96.6	118.0	80.0	118.9	104.8	118.9
Weight category (kg)							
< 55	0	1 (20.0%)	0	2 (50.0%)	5 (13.9%)	0	8 (15.1%)
55 - 75	1 (100.0%)	3 (60.0%)	1 (33.3%)	1 (25.0%)	17 (47.2%)	2 (50.0%)	25 (47.2%)
≥ 75	0	1 (20.0%)	2 (66.7%)	1 (25.0%)	14 (38.9%)	2 (50.0%)	20 (37.7%)
Height (cm)							
n	1	5	3	4	36	4	53
Mean	170.0	165.2	176.0	159.4	169.8	170.5	169.0
SD		14.52	11.53	8.28	8.93	9.98	9.83
Median	170.0	164.0	180.0	158.5	171.0	171.0	170.0
Min	170.0	153.0	163.0	150.5	148.0	160.0	148.0
Max	170.0	189.0	185.0	170.0	192.0	180.0	192.0
Body surface area (m^2)							
n	1	5	3	4	36	4	53
Mean	1.8	1.8	2.1	1.6	1.9	2.0	1.9
SD		0.31	0.40	0.22	0.24	0.30	0.27
Median	1.8	1.7	2.0	1.6	1.9	2.0	1.9
Min	1.8	1.5	1.7	1.4	1.4	1.6	1.4
Max	1.8	2.3	2.5	1.9	2.4	2.3	2.5
Body Mass Index (kg/m^2)							
n	1	5	3	4	36	4	53
Mean	23.7	24.5	28.1	23.6	25.9	27.0	25.7

Demographic Variable	BKM120 40 mg/ Ptx 70mg N=1	BKM120 40 mg/ Ptx 80mg N=5	BKM120 60 mg/ Ptx 80mg N=3	BKM120 80 mg/ Ptx 80mg N=4	BKM120 100 mg/ Ptx 80mg N=36	BKM120 120 mg/ Ptx 80mg N=4	All BKM120/ Ptx N=53
SD		2.56	5.62	6.24	6.34	4.79	5.77
Median	23.7	24.5	25.6	20.9	24.2	26.7	24.2
Min	23.7	21.2	24.1	19.7	17.9	21.5	17.9
Max	23.7	27.0	34.5	32.9	48.4	33.1	48.4
WHO Performance Status							
0	0	2 (40.0%)	0	2 (50.0%)	12 (33.3%)	1 (25.0%)	17 (32.1%)
1	0	3 (60.0%)	3 (100.0%)	2 (50.0%)	24 (66.7%)	2 (50.0%)	34 (64.2%)
2	1 (100.0%)	0	0	0	0	1 (25.0%)	2 (3.8%)

Body Mass Index: BMI [kg/m^2] = weight[kg] / (height[m]**2).

Body Surface Area (Gehan and George):
BSA[m^2]=234.94*(height[cm]**0.422)*(weight[kg]**0.515)/10000.

WHO performance status: 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 house work, office work; 2 - Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours; 3 - Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours; 4 - Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.

BKM120 triple-agent combination:

Demographics at baseline, by treatment group BKM120/paclitaxel/Trastuzumab (Full analysis set)

Demographic Variable	BKM120 100 mg/ Ptx 80mg/ Tz N=11	All BKM120/ Ptx/Tz N=11
Age (Years)		
n	11	11
Mean	59.2	59.2
SD	13.50	13.50
Median	62.0	62.0
Min	34.0	34.0
Max	76.0	76.0
Age category (Years)		

Demographic Variable	BKM120 100 mg/ Ptx 80mg/ Tz N=11	All BKM120/ Ptx/Tz N=11
< 65	7 (63.6%)	7 (63.6%)
≥ 65	4 (36.4%)	4 (36.4%)
Sex		
Female	11 (100.0%)	11 (100.0%)
If Female- child bearing potential		
Able to bear children	2 (18.2%)	2 (18.2%)
Post-menopausal	7 (63.6%)	7 (63.6%)
Sterile - of child bearing age	2 (18.2%)	2 (18.2%)
Race		
Caucasian	11 (100.0%)	11 (100.0%)
Ethnicity		
Hispanic/Latino	5 (45.5%)	5 (45.5%)
Other	6 (54.5%)	6 (54.5%)
Weight (kg)		
n	11	11
Mean	62.6	62.6
SD	10.09	10.09
Median	63.9	63.9
Min	45.5	45.5
Max	76.0	76.0
Weight category (kg)		
< 55	3 (27.3%)	3 (27.3%)
55 - 75	6 (54.5%)	6 (54.5%)
≥ 75	2 (18.2%)	2 (18.2%)
Height (cm)		
n	11	11
Mean	160.3	160.3
SD	5.33	5.33
Median	158.0	158.0
Min	153.0	153.0
Max	168.0	168.0
Body surface area (m^2)		
n	11	11
Mean	1.7	1.7

Demographic Variable	BKM120 100 mg/ Ptx 80mg/ Tz N=11	All BKM120/ Ptx/Tz N=11
SD	0.15	0.15
Median	1.7	1.7
Min	1.4	1.4
Max	1.9	1.9
Body Mass Index (kg/m^2)		
n	11	11
Mean	24.4	24.4
SD	4.20	4.20
Median	22.9	22.9
Min	18.1	18.1
Max	30.4	30.4
WHO Performance Status		
0	4 (36.4%)	4 (36.4%)
1	7 (63.6%)	7 (63.6%)

Body Mass Index: BMI [kg/m^2] = weight[kg] / (height[m]**2).

Body Surface Area (Gehan and George):
BSA[m^2]=234.94*(height[cm]**0.422)*(weight[kg]**0.515)/10000.

WHO performance status: 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 house work, office work; 2 - Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours; 3 - Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours; 4 - Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.

Summary of Efficacy

Primary Outcome Results

Summary of declared MTD by treatment arm

Treatment arms	Declared MTD
BEZ235 dual combination	BEZ235 800 mg in combination with 80 mg/m2/w Ptx
BEZ235 triple-agent combination	BEZ235 400 mg in combination with 80 mg/m^2/w Ptx and 2 mg/kg/w Tz
BKM120 dual combination	100 mg for BKM120 in combination with 80 mg/m2/w Ptx.
BKM120 triple-agent combination	100 mg for BKM120 in combination with

Treatment arms	Declared MTD
	80 mg/m^2/w Ptx and 2 mg/kg/w Tz.

BEZ235 dual combination:

Summary of posterior distribution of DLT rates at Cycle 1, at end of study (dose escalation part) Dose determining set - BEZ235/paclitaxel

		Posterior probabilities (%) that Pr(DLT) is in interval:					Quantiles		
Paclitaxel dose (mg/m^2)	BEZ235 dose (mg)	0-0.16	0.16-0.35	0.35-1	Mean	SD	2.5%	50%	97.5%
60.0	200.0	0.860	0.137	0.003	0.084	0.069	0.002	0.068	0.252
	400.0	0.768	0.226	0.006	0.111	0.074	0.008	0.099	0.286
	600.0	0.604	0.381	0.015	0.147	0.079	0.024	0.138	0.327
	800.0	0.348	0.587	0.065	0.202	0.090	0.054	0.193	0.404
	1000.0	0.152	0.554	0.295	0.295	0.138	0.092	0.271	0.633
	1200.0	0.105	0.421	0.474	0.395	0.225	0.103	0.336	0.958
	1400.0	0.084	0.355	0.561	0.458	0.261	0.110	0.390	0.997
70.0	200.0	0.780	0.214	0.006	0.106	0.075	0.004	0.093	0.284
	400.0	0.674	0.315	0.011	0.133	0.078	0.016	0.123	0.311
	600.0	0.501	0.475	0.024	0.169	0.080	0.042	0.160	0.348
	800.0	0.256	0.658	0.086	0.223	0.088	0.078	0.213	0.420
	1000.0	0.105	0.561	0.335	0.312	0.136	0.110	0.290	0.644
	1200.0	0.073	0.421	0.506	0.410	0.220	0.120	0.353	0.960
	1400.0	0.059	0.353	0.588	0.471	0.255	0.126	0.405	0.997
80.0	200.0	0.612	0.366	0.023	0.144	0.089	0.009	0.132	0.345
	400.0	0.498	0.468	0.034	0.170	0.088	0.028	0.161	0.366
	600.0	0.330	0.610	0.060	0.205	0.086	0.063	0.196	0.395
	800.0	0.140	0.707	0.153	0.256	0.091	0.103	0.248	0.454
	1000.0	0.058	0.525	0.417	0.341	0.136	0.131	0.322	0.663
	1200.0	0.041	0.389	0.570	0.434	0.214	0.142	0.382	0.963
	1400.0	0.032	0.326	0.641	0.493	0.247	0.150	0.432	0.997
90.0	200.0	0.394	0.483	0.123	0.206	0.118	0.021	0.192	0.471
	400.0	0.296	0.552	0.152	0.231	0.114	0.047	0.218	0.485
	600.0	0.173	0.622	0.204	0.263	0.109	0.084	0.251	0.505
	800.0	0.065	0.599	0.336	0.311	0.108	0.128	0.302	0.543
	1000.0	0.028	0.404	0.568	0.389	0.141	0.156	0.374	0.704
	1200.0	0.020	0.300	0.681	0.473	0.207	0.170	0.433	0.967

Paclitaxel dose (mg/m^2)	BEZ235 dose (mg)	Posterior probabilities (%) that Pr(DLT) is in interval: 0-0.16	0.16-0.35	0.35-1	Mean	SD	Quantiles 2.5%	50%	97.5%
	1400.0	0.016	0.250	0.734	0.528	0.235	0.178	0.480	0.997
100.0	200.0	0.213	0.443	0.344	0.300	0.162	0.049	0.277	0.663
	400.0	0.151	0.463	0.386	0.321	0.157	0.075	0.300	0.671
	600.0	0.081	0.467	0.452	0.350	0.150	0.111	0.330	0.684
	800.0	0.029	0.398	0.572	0.392	0.144	0.154	0.377	0.708
	1000.0	0.013	0.256	0.732	0.460	0.159	0.185	0.449	0.790
	1200.0	0.009	0.191	0.800	0.534	0.203	0.200	0.511	0.973
	1400.0	0.008	0.158	0.835	0.581	0.224	0.211	0.557	0.998

- A dose-limiting toxicity (DLT) is defined as an adverse event or abnormal laboratory value assessed as clinically relevant, occurring ≤28 days following the first administration of BEZ235 (Cycle 1) in combination with paclitaxel

BEZ235 triple-agent combination:

Summary of posterior distribution of DLT rates at Cycle 1, at end of study (dose escalation part) Dose determining set - BEZ235/paclitaxel/trastuzumab

Paclitaxel dose (mg/m^2)	BEZ235 dose (mg)	Posterior probabilities (%) that Pr(DLT) is in interval: 0-0.16	0.16-0.35	0.35-1	Mean	SD	Quantiles 2.5%	50%	97.5%
60.0	200.0	0.836	0.153	0.010	0.090	0.078	0.002	0.070	0.292
	400.0	0.676	0.297	0.026	0.135	0.090	0.015	0.117	0.354
	600.0	0.406	0.494	0.100	0.200	0.108	0.035	0.185	0.447
	800.0	0.195	0.492	0.313	0.291	0.146	0.065	0.270	0.623
	1000.0	0.085	0.363	0.552	0.406	0.196	0.108	0.378	0.830
	1200.0	0.060	0.270	0.671	0.504	0.247	0.121	0.471	0.977
	1400.0	0.048	0.227	0.726	0.563	0.268	0.129	0.546	0.998
70.0	200.0	0.763	0.224	0.013	0.112	0.081	0.005	0.096	0.310
	400.0	0.585	0.382	0.033	0.155	0.088	0.027	0.141	0.367
	600.0	0.316	0.568	0.116	0.220	0.103	0.062	0.205	0.456
	800.0	0.134	0.522	0.344	0.309	0.140	0.095	0.288	0.629
	1000.0	0.055	0.362	0.583	0.421	0.191	0.129	0.393	0.834
	1200.0	0.039	0.268	0.693	0.516	0.242	0.142	0.484	0.978
	1400.0	0.032	0.223	0.745	0.573	0.262	0.149	0.556	0.998

Paclitaxel dose (mg/m^2)	BEZ235 dose (mg)	Posterior probabilities (%) that Pr(DLT) is in interval: 0-0.16	0.16-0.35	0.35-1	Mean	SD	Quantiles 2.5%	50%	97.5%
80.0	200.0	0.596	0.378	0.026	0.148	0.090	0.009	0.137	0.352
	400.0	0.408	0.535	0.057	0.191	0.091	0.042	0.180	0.398
	600.0	0.177	0.658	0.165	0.253	0.100	0.093	0.242	0.477
	800.0	0.063	0.522	0.415	0.339	0.133	0.130	0.321	0.641
	1000.0	0.027	0.328	0.645	0.445	0.184	0.157	0.420	0.840
	1200.0	0.019	0.242	0.739	0.535	0.233	0.169	0.505	0.979
	1400.0	0.016	0.201	0.783	0.590	0.252	0.178	0.574	0.998
90.0	200.0	0.374	0.505	0.121	0.209	0.115	0.021	0.197	0.460
	400.0	0.224	0.596	0.180	0.249	0.110	0.062	0.239	0.487
	600.0	0.078	0.592	0.330	0.307	0.110	0.120	0.298	0.543
	800.0	0.024	0.401	0.575	0.387	0.133	0.161	0.376	0.674
	1000.0	0.012	0.242	0.746	0.484	0.178	0.186	0.467	0.854
	1200.0	0.008	0.182	0.810	0.567	0.221	0.200	0.546	0.981
	1400.0	0.007	0.149	0.844	0.618	0.238	0.210	0.608	0.998
100.0	200.0	0.198	0.454	0.348	0.302	0.158	0.050	0.283	0.655
	400.0	0.107	0.467	0.426	0.337	0.150	0.092	0.320	0.669
	600.0	0.035	0.397	0.567	0.389	0.143	0.147	0.375	0.698
	800.0	0.011	0.246	0.743	0.459	0.151	0.190	0.451	0.764
	1000.0	0.005	0.149	0.846	0.544	0.178	0.219	0.540	0.883
	1200.0	0.004	0.110	0.886	0.616	0.209	0.235	0.612	0.984
	1400.0	0.003	0.091	0.906	0.662	0.222	0.247	0.667	0.998

- A dose-limiting toxicity (DLT) is defined as an adverse event or abnormal laboratory value assessed as clinically relevant, occurring ≤ 28 days following the first administration of BEZ235 (Cycle 1) in combination with paclitaxel and standard Tz

BKM120 dual combination:

Summary of posterior distribution of DLT rates at Cycle 1, at end of study (dose escalation part) Dose determining set - BKM120/paclitaxel

Paclitaxel dose (mg/m^2)	BKM120 dose (mg)	Posterior probabilities (%) that Pr(DLT) is in interval: 0-0.16	0.16-0.35	0.35-1	Mean	SD	Quantiles 2.5%	50%	97.5%
60.0	20.0	0.998	0.002	0.000	0.016	0.023	0.000	0.006	0.083

Paclitaxel dose (mg/m^2)	BKM120 dose (mg)	Posterior probabilities (%) that Pr(DLT) is in interval: 0-0.16	0.16-0.35	0.35-1	Mean	SD	Quantiles 2.5%	50%	97.5%
	40.0	0.996	0.004	0.000	0.025	0.029	0.000	0.015	0.106
	60.0	0.988	0.012	0.000	0.044	0.036	0.005	0.034	0.139
	80.0	0.941	0.059	0.000	0.083	0.043	0.023	0.075	0.188
	100.0	0.586	0.400	0.014	0.155	0.072	0.047	0.144	0.324
	120.0	0.270	0.494	0.236	0.260	0.139	0.066	0.232	0.591
	150.0	0.123	0.333	0.544	0.418	0.226	0.089	0.382	0.878
70.0	20.0	0.996	0.004	0.000	0.022	0.029	0.000	0.011	0.103
	40.0	0.993	0.007	0.000	0.032	0.034	0.001	0.020	0.123
	60.0	0.980	0.020	0.000	0.050	0.039	0.005	0.040	0.153
	80.0	0.924	0.076	0.000	0.089	0.045	0.025	0.081	0.199
	100.0	0.552	0.432	0.016	0.161	0.072	0.052	0.150	0.329
	120.0	0.247	0.510	0.243	0.266	0.138	0.073	0.238	0.594
	150.0	0.109	0.339	0.552	0.423	0.224	0.098	0.386	0.879
80.0	20.0	0.985	0.015	0.000	0.036	0.040	0.000	0.023	0.142
	40.0	0.977	0.023	0.000	0.045	0.043	0.001	0.033	0.157
	60.0	0.955	0.045	0.000	0.064	0.047	0.007	0.052	0.183
	80.0	0.869	0.131	0.000	0.102	0.051	0.029	0.093	0.224
	100.0	0.479	0.500	0.021	0.174	0.073	0.060	0.164	0.341
	120.0	0.204	0.535	0.261	0.277	0.136	0.083	0.250	0.600
	150.0	0.086	0.345	0.568	0.432	0.220	0.110	0.395	0.881
90.0	20.0	0.907	0.090	0.003	0.068	0.065	0.000	0.050	0.234
	40.0	0.886	0.111	0.003	0.077	0.067	0.002	0.059	0.247
	60.0	0.840	0.155	0.005	0.095	0.068	0.010	0.079	0.267
	80.0	0.710	0.281	0.009	0.132	0.069	0.035	0.119	0.300
	100.0	0.345	0.600	0.054	0.202	0.083	0.071	0.192	0.390
	120.0	0.138	0.540	0.321	0.302	0.136	0.098	0.281	0.618
	150.0	0.056	0.328	0.616	0.453	0.214	0.128	0.421	0.886
100.0	20.0	0.646	0.279	0.075	0.146	0.123	0.003	0.113	0.468
	40.0	0.621	0.298	0.081	0.155	0.124	0.008	0.122	0.475
	60.0	0.564	0.342	0.093	0.171	0.123	0.020	0.140	0.486
	80.0	0.432	0.445	0.122	0.206	0.121	0.048	0.178	0.510
	100.0	0.183	0.588	0.229	0.270	0.121	0.090	0.251	0.557
	120.0	0.070	0.436	0.494	0.364	0.150	0.121	0.348	0.689
	150.0	0.028	0.246	0.726	0.502	0.208	0.156	0.487	0.900

Paclitaxel dose (mg/m^2)	BKM120 dose (mg)	Posterior probabilities (%) that Pr(DLT) is in interval: 0-0.16	0.16-0.35	0.35-1	Mean	SD	Quantiles 2.5%	50%	97.5%
- A dose-limiting toxicity (DLT) is defined as an adverse event or abnormal laboratory value assessed as clinically relevant, occurring ≤28 days following the first administration of BKM120 (Cycle 1) in combination with paclitaxel									

BKM120 triple-agent combination:

Summary of posterior distribution of DLT rates at Cycle 1, at end of study (dose escalation part) Dose determining set - BKM120/paclitaxel/trastuzumab

Paclitaxel dose (mg/m^2)	BKM120 dose (mg)	Posterior probabilities (%) that Pr(DLT) is in interval: -- 0-0.16	0.16-0.35	0.35-1	Mean	SD	Quantiles -- 2.5%	50%	97.5%
60.0	20.0	0.998	0.002	00	0.016	0.024	0.000	0.005	0.087
	40.0	0.995	0.005	00	0.026	0.031	0.000	0.015	0.113
	60.0	0.982	0.018	00	0.047	0.039	0.005	0.036	0.149
	80.0	0.913	0.087	00	0.090	0.047	0.026	0.081	0.206
	100.0	0.507	0.473	0.021	0.169	0.074	0.055	0.159	0.341
	120.0	0.203	0.516	0.282	0.282	0.138	0.078	0.259	0.598
	150.0	0.086	0.301	0.613	0.448	0.221	0.105	0.424	0.880
70.0	20.0	0.996	0.004	0.000	0.023	0.030	0.000	0.011	0.108
	40.0	0.991	0.009	0.000	0.033	0.036	0.001	0.021	0.129
	60.0	0.974	0.026	0.000	0.054	0.042	0.006	0.043	0.162
	80.0	0.892	0.107	0.000	0.097	0.049	0.029	0.088	0.214
	100.0	0.470	0.507	0.022	0.176	0.073	0.063	0.165	0.345
	120.0	0.179	0.530	0.291	0.288	0.136	0.087	0.265	0.600
	150.0	0.073	0.306	0.622	0.453	0.218	0.115	0.429	0.880
80.0	20.0	0.983	0.017	0.000	0.038	0.041	0.000	0.024	0.147
	40.0	0.972	0.028	0.000	0.048	0.045	0.001	0.035	0.164
	60.0	0.943	0.057	0.000	0.069	0.050	0.007	0.057	0.191
	80.0	0.828	0.172	0.001	0.111	0.053	0.033	0.102	0.237
	100.0	0.389	0.582	0.028	0.189	0.073	0.073	0.179	0.356
	120.0	0.135	0.552	0.313	0.300	0.133	0.101	0.277	0.604
	150.0	0.052	0.309	0.640	0.463	0.213	0.132	0.439	0.882

Paclitaxel dose (mg/m^2)	BKM120 dose (mg)	Posterior probabilities (%) that Pr(DLT) is in interval: -- 0-0.16	0.16-0.35	0.35-1	Mean	SD	Quantiles -- 2.5%	50%	97.5%
90.0	20.0	0.892	0.105	0.003	0.072	0.067	0.000	0.055	0.245
	40.0	0.867	0.129	0.004	0.082	0.069	0.002	0.066	0.256
	60.0	0.811	0.184	0.005	0.102	0.071	0.011	0.087	0.276
	80.0	0.648	0.340	0.011	0.143	0.071	0.040	0.131	0.312
	100.0	0.253	0.678	0.069	0.219	0.082	0.087	0.210	0.401
	120.0	0.080	0.534	0.385	0.327	0.132	0.120	0.309	0.622
	150.0	0.028	0.280	0.692	0.485	0.206	0.155	0.464	0.887
100.0	20.0	0.611	0.304	0.085	0.156	0.126	0.003	0.124	0.477
	40.0	0.582	0.326	0.092	0.165	0.126	0.008	0.134	0.484
	60.0	0.517	0.375	0.108	0.183	0.125	0.021	0.155	0.496
	80.0	0.367	0.489	0.144	0.221	0.122	0.055	0.196	0.519
	100.0	0.121	0.601	0.278	0.291	0.120	0.108	0.274	0.567
	120.0	0.036	0.393	0.571	0.390	0.145	0.147	0.377	0.693
	150.0	0.013	0.191	0.796	0.535	0.198	0.186	0.526	0.902

- A dose-limiting toxicity (DLT) is defined as an adverse event or abnormal laboratory value assessed as clinically relevant, occurring ≤28 days following the first administration of BKM120 (Cycle 1) in combination with paclitaxel and standard Tz

Secondary outcome result(s)

BEZ235 dual combination:

Best overall response as per Investigator review by treatment group Full analysis set - BEZ235/paclitaxel

	BEZ235 400 mg/ Ptx 70 mg (N=2) n (%)	BEZ235 400 mg/ Ptx 80 mg (N=3) n (%)	BEZ235 600 mg/ Ptx 80 mg (N=4) n (%)	BEZ235 800 mg/ Ptx 80 mg (N=26) n (%)	All BEZ235/ Ptx (N=35) n (%)
Best overall response					
Complete Response (CR)	0	0	0	0	0
Partial Response (PR)	0	0	0	3 (11.5)	3 (8.6)
Stable Disease (SD)	1 (50.0)	2 (66.7)	1 (25.0)	14 (53.8)	18 (51.4)
Progressive Disease (PD)	1 (50.0)	1 (33.3)	2 (50.0)	5 (19.2)	9 (25.7)

	BEZ235 400 mg/ Ptx 70 mg (N=2) n (%)	BEZ235 400 mg/ Ptx 80 mg (N=3) n (%)	BEZ235 600 mg/ Ptx 80 mg (N=4) n (%)	BEZ235 800 mg/ Ptx 80 mg (N=26) n (%)	All BEZ235/ Ptx (N=35) n (%)
Unknown	0	0	1 (25.0)	4 (15.4)	5 (14.3)
Objective Response Rate ORR (CR or PR)	0	0	0	3 (11.5)	3 (8.6)
90 % CI for ORR	[0.0; 77.6]	[0.0; 63.2]	[0.0; 52.7]	[3.2; 27.2]	[2.4; 20.7]
Disease control rate DCR (CR or PR or SD)	1 (50.0)	2 (66.7)	1 (25.0)	17 (65.4)	21 (60.0)
90 % CI for DCR	[2.5; 97.5]	[13.5; 98.3]	[1.3; 75.1]	[47.4; 80.6]	[44.7; 74.0]

-Estimate (90% CI) for ORR and DCR were obtained using exact binomial 90% confidence interval

BEZ235 triple-agent combination:

Best overall response as per Investigator review by treatment group Full analysis set - BEZ235/paclitaxel/Trastuzumab

	BEZ235 400 mg/ Ptx 80mg/ Tz (N=6) n (%)	BEZ235 600 mg/ Ptx 80mg/ Tz (N=5) n (%)	All BEZ235/ Ptx/Tz (N=11) n (%)
Best overall response			
Complete Response (CR)	1 (16.7)	1 (20.0)	2 (18.2)
Partial Response (PR)	3 (50.0)	1 (20.0)	4 (36.4)
Stable Disease (SD)	1 (16.7)	2 (40.0)	3 (27.3)
Progressive Disease (PD)	1 (16.7)	0	1 (9.1)
Unknown	0	1 (20.0)	1 (9.1)
Objective Response Rate ORR (CR or PR)	4 (66.7)	2 (40.0)	6 (54.5)
90 % CI for ORR	[27.1; 93.7]	[7.6; 81.1]	[27.1; 80.0]
Disease control rate DCR (CR or PR or SD)	5 (83.3)	4 (80.0)	9 (81.8)
90 % CI for DCR	[41.8; 99.1]	[34.3; 99.0]	[53.0; 96.7]

- Estimate (90%CI) for ORR and DCR were obtained using exact binomial 90% confidence interval

BKM120 dual combination:

Best overall response as per Investigator review by treatment group Full analysis set - BKM120/paclitaxel

	BKM120 40 mg/ Ptx 70 mg (N=1) n (%)	BKM120 40 mg/ Ptx 80 mg (N=5) n (%)	BKM120 60 mg/ Ptx 80 mg (N=3) n (%)	BKM120 80 mg/ Ptx 80 mg (N=4) n (%)	BKM120 100 mg/ Ptx 80 mg (N=36) n (%)	BKM120 120 mg/ Ptx 80 mg (N=4) n (%)	All BKM120/ Ptx (N=53) n (%)
Best overall response							
Complete Response (CR)	0	0	0	0	1 (2.8)	0	1 (1.9)
Partial Response (PR)	0	1 (20.0)	0	2 (50.0)	5 (13.9)	0	8 (15.1)
Stable Disease (SD)	1 (100.0)	2 (40.0)	2 (66.7)	1 (25.0)	20 (55.6)	1 (25.0)	27 (50.9)
Progressive Disease (PD)	0	2 (40.0)	1 (33.3)	0	9 (25.0)	2 (50.0)	14 (26.4)
Unknown	0	0	0	1 (25.0)	1 (2.8)	1 (25.0)	3 (5.7)
Objective Response Rate ORR (CR or PR)	0	1 (20.0)	0	2 (50.0)	6 (16.7)	0	9 (17.0)
90 % CI for ORR	[0.0; 95.0]	[1.0; 65.7]	[0.0; 63.2]	[9.8; 90.2]	[7.5; 30.3]	[0.0; 52.7]	[9.2; 27.8]
Disease control rate DCR (CR or PR or SD)	1 (100.0)	3 (60.0)	2 (66.7)	3 (75.0)	26 (72.2)	1 (25.0)	36 (67.9)
90 % CI for DCR	[5.0; 100.0]	[18.9; 92.4]	[13.5; 98.3]	[24.9; 98.7]	[57.5; 84.1]	[1.3; 75.1]	[55.9; 78.4]

- Estimate (90% CI) for ORR and DCR were obtained using exact binomial 90% confidence interval

BKM120 triple-agent combination:

Best overall response as per Investigator review by treatment group Full analysis set - BKM120/paclitaxel/Trastuzumab

	BKM120 100 mg/ Ptx 80mg/ Tz (N=11) n (%)	All BKM120/ Ptx/Tz (N=11) n (%)
Best overall response		
Complete Response (CR)	0	0
Partial Response (PR)	3 (27.3)	3 (27.3)
Stable Disease (SD)	5 (45.5)	5 (45.5)
Progressive Disease (PD)	2 (18.2)	2 (18.2)

	BKM120 100 mg/ Ptx 80mg/ Tz (N=11) n (%)	All BKM120/ Ptx/Tz (N=11) n (%)
Unknown	1 (9.1)	1 (9.1)
Objective Response Rate ORR (CR or PR)	3 (27.3)	3 (27.3)
90 % CI for ORR	[7.9; 56.4]	[7.9; 56.4]
Disease control rate DCR (CR or PR or SD)	8 (72.7)	8 (72.7)
90 % CI for DCR	[43.6; 92.1]	[43.6; 92.1]

Estimate (90%CI) for ORR and DCR were obtained using exact binomial 90% confidence interval

BEZ235 dual combination:

Summary of BEZ235 primary pharmacokinetic parameters by treatment after repeated oral daily dose of BEZ235 (Cycle 1, Day 8 and Cycle 1, Day 22) Full analysis set - BEZ235/paclitaxel

Cycle and Day of sampling	Treatment	AUC0-24 (h*ng/mL)	Cmax (ng/mL)	CL/F (L/h)	T1/2 (h)	Tmax (h)
Cycle 1 Day 8	BEZ235 400 mg/Ptx 70mg (N=2)	7170 [4700 ; 9630] (2)	554 [280 ; 827] (2)	41.5 [41.5 ; 41.5] (1)	4.57 [4.57 ; 4.57] (1)	13 [2.07 ; 23.9] (2)
	BEZ235 400 mg/Ptx 80mg (N=3)	2760 [1380 ; 3340] (3)	220 [179 ; 356] (3)	145 [120 ; 291] (3)	5.43 [2.56 ; 6.63] (3)	2.85 [1.97 ; 3.98] (3)
	BEZ235 600 mg/Ptx 80mg (N=4)	1100 [830 ; 13400] (3)	194 [152 ; 1020] (3)	546 [44.8 ; 723] (3)	5.93 [5.89 ; 5.97] (2)	2.92 [2.85 ; 4] (3)
	BEZ235 800 mg/Ptx 80mg (N=26)	11000 [1730 ; 39000] (15)	914 [37.4 ; 2270] (19)	72.6 [20.5 ; 462] (15)	4.41 [2.76 ; 17.5] (12)	3.98 [0.983 ; 8.3] (19)
Cycle 1 Day 22	BEZ235 400 mg/Ptx 70mg (N=2)	6550 [6450 ; 6650] (2)	491 [391 ; 590] (2)	62 [62 ; 62] (1)	4.95 [4.95 ; 4.95] (1)	4.32 [2.8 ; 5.83] (2)
	BEZ235 400 mg/Ptx 80mg (N=3)	923 [923 ; 923] (1)	122 [122 ; 122] (1)	433 [433 ; 433] (1)	7.13 [7.13 ; 7.13] (1)	0.917 [0.917 ; 0.917] (1)

Cycle and Day of sampling	Treatment	AUC0-24 (h*ng/mL)	Cmax (ng/mL)	CL/F (L/h)	T1/2 (h)	Tmax (h)
	BEZ235 600 mg/Ptx 80mg (N=4)	4850 [871 ; 8820] (2)	177 [68.4 ; 986] (3)	379 [68 ; 689] (2)	4.17 [3.61 ; 7.28] (3)	3 [2.97 ; 3.07] (3)
	BEZ235 800 mg/Ptx 80mg (N=26)	7130 [1870 ; 35100] (12)	643 [63.7 ; 2670] (15)	132 [24.6 ; 427] (10)	3.46 [2.17 ; 5.63] (8)	4 [1.5 ; 24] (15)

Median [Min; Max] (n)

Data from patients with less than six continuous days of BEZ235 daily dosing at the planned dose (dose assigned at study entry) prior to the C1D8 or C1D22 or vomiting within the 4 hours post-dose on the Day of PK sampling were excluded from the analysis.

BEZ235 triple-agent combination

Summary of BEZ235 primary pharmacokinetic parameters by treatment after repeated oral daily dose of BEZ235 (Cycle 1, Day 8 and Cycle 1, Day 22) Full analysis set - BEZ235/paclitaxel/trastuzumab

Cycle and Day of sampling	Treatment	AUC0-24 (h*ng/mL)	Cmax (ng/mL)	CL/F (L/h)	T1/2 (h)	Tmax (h)
Cycle 1 Day 8	BEZ235 400 mg/Ptx 80mg/Tz (N=6)	3590 [2190 ; 12200] (5)	374 [303 ; 851] (5)	111 [32.9 ; 182] (5)	3.99 [3.41 ; 7.71] (3)	3 [1.97 ; 7.98] (5)
	BEZ235 600 mg/Ptx 80mg/Tz (N=5)	9500 [7140 ; 15100] (4)	1110 [792 ; 1510] (4)	63.4 [39.8 ; 84] (4)	4.48 [3.87 ; 5.35] (3)	3.03 [2.95 ; 4] (4)
Cycle 1 Day 22	BEZ235 400 mg/Ptx 80mg/Tz (N=6)	2730 [1560 ; 3130] (3)	236 [75.6 ; 396] (5)	146 [128 ; 257] (3)	3.3 [2.46 ; 12.4] (3)	3 [2.93 ; 3.98] (5)
	BEZ235 600 mg/Ptx 80mg/Tz (N=5)	6520 [4820 ; 6820] (3)	704 [261 ; 881] (3)	92.1 [87.9 ; 124] (3)	4.37 [4.37 ; 4.37] (1)	3 [2 ; 5.97] (3)

Median [Min ; Max] (n)

Data from patients with less than six continuous days of BEZ235 daily dosing at the planned dose (dose assigned at study entry) prior to the C1D8 or C1D22 or vomiting within the 4 hours post-dose on the Day of PK sampling were excluded from the analysis.

BKM120 dual combination

Summary of BKM120 primary pharmacokinetic parameters by treatment after repeated oral daily dose of BKM120 (Cycle 1, Day 8 and Cycle 1, Day 22) Full analysis set - BKM120/paclitaxel

Cycle and Day of sampling	Treatment	AUC0-24 (h*ng/mL)	Cmax (ng/mL)	CL/F (L/h)	T1/2 (h)	Tmax (h)
Cycle 1 Day 8	BKM120 40 mg/Ptx 70mg (N=1)	7870 [7870 ; 7870] (1)	753 [753 ; 753] (1)	5.08 [5.08 ; 5.08] (1)	28.8 [28.8 ; 28.8] (1)	1.48 [1.48 ; 1.48] (1)
	BKM120 40 mg/Ptx 80mg (N=5)	8290 [3590 ; 19900] (4)	724 [223 ; 1370] (4)	4.83 [2.01 ; 11.1] (4)	28.2 [24.9 ; 31.6] (2)	1.43 [0.933 ; 1.95] (4)
	BKM120 60 mg/Ptx 80mg (N=3)	8580 [8440 ; 8720] (2)	591 [518 ; 664] (2)	7 [6.88 ; 7.11] (2)	22.6 [18.9 ; 26.4] (2)	1.93 [1 ; 2.85] (2)
	BKM120 80 mg/Ptx 80mg (N=4)	11300 [6990 ; 15600] (2)	980 [630 ; 1330] (2)	8.29 [5.14 ; 11.4] (2)	9.74 [9.74 ; 9.74] (1)	2.48 [0.983 ; 3.98] (2)
	BKM120 100 mg/Ptx 80mg (N=36)	15600 [4550 ; 25600] (27)	980 [291 ; 1570] (27)	6.4 [4.26 ; 22] (24)	20.6 [11.4 ; 68.4] (12)	2.07 [0.483 ; 5.98] (27)
	BKM120 120 mg/Ptx 80mg (N=4)	21200 [17300 ; 27900] (4)	1450 [1350 ; 1820] (4)	5.66 [4.3 ; 6.95] (4)	25.5 [16.9 ; 34] (2)	1.74 [0.95 ; 4.02] (4)
Cycle 1 Day 22	BKM120 40 mg/Ptx 70mg (N=1)	11100 [11100 ; 11100] (1)	576 [576 ; 576] (1)	3.61 [3.61 ; 3.61] (1)		24 [24 ; 24] (1)
	BKM120 40 mg/Ptx 80mg (N=5)	9420 [3840 ; 14200] (4)	736 [285 ; 929] (4)	4.25 [2.81 ; 10.4] (4)	46.2 [46.2 ; 46.2] (1)	2 [0.983 ; 2.05] (4)
	BKM120 60 mg/Ptx 80mg (N=3)	9670 [8790 ; 10500] (2)	695 [634 ; 755] (2)	6.26 [5.69 ; 6.83] (2)		2 [1 ; 3] (2)
	BKM120 80 mg/Ptx 80mg (N=4)	16900 [16100 ; 17700] (2)	1550 [1500 ; 1590] (2)	4.75 [4.52 ; 4.98] (2)	17.1 [17.1 ; 17.1] (1)	2.03 [1.07 ; 3] (2)
	BKM120 100 mg/Ptx 80mg (N=36)	13700 [3940 ; 25400] (20)	1030 [317 ; 2000] (21)	7.36 [3.93 ; 25.4] (18)	27 [17 ; 43.5] (10)	2 [0.467 ; 8] (21)

Cycle and Day of sampling	Treatment	AUC0-24 (h*ng/mL)	Cmax (ng/mL)	CL/F (L/h)	T1/2 (h)	Tmax (h)

Median [Min ; Max] (n)

Data from patients with less than six continuous days of BKM120 daily dosing at the planned dose (dose assigned at study entry) prior to the C1D8 or C1D22 or vomiting within the 4 hours post-dose on the Day of PK sampling were excluded from the analysis.

BKM120 triple-agent combination

Summary of BKM120 primary pharmacokinetic parameters by treatment after repeated oral daily dose of BKM120 (Cycle 1, Day 8 and Cycle 1, Day 22) Full analysis set - BKM120/paclitaxel/trastuzumab

Cycle and Day of sampling	Treatment	AUC0-24 (h*ng/mL)	Cmax (ng/mL)	CL/F (L/h)	T1/2 (h)	Tmax (h)
Cycle 1 Day 8	BKM120 100 mg/Ptx 80mg/Tz (N=11)	15800 [9990 ; 32200] (10)	1440 [928 ; 2020] (10)	5.92 [3.11 ; 10] (9)	19.2 [17.1 ; 21.2] (2)	2.5 [1 ; 22.8] (10)
Cycle 1 Day 22	BKM120 100 mg/Ptx 80mg/Tz (N=11)	18100 [11400 ; 30900] (8)	1450 [803 ; 2770] (8)	4.95 [2.59 ; 8.81] (7)	33.8 [5.84 ; 65] (4)	2 [0.083 ; 4] (8)

Median [Min ; Max] (n)

Data from patients with less than six continuous days of BKM120 daily dosing at the planned dose (dose assigned at study entry) prior to the C1D8 or C1D22 or vomiting within the 4 hours post-dose on the Day of PK sampling were excluded from the analysis.

Paclitaxel PK results

Paclitaxel in combination with BEZ235 with or without trastuzumab

Summary of paclitaxel primary pharmacokinetic parameters by treatment, administered alone (Cycle 1, Day 1) or in combination with repeated oral daily dose of BEZ235 (Cycle 1, Day 8 and Cycle 1, Day 22) Full analysis set - BEZ235/paclitaxel

Cycle and Day of sampling	Treatment	AUC0-24 (h*ng/mL)	Cmax (ng/mL)	T1/2 (h)	Tmax (h)
Cycle 1 Day 1	BEZ235 400 mg/Ptx 70mg (N=2)	3590 [3170 ; 4010] (2)	2910 [2570 ; 3240] (2)	10.8 [10.7 ; 11] (2)	1.02 [1 ; 1.03] (2)
	BEZ235 400 mg/Ptx 80mg (N=3)	4040 [3610 ; 5950] (3)	2270 [2200 ; 3310] (3)	15.2 [11.8 ; 18.7] (2)	1.1 [1 ; 1.17] (3)
	BEZ235 600 mg/Ptx 80mg (N=4)	3310 [2860 ; 3950] (4)	2050 [2000 ; 2960] (4)	10.1 [7.64 ; 12.3] (4)	1.04 [1 ; 1.07] (4)
	BEZ235 800 mg/Ptx 80mg (N=26)	3480 [1600 ; 31100] (26)	2240 [1120 ; 50400] (26)	10.7 [7.95 ; 14.8] (26)	1 [1 ; 1.37] (26)
Cycle 1 Day 8	BEZ235 400 mg/Ptx 70mg (N=2)	3430 [3190 ; 3670] (2)	2460 [2200 ; 2720] (2)	10.8 [9.93 ; 11.7] (2)	1.02 [1 ; 1.03] (2)
	BEZ235 400 mg/Ptx 80mg (N=3)	3380 [2790 ; 6270] (3)	2230 [1710 ; 4740] (3)	12.2 [11.2 ; 13.2] (2)	1.02 [0.983 ; 1.03] (3)
	BEZ235 600 mg/Ptx 80mg (N=4)	3490 [3060 ; 4430] (3)	3100 [1650 ; 3330] (3)	10.2 [9.42 ; 10.6] (3)	1 [1 ; 1.03] (3)
	BEZ235 800 mg/Ptx 80mg (N=26)	3300 [1550 ; 7170] (24)	2140 [1130 ; 4260] (25)	11.2 [7.41 ; 16.8] (22)	1.05 [0.867 ; 1.25] (25)
Cycle 1 Day 22	BEZ235 400 mg/Ptx 70mg (N=2)	3700 [3200 ; 4210] (2)	2620 [2580 ; 2650] (2)	10.1 [10.1 ; 10.1] (1)	1.05 [1.03 ; 1.07] (2)
	BEZ235 400 mg/Ptx 80mg (N=3)	2840 [2750 ; 2930] (2)	1880 [1270 ; 2480] (2)	18.4 [18 ; 18.8] (2)	1.02 [1 ; 1.03] (2)
	BEZ235 600 mg/Ptx 80mg (N=4)	3390 [2640 ; 3930] (3)	2350 [1760 ; 2990] (3)	10.8 [8.73 ; 12.8] (2)	1.03 [1.03 ; 1.05] (3)
	BEZ235 800 mg/Ptx 80mg (N=26)	3410 [2010 ; 17000] (21)	2200 [842 ; 25400] (22)	11.8 [4.09 ; 21.2] (22)	1.03 [1 ; 1.25] (22)

Median [Min ; Max] (n)

Summary of paclitaxel primary pharmacokinetic parameters by treatment, administered alone (Cycle 1, Day 1) or in combination with repeated oral daily dose of BEZ235 (Cycle 1, Day 8 and Cycle 1, Day 22) Full analysis set - BEZ235/paclitaxel/trastuzumab

Cycle and Day of sampling	Treatment	AUC0-24 (h*ng/mL)	Cmax (ng/mL)	T1/2 (h)	Tmax (h)
Cycle 1 Day 1	BEZ235 400 mg/Ptx 80mg/Tz (N=6)	3840 [2360 ; 78000] (6)	3120 [1400 ; 129000] (6)	11 [9.03 ; 12.8] (6)	1.01 [1 ; 1.5] (6)
	BEZ235 600 mg/Ptx 80mg/Tz (N=5)	3230 [2540 ; 5670] (5)	1980 [1720 ; 4400] (5)	11.3 [9.83 ; 12.4] (5)	1 [1 ; 1.27] (5)

Cycle and Day of sampling	Treatment	AUC0-24 (h*ng/mL)	Cmax (ng/mL)	T1/2 (h)	Tmax (h)
Cycle 1 Day 8	BEZ235 400 mg/Ptx 80mg/Tz (N=6)	3530 [2430 ; 47500] (6)	2600 [1530 ; 77100] (6)	10.7 [9.14 ; 11.6] (6)	1 [0.933 ; 1.08] (6)
	BEZ235 600 mg/Ptx 80mg/Tz (N=5)	4250 [3110 ; 5710] (5)	2440 [1940 ; 6940] (5)	11.4 [8.42 ; 14] (5)	1.17 [1 ; 1.33] (5)
Cycle 1 Day 22	BEZ235 400 mg/Ptx 80mg/Tz (N=6)	3770 [2890 ; 20500] (4)	2500 [1630 ; 30600] (5)	10.4 [9.85 ; 13.4] (5)	1 [1 ; 1.1] (5)
	BEZ235 600 mg/Ptx 80mg/Tz (N=5)	3300 [2430 ; 4410] (3)	2410 [1140 ; 2970] (3)	12.4 [9.38 ; 16.7] (3)	1 [1 ; 1.05] (3)

Median [Min ; Max] (n)

Paclitaxel in combination with BKM120 with or without trastuzumab

Summary of paclitaxel primary pharmacokinetic parameters by treatment, administered alone (Cycle 1, Day 1) or in combination with repeated oral daily dose of BKM120 (Cycle 1, Day 8 and Cycle 1, Day 22) Full analysis set - BKM120/paclitaxel

Cycle and Day of sampling	Treatment	AUC0-24 (h*ng/mL)	Cmax (ng/mL)	T1/2 (h)	Tmax (h)
Cycle 1 Day 1	BKM120 40 mg/Ptx 70mg (N=1)	2990 [2990 ; 2990] (1)	2520 [2520 ; 2520] (1)	12.7 [12.7 ; 12.7] (1)	1 [1 ; 1] (1)
	BKM120 40 mg/Ptx 80mg (N=5)	4800 [2410 ; 4940] (5)	3340 [1660 ; 4120] (5)	12.2 [8.86 ; 14.5] (4)	1.05 [1 ; 1.17] (5)
	BKM120 60 mg/Ptx 80mg (N=3)	4250 [4230 ; 13200] (3)	3860 [3680 ; 4050] (3)	15.3 [9.57 ; 21.1] (2)	1 [1 ; 1] (3)
	BKM120 80 mg/Ptx 80mg (N=4)	2490 [2040 ; 4880] (4)	1550 [892 ; 2840] (4)	11.3 [10 ; 12.5] (2)	1.13 [1.03 ; 1.33] (4)
	BKM120 100 mg/Ptx 80mg (N=36)	3280 [1450 ; 27000] (35)	2510 [575 ; 42800] (35)	10.3 [7.72 ; 18.5] (34)	1.02 [1 ; 1.33] (35)
	BKM120 120 mg/Ptx 80mg (N=4)	2600 [1950 ; 3720] (4)	1820 [1360 ; 2230] (4)	11.6 [10.2 ; 13.1] (4)	1.08 [1 ; 1.33] (4)
Cycle 1 Day 8	BKM120 40 mg/Ptx 70mg (N=1)	2300 [2300 ; 2300] (1)	1710 [1710 ; 1710] (1)	14.1 [14.1 ; 14.1] (1)	1.08 [1.08 ; 1.08] (1)
	BKM120 40 mg/Ptx 80mg (N=5)	4310 [1710 ; 8640] (5)	3090 [929 ; 4950] (5)	12.6 [10.9 ; 13.5] (5)	1.03 [0.983 ; 1.08] (5)

Cycle and Day of sampling	Treatment	AUC0-24 (h*ng/mL)	Cmax (ng/mL)	T1/2 (h)	Tmax (h)
	BKM120 60 mg/Ptx 80mg (N=3)	4480 [2470 ; 6030] (3)	3510 [1470 ; 4360] (3)	11.6 [9.24 ; 13.7] (3)	1 [1 ; 1] (3)
	BKM120 80 mg/Ptx 80mg (N=4)	3650 [3310 ; 3870] (3)	2670 [2560 ; 3510] (3)	12.1 [10.8 ; 13.1] (3)	1.13 [1.02 ; 1.15] (3)
	BKM120 100 mg/Ptx 80mg (N=36)	3330 [1670 ; 10100] (32)	2290 [547 ; 26900] (33)	10.9 [3.75 ; 22.8] (31)	1.05 [0.95 ; 1.67] (33)
	BKM120 120 mg/Ptx 80mg (N=4)	3680 [2540 ; 4060] (4)	2070 [1590 ; 2200] (4)	9.73 [8.88 ; 14.9] (4)	1.11 [1 ; 1.2] (4)
Cycle 1 Day 22	BKM120 40 mg/Ptx 70mg (N=1)	2840 [2840 ; 2840] (1)	2260 [2260 ; 2260] (1)	13 [13 ; 13] (1)	1.08 [1.08 ; 1.08] (1)
	BKM120 40 mg/Ptx 80mg (N=5)	3960 [1810 ; 6980] (5)	2570 [1210 ; 4220] (5)	10.1 [9.22 ; 22.7] (5)	1.08 [1 ; 1.5] (5)
	BKM120 60 mg/Ptx 80mg (N=3)	3310 [1760 ; 5470] (3)	2690 [424 ; 3530] (3)	12.7 [11.1 ; 14.4] (2)	1 [0.983 ; 1] (3)
	BKM120 80 mg/Ptx 80mg (N=4)	3310 [2480 ; 4730] (3)	2360 [1490 ; 4170] (3)	16.9 [10.5 ; 20.1] (3)	1.03 [1.03 ; 1.08] (3)
	BKM120 100 mg/Ptx 80mg (N=36)	3150 [1310 ; 121000] (24)	2290 [464 ; 287000] (24)	10.7 [6.31 ; 21.4] (23)	1.03 [0.867 ; 2.5] (24)

Median [Min ; Max] (n)

Summary of paclitaxel primary pharmacokinetic parameters by treatment, administered alone (Cycle 1, Day 1) or in combination with repeated oral daily dose of BKM120 (Cycle 1, Day 8 and Cycle 1, Day 22) Full analysis set - BKM120/paclitaxel/Trastuzumab

Cycle and Day of sampling	Treatment	AUC0-24 (h*ng/mL)	Cmax (ng/mL)	T1/2 (h)	Tmax (h)
Cycle 1 Day 1	BKM120 100 mg/Ptx 80mg/Tz (N=11)	3600 [2770 ; 4890] (11)	2620 [1750 ; 3780] (11)	10.3 [7.87 ; 13.8] (10)	1.08 [1 ; 1.58] (11)
Cycle 1 Day 8	BKM120 100 mg/Ptx 80mg/Tz (N=11)	4030 [2360 ; 7080] (11)	3430 [1840 ; 9050] (11)	12.1 [8.15 ; 15.6] (11)	1 [1 ; 1.12] (11)
Cycle 1 Day 22	BKM120 100 mg/Ptx 80mg/Tz (N=11)	4550 [2750 ; 6290] (9)	3020 [1730 ; 6010] (9)	11.1 [8.52 ; 14.6] (9)	1.05 [0.917 ; 122] (9)

Median [Min ; Max] (n)

Summary of Safety

Safety Results

BEZ235 dual combination:

Frequent AEs (greater than or equal to 10%) in all patients and at MTD, regardless of. study drug relationship, by system organ class (SOC) and treatment group Safety set - BEZ235/paclitaxel

Primary System Organ Class	BEZ235 400 mg/ Ptx 70mg N=3 n (%)	BEZ235 400 mg/ Ptx 80mg N=2 n (%)	BEZ235 600 mg/ Ptx 80mg N=4 n (%)	BEZ235 800 mg/ Ptx 80mg N=26 n (%)	All BEZ235/ Ptx N=35 n (%)
-Total	3 (100.0)	2 (100.0)	4 (100.0)	26 (100.0)	35 (100.0)
Gastrointestinal disorders	3 (100.0)	2 (100.0)	4 (100.0)	26 (100.0)	35 (100.0)
General disorders and administration site conditions	2 (66.7)	1 (50.0)	4 (100.0)	26 (100.0)	33 (94.3)
Nervous system disorders	1 (33.3)	1 (50.0)	2 (50.0)	20 (76.9)	24 (68.6)
Metabolism and nutrition disorders	1 (33.3)	2 (100.0)	1 (25.0)	18 (69.2)	22 (62.9)
Infections and infestations	3 (100.0)	1 (50.0)	2 (50.0)	15 (57.7)	21 (60.0)
Skin and subcutaneous tissue disorders	2 (66.7)	0	2 (50.0)	17 (65.4)	21 (60.0)
Investigations	2 (66.7)	0	1 (25.0)	16 (61.5)	19 (54.3)
Musculoskeletal and connective tissue disorders	1 (33.3)	0	2 (50.0)	16 (61.5)	19 (54.3)
Blood and lymphatic system disorders	1 (33.3)	2 (100.0)	2 (50.0)	13 (50.0)	18 (51.4)
Respiratory, thoracic and mediastinal disorders	1 (33.3)	0	0	14 (53.8)	15 (42.9)
Psychiatric disorders	2 (66.7)	0	1 (25.0)	7 (26.9)	10 (28.6)
Cardiac disorders	0	0	0	7 (26.9)	7 (20.0)
Renal and urinary disorders	0	0	1 (25.0)	3 (11.5)	4 (11.4)
Vascular disorders	0	1 (50.0)	0	3 (11.5)	4 (11.4)
Injury, poisoning and procedural complications	0	0	0	3 (11.5)	3 (8.6)

Primary System Organ Class	BEZ235 400 mg/ Ptx 70mg N=3 n (%)	BEZ235 400 mg/ Ptx 80mg N=2 n (%)	BEZ235 600 mg/ Ptx 80mg N=4 n (%)	BEZ235 800 mg/ Ptx 80mg N=26 n (%)	All BEZ235/ Ptx N=35 n (%)

- Primary system organ classes are sorted in descending frequency, as reported in the all patients column.
- A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.
- A patient with multiple adverse events within a primary system organ class is counted only once in the total row.
- Only AEs occurring after C1D1 and within 28 days of the last study treatment are reported

BEZ235 triple-agent combination:

Frequent AEs (greater than or equal to 10% in all patients and at MTD), regardless of study drug relationship, by system organ class (SOC) and treatment group Safety set - BEZ235/paclitaxel/trastuzumab

Primary System Organ Class	BEZ235 400 mg/ Ptx 80mg/ Tz N=6 n (%)	BEZ235 600 mg/ Ptx 80mg/ Tz N=5 n (%)	All BEZ235/ Ptx/Tz N=11 n (%)
Total	6 (100.0)	5 (100.0)	11 (100.0)
Blood and lymphatic system disorders	6 (100.0)	5 (100.0)	11 (100.0)
Gastrointestinal disorders	6 (100.0)	5 (100.0)	11 (100.0)
General disorders and administration site conditions	6 (100.0)	5 (100.0)	11 (100.0)
Infections and infestations	5 (83.3)	4 (80.0)	9 (81.8)
Nervous system disorders	6 (100.0)	3 (60.0)	9 (81.8)
Respiratory, thoracic and mediastinal disorders	4 (66.7)	5 (100.0)	9 (81.8)
Skin and subcutaneous tissue disorders	5 (83.3)	4 (80.0)	9 (81.8)
Metabolism and nutrition disorders	6 (100.0)	2 (40.0)	8 (72.7)
Musculoskeletal and connective tissue disorders	5 (83.3)	3 (60.0)	8 (72.7)
Investigations	4 (66.7)	3 (60.0)	7 (63.6)
Eye disorders	4 (66.7)	2 (40.0)	6 (54.5)
Vascular disorders	3 (50.0)	2 (40.0)	5 (45.5)
Psychiatric disorders	3 (50.0)	1 (20.0)	4 (36.4)
Renal and urinary disorders	2 (33.3)	2 (40.0)	4 (36.4)
Reproductive system and breast disorders	2 (33.3)	1 (20.0)	3 (27.3)

Primary System Organ Class	BEZ235 400 mg/ Ptx 80mg/ Tz N=6 n (%)	BEZ235 600 mg/ Ptx 80mg/ Tz N=5 n (%)	All BEZ235/ Ptx/Tz N=11 n (%)
Cardiac disorders	1 (16.7)	1 (20.0)	2 (18.2)

- Primary system organ classes are sorted in descending frequency, as reported in the all patients column.
- A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.
- A patient with multiple adverse events within a primary system organ class is counted only once in the total row.
- Only AEs occurring after C1D1 and within 28 days of the last study treatment are reported

BKM120 dual combination:

Frequent AEs (greater than or equal to 10%) in all patients and at MTD), regardless of study drug relationship, by system organ class (SOC) and treatment group Safety set - BKM120/paclitaxel

Primary System Organ Class	BKM120 40 mg/ Ptx 70mg N=1 n (%)	BKM120 40 mg/ Ptx 80mg N=5 n (%)	BKM120 60 mg/ Ptx 80mg N=3 n (%)	BKM120 80 mg/ Ptx 80mg N=4 n (%)	BKM120 100 mg/ Ptx 70mg N=1 n (%)	BKM120 100 mg/ Ptx 80mg N=35 n (%)	BKM120 120 mg/ Ptx 70mg N=1 n (%)	BKM120 120 mg/ Ptx 80mg N=3 n (%)	All BKM120/ Ptx N=53 n (%)
-Total	1 (100.0)	5 (100.0)	3 (100.0)	4 (100.0)	1 (100.0)	35 (100.0)	1 (100.0)	3 (100.0)	53 (100.0)
Gastrointestinal disorders	1 (100.0)	4 (80.0)	2 (66.7)	4 (100.0)	1 (100.0)	33 (94.3)	1 (100.0)	3 (100.0)	49 (92.5)
General disorders and administration site conditions	1 (100.0)	5 (100.0)	2 (66.7)	3 (75.0)	1 (100.0)	30 (85.7)	1 (100.0)	3 (100.0)	46 (86.8)
Metabolism and nutrition disorders	1 (100.0)	4 (80.0)	3 (100.0)	3 (75.0)	1 (100.0)	30 (85.7)	1 (100.0)	3 (100.0)	46 (86.8)
Skin and subcutaneous tissue disorders	1 (100.0)	2 (40.0)	1 (33.3)	3 (75.0)	1 (100.0)	27 (77.1)	1 (100.0)	1 (33.3)	37 (69.8)
Respiratory, thoracic and mediastinal disorders	1 (100.0)	5 (100.0)	1 (33.3)	2 (50.0)	0	23 (65.7)	0	3 (100.0)	35 (66.0)

Primary System Organ Class	BKM120 40 mg/ Ptx 70mg N=1 n (%)	BKM120 40 mg/ Ptx 80mg N=5 n (%)	BKM120 60 mg/ Ptx 80mg N=3 n (%)	BKM120 80 mg/ Ptx 80mg N=4 n (%)	BKM120 100 mg/ Ptx 70mg N=1 n (%)	BKM120 100 mg/ Ptx 80mg N=35 n (%)	BKM120 120 mg/ Ptx 70mg N=1 n (%)	BKM120 120 mg/ Ptx 80mg N=3 n (%)	All BKM120/ Ptx N=53 n (%)
Nervous system disorders	1 (100.0)	1 (20.0)	0	3 (75.0)	0	27 (77.1)	0	2 (66.7)	34 (64.2)
Infections and infestations	1 (100.0)	3 (60.0)	1 (33.3)	2 (50.0)	1 (100.0)	19 (54.3)	1 (100.0)	1 (33.3)	29 (54.7)
Blood and lymphatic system disorders	1 (100.0)	3 (60.0)	1 (33.3)	2 (50.0)	0	19 (54.3)	0	2 (66.7)	28 (52.8)
Investigations	0	1 (20.0)	0	2 (50.0)	1 (100.0)	21 (60.0)	0	3 (100.0)	28 (52.8)
Musculoskeletal and connective tissue disorders	0	4 (80.0)	0	2 (50.0)	1 (100.0)	20 (57.1)	0	1 (33.3)	28 (52.8)
Psychiatric disorders	0	0	1 (33.3)	2 (50.0)	0	16 (45.7)	0	2 (66.7)	21 (39.6)
Eye disorders	0	1 (20.0)	0	2 (50.0)	0	9 (25.7)	0	0	12 (22.6)
Injury, poisoning and procedural complications	0	1 (20.0)	0	1 (25.0)	0	4 (11.4)	0	1 (33.3)	7 (13.2)
Vascular disorders	0	2 (40.0)	0	2 (50.0)	0	2 (5.7)	0	1 (33.3)	7 (13.2)
Cardiac disorders	0	0	0	0	0	5 (14.3)	0	1 (33.3)	6 (11.3)
Renal and urinary disorders	0	0	0	0	0	6 (17.1)	0	0	6 (11.3)
Ear and labyrinth disorders	0	0	0	1 (25.0)	0	4 (11.4)	0	0	5 (9.4)

- Primary system organ classes are sorted in descending frequency, as reported in the all patients column.

- A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.

- A patient with multiple adverse events within a primary system organ class is counted only once in the total row.

- Only AEs occurring after C1D1 and within 28 days of the last study treatment are reported

BKM120 triple agent combination:

Frequent AEs (greater than or equal to 10%) in all patients and at MTD, regardless of study drug relationship, by system organ class (SOC) and treatment group Safety set - BKM120/paclitaxel/Trastuzumab

Primary System Organ Class	BKM120 100 mg/ Ptx 80mg/ Tz N=11 n (%)	All BKM120/ Ptx/Tz N=11 n (%)
-Total	11 (100.0)	11 (100.0)
Gastrointestinal disorders	11 (100.0)	11 (100.0)
General disorders and administration site conditions	11 (100.0)	11 (100.0)
Nervous system disorders	9 (81.8)	9 (81.8)
Blood and lymphatic system disorders	7 (63.6)	7 (63.6)
Infections and infestations	7 (63.6)	7 (63.6)
Metabolism and nutrition disorders	7 (63.6)	7 (63.6)
Musculoskeletal and connective tissue disorders	7 (63.6)	7 (63.6)
Respiratory, thoracic and mediastinal disorders	7 (63.6)	7 (63.6)
Skin and subcutaneous tissue disorders	7 (63.6)	7 (63.6)
Investigations	5 (45.5)	5 (45.5)
Psychiatric disorders	5 (45.5)	5 (45.5)
Ear and labyrinth disorders	4 (36.4)	4 (36.4)
Eye disorders	3 (27.3)	3 (27.3)
Renal and urinary disorders	3 (27.3)	3 (27.3)
Vascular disorders	3 (27.3)	3 (27.3)

- Primary system organ classes are sorted in descending frequency, as reported in the all patients column.
- A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.
- A patient with multiple adverse events within a primary system organ class is counted only once in the total row.
- Only AEs occurring after C1D1 and within 28 days of the last study treatment are reported

Most Frequently Reported AEs Overall by Preferred Term n (%)

BEZ235 dual combination:

Frequent AEs (all grades, greater than or equal to 10%) in all patients and at MTD, regardless of study drug relationship, by preferred term and treatment group (Safety set - BEZ235/paclitaxel)

Preferred term	BEZ235 400 mg/ Ptx 70mg N=3 n (%)	BEZ235 400 mg/ Ptx 80mg N=2 n (%)	BEZ235 600 mg/ Ptx 80mg N=4 n (%)	BEZ235 800 mg/ Ptx 80mg N=26 n (%)	All BEZ235/ Ptx N=35 n (%)
-Total	3 (100.0)	2 (100.0)	4 (100.0)	26 (100.0)	35 (100.0)
Diarrhea	1 (33.3)	1 (50.0)	4 (100.0)	24 (92.3)	30 (85.7)
Nausea	2 (66.7)	1 (50.0)	3 (75.0)	21 (80.8)	27 (77.1)
Vomiting	2 (66.7)	1 (50.0)	2 (50.0)	16 (61.5)	21 (60.0)
Alopecia	1 (33.3)	0	2 (50.0)	13 (50.0)	16 (45.7)
Asthenia	0	1 (50.0)	1 (25.0)	14 (53.8)	16 (45.7)
Anaemia	1 (33.3)	2 (100.0)	2 (50.0)	10 (38.5)	15 (42.9)
Fatigue	1 (33.3)	1 (50.0)	2 (50.0)	11 (42.3)	15 (42.9)
Decreased appetite	1 (33.3)	0	0	12 (46.2)	13 (37.1)
Stomatitis	0	0	1 (25.0)	10 (38.5)	11 (31.4)
Dysgeusia	1 (33.3)	0	1 (25.0)	7 (26.9)	9 (25.7)
Dyspepsia	0	0	1 (25.0)	8 (30.8)	9 (25.7)
Abdominal pain	0	0	0	8 (30.8)	8 (22.9)
Hyperglycemia	0	2 (100.0)	1 (25.0)	5 (19.2)	8 (22.9)
Cough	1 (33.3)	0	0	6 (23.1)	7 (20.0)
Neurotoxicity	0	0	1 (25.0)	6 (23.1)	7 (20.0)
Pyrexia	1 (33.3)	0	0	6 (23.1)	7 (20.0)
Abdominal pain upper	0	0	0	6 (23.1)	6 (17.1)
Chest pain	1 (33.3)	0	1 (25.0)	4 (15.4)	6 (17.1)
Constipation	0	0	0	6 (23.1)	6 (17.1)
Dermatitis acneiform	1 (33.3)	0	1 (25.0)	4 (15.4)	6 (17.1)
Myalgia	0	0	1 (25.0)	5 (19.2)	6 (17.1)
Nasopharyngitis	1 (33.3)	0	0	5 (19.2)	6 (17.1)
Oedema peripheral	1 (33.3)	0	0	5 (19.2)	6 (17.1)
Alanine aminotransferase increased	0	0	0	5 (19.2)	5 (14.3)
Dyspnoea	0	0	0	5 (19.2)	5 (14.3)
Headache	0	0	0	5 (19.2)	5 (14.3)
Hypophosphataemia	0	0	0	5 (19.2)	5 (14.3)
Paraesthesia	0	1 (50.0)	1 (25.0)	3 (11.5)	5 (14.3)

Preferred term	BEZ235 400 mg/ Ptx 70mg N=3 n (%)	BEZ235 400 mg/ Ptx 80mg N=2 n (%)	BEZ235 600 mg/ Ptx 80mg N=4 n (%)	BEZ235 800 mg/ Ptx 80mg N=26 n (%)	All BEZ235/ Ptx N=35 n (%)
Peripheral sensory neuropathy	1 (33.3)	0	0	4 (15.4)	5 (14.3)
Aspartate aminotransferase increased	0	0	0	4 (15.4)	4 (11.4)
Back pain	0	0	1 (25.0)	3 (11.5)	4 (11.4)
Depression	0	0	1 (25.0)	3 (11.5)	4 (11.4)
Epistaxis	1 (33.3)	0	0	3 (11.5)	4 (11.4)
Erythema	0	0	0	4 (15.4)	4 (11.4)
Hyponatremia	0	2 (100.0)	1 (25.0)	1 (3.8)	4 (11.4)
Musculoskeletal pain	0	0	0	4 (15.4)	4 (11.4)
Nail toxicity	0	0	0	4 (15.4)	4 (11.4)
Neutropenia	0	0	0	4 (15.4)	4 (11.4)
Pain in extremity	0	0	0	4 (15.4)	4 (11.4)
Polyneuropathy	0	0	1 (25.0)	3 (11.5)	4 (11.4)
Abdominal discomfort	0	0	0	3 (11.5)	3 (8.6)
Discomfort	0	0	0	3 (11.5)	3 (8.6)
Flatulence	0	0	0	3 (11.5)	3 (8.6)
Hypoalbuminemia	0	0	0	3 (11.5)	3 (8.6)
Insomnia	0	0	0	3 (11.5)	3 (8.6)
Leukopenia	0	0	0	3 (11.5)	3 (8.6)
Neutrophil count decreased	0	0	0	3 (11.5)	3 (8.6)
Pruritus	0	0	0	3 (11.5)	3 (8.6)
Sepsis	0	0	0	3 (11.5)	3 (8.6)

- Preferred terms are sorted in descending frequency, as reported in the all patients column.
- A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.
- A patient with multiple adverse events is counted only once in the total row.
- Only AEs occurring after C1D1 and within 28 days of the last study treatment are reported.

BEZ235 triple-agent combination:

Frequent AEs (greater than or equal to 10%) in all patients and at MTD, regardless of study drug relationship, by preferred term and treatment group (Safety set - BEZ235/paclitaxel/trastuzumab)

	BEZ235 400 mg/ Ptx 80mg/ Tz N=6	BEZ235 600 mg/ Ptx 80mg/ Tz N=5	All BEZ235/ Ptx/Tz N=11

Preferred term	All grades n (%)	All grades n (%)	All grades n (%)
- Total	6 (100.0)	5 (100.0)	11 (100.0)
Diarrhoea	6 (100.0)	5 (100.0)	11 (100.0)
Nausea	6 (100.0)	5 (100.0)	11 (100.0)
Alopecia	4 (66.7)	3 (60.0)	7 (63.6)
Anaemia	4 (66.7)	3 (60.0)	7 (63.6)
Asthenia	5 (83.3)	2 (40.0)	7 (63.6)
Cough	4 (66.7)	3 (60.0)	7 (63.6)
Stomatitis	4 (66.7)	3 (60.0)	7 (63.6)
Vomiting	3 (50.0)	4 (80.0)	7 (63.6)
Headache	5 (83.3)	1 (20.0)	6 (54.5)
Decreased appetite	4 (66.7)	1 (20.0)	5 (45.5)
Neutropenia	2 (33.3)	3 (60.0)	5 (45.5)
Pyrexia	2 (33.3)	3 (60.0)	5 (45.5)
Abdominal pain upper	2 (33.3)	2 (40.0)	4 (36.4)
Aspartate aminotransferase increased	3 (50.0)	1 (20.0)	4 (36.4)
Back pain	1 (16.7)	3 (60.0)	4 (36.4)
Dry eye	3 (50.0)	1 (20.0)	4 (36.4)
Epistaxis	1 (16.7)	3 (60.0)	4 (36.4)
Nasopharyngitis	2 (33.3)	2 (40.0)	4 (36.4)
Neurotoxicity	4 (66.7)	0	4 (36.4)
Paronychia	3 (50.0)	1 (20.0)	4 (36.4)
Rash	2 (33.3)	2 (40.0)	4 (36.4)
Alanine aminotransferase increased	3 (50.0)	0	3 (27.3)
Dermatitis acneiform	2 (33.3)	1 (20.0)	3 (27.3)
Dyspnoea	2 (33.3)	1 (20.0)	3 (27.3)
Fatigue	1 (16.7)	2 (40.0)	3 (27.3)
Gamma-glutamyltransferase increased	2 (33.3)	1 (20.0)	3 (27.3)
Influenza like illness	1 (16.7)	2 (40.0)	3 (27.3)
Nail disorder	2 (33.3)	1 (20.0)	3 (27.3)
Neuropathy peripheral	1 (16.7)	2 (40.0)	3 (27.3)
Oedema peripheral	1 (16.7)	2 (40.0)	3 (27.3)
Pruritus	1 (16.7)	2 (40.0)	3 (27.3)
Rash maculo-papular	2 (33.3)	1 (20.0)	3 (27.3)
Abdominal pain	0	2 (40.0)	2 (18.2)
Arthralgia	1 (16.7)	1 (20.0)	2 (18.2)
Blood alkaline phosphatase increased	1 (16.7)	1 (20.0)	2 (18.2)
Bronchitis	2 (33.3)	0	2 (18.2)
Chills	0	2 (40.0)	2 (18.2)
Conjunctivitis	1 (16.7)	1 (20.0)	2 (18.2)

Preferred term	BEZ235 400 mg/ Ptx 80mg/ Tz N=6 All grades n (%)	BEZ235 600 mg/ Ptx 80mg/ Tz N=5 All grades n (%)	All BEZ235/ Ptx/Tz N=11 All grades n (%)
Constipation	2 (33.3)	0	2 (18.2)
Cystitis	1 (16.7)	1 (20.0)	2 (18.2)
Depression	2 (33.3)	0	2 (18.2)
Dry skin	0	2 (40.0)	2 (18.2)
Dyspepsia	1 (16.7)	1 (20.0)	2 (18.2)
Dysphonia	2 (33.3)	0	2 (18.2)
Eczema	0	2 (40.0)	2 (18.2)
Erythema	0	2 (40.0)	2 (18.2)
Eye pruritus	2 (33.3)	0	2 (18.2)
Hypertension	2 (33.3)	0	2 (18.2)
Hypokalaemia	1 (16.7)	1 (20.0)	2 (18.2)
Hypomagnesaemia	1 (16.7)	1 (20.0)	2 (18.2)
Hyponatraemia	2 (33.3)	0	2 (18.2)
Leukopenia	1 (16.7)	1 (20.0)	2 (18.2)
Lymphopenia	1 (16.7)	1 (20.0)	2 (18.2)
Muscle spasms	1 (16.7)	1 (20.0)	2 (18.2)
Musculoskeletal pain	2 (33.3)	0	2 (18.2)
Nail toxicity	2 (33.3)	0	2 (18.2)
Nasal inflammation	1 (16.7)	1 (20.0)	2 (18.2)
Neck pain	2 (33.3)	0	2 (18.2)
Peripheral sensory neuropathy	1 (16.7)	1 (20.0)	2 (18.2)
Pollakiuria	1 (16.7)	1 (20.0)	2 (18.2)
Rash papular	2 (33.3)	0	2 (18.2)
Skin infection	1 (16.7)	1 (20.0)	2 (18.2)
Thrombocytopenia	0	2 (40.0)	2 (18.2)
Upper respiratory tract infection	1 (16.7)	1 (20.0)	2 (18.2)
Urinary tract infection	2 (33.3)	0	2 (18.2)

- Preferred terms are sorted in descending frequency of ‘All grades’ column, as reported in the ‘All patients’ column.
- A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.
- A patient with multiple adverse events is counted only once in the total row.
- Only AEs occurring after C1D1 and within 28 days of the last study treatment are reported.

NOVARTIS

Clinical Trial Results Website

BKM120 dual combination:

Frequent AEs (greater than or equal to 10%) in all patients and at MTD, regardless of study drug relationship, by preferred term and treatment group (Safety set - BKM120/paclitaxel)

Preferred term	BKM120 40 mg/ Ptx 70 mg N=1 n (%)	BKM120 40 mg/ Ptx 80 mg N=5 n (%)	BKM120 60 mg/ Ptx 80 mg N=3 n (%)	BKM120 80 mg/ Ptx 80 mg N=4 n (%)	BKM120 100 mg/ Ptx 70 mg N=1 n (%)	BKM120 100 mg/ Ptx 80 mg N=35 n (%)	BKM120 120 mg/ Ptx 70 mg N=1 n (%)	BKM120 120 mg/ Ptx 80 mg N=3 n (%)	All BKM120/ Ptx N=53 n (%)
- Total	1 (100.0)	5 (100.0)	3 (100.0)	4 (100.0)	1 (100.0)	35 (100.0)	1 (100.0)	3 (100.0)	53 (100.0)
Diarrhoea	0	0	2 (66.7)	4 (100.0)	1 (100.0)	24 (68.6)	0	2 (66.7)	33 (62.3)
Nausea	1 (100.0)	2 (40.0)	2 (66.7)	3 (75.0)	0	21 (60.0)	0	2 (66.7)	31 (58.5)
Asthenia	0	4 (80.0)	1 (33.3)	0	0	21 (60.0)	1 (100.0)	2 (66.7)	29 (54.7)
Decreased appetite	0	1 (20.0)	2 (66.7)	2 (50.0)	0	18 (51.4)	0	3 (100.0)	26 (49.1)
Fatigue	1 (100.0)	3 (60.0)	1 (33.3)	3 (75.0)	1 (100.0)	11 (31.4)	0	2 (66.7)	22 (41.5)
Anemia	1 (100.0)	3 (60.0)	1 (33.3)	1 (25.0)	0	14 (40.0)	0	1 (33.3)	21 (39.6)
Alopecia	0	2 (40.0)	0	1 (25.0)	1 (100.0)	15 (42.9)	1 (100.0)	0	20 (37.7)
Constipation	1 (100.0)	1 (20.0)	0	1 (25.0)	0	13 (37.1)	1 (100.0)	1 (33.3)	18 (34.0)
Hyperglycemia	0	2 (40.0)	2 (66.7)	0	0	12 (34.3)	1 (100.0)	1 (33.3)	18 (34.0)
Vomiting	0	1 (20.0)	0	0	0	13 (37.1)	0	2 (66.7)	16 (30.2)
Stomatitis	0	0	0	0	1 (100.0)	12 (34.3)	0	2 (66.7)	15 (28.3)
Cough	0	0	0	2 (50.0)	0	11 (31.4)	0	0	13 (24.5)
Dry skin	0	0	0	1 (25.0)	0	11 (31.4)	0	0	12 (22.6)
Dyspnea	0	1 (20.0)	0	1 (25.0)	0	7 (20.0)	0	3 (100.0)	12 (22.6)
Epistaxis	1 (100.0)	3 (60.0)	0	2 (50.0)	0	6 (17.1)	0	0	12 (22.6)
Depression	0	0	1 (33.3)	1 (25.0)	0	7 (20.0)	0	2 (66.7)	11 (20.8)
Dysgeusia	1 (100.0)	0	0	0	0	9 (25.7)	0	1 (33.3)	11 (20.8)

Preferred term	BKM120 40 mg/ Ptx 70 mg N=1 n (%)	BKM120 40 mg/ Ptx 80 mg N=5 n (%)	BKM120 60 mg/ Ptx 80 mg N=3 n (%)	BKM120 80 mg/ Ptx 80 mg N=4 n (%)	BKM120 100 mg/ Ptx 70 mg N=1 n (%)	BKM120 100 mg/ Ptx 80 mg N=35 n (%)	BKM120 120 mg/ Ptx 70 mg N=1 n (%)	BKM120 120 mg/ Ptx 80 mg N=3 n (%)	All BKM120/ Ptx N=53 n (%)
Neurotoxicity	0	0	0	0	0	10 (28.6)	0	1 (33.3)	11 (20.8)
Pyrexia	0	2 (40.0)	0	0	0	9 (25.7)	0	0	11 (20.8)
Oedema peripheral	1 (100.0)	0	0	1 (25.0)	0	6 (17.1)	0	2 (66.7)	10 (18.9)
Abdominal pain	0	0	0	1 (25.0)	0	8 (22.9)	0	0	9 (17.0)
Back pain	0	2 (40.0)	0	0	1 (100.0)	5 (14.3)	0	1 (33.3)	9 (17.0)
Pruritus	0	0	0	1 (25.0)	0	8 (22.9)	0	0	9 (17.0)
Hypomagnesaemia	0	0	1 (33.3)	0	0	7 (20.0)	0	0	8 (15.1)
Neutropenia	0	2 (40.0)	0	1 (25.0)	0	5 (14.3)	0	0	8 (15.1)
Peripheral sensory neuropathy	0	0	0	2 (50.0)	0	6 (17.1)	0	0	8 (15.1)
Rash maculo-papular	0	0	0	0	0	7 (20.0)	1 (100.0)	0	8 (15.1)
Weight decreased	0	1 (20.0)	0	1 (25.0)	0	6 (17.1)	0	0	8 (15.1)
Dyspepsia	0	1 (20.0)	0	0	0	6 (17.1)	0	0	7 (13.2)
Nasopharyngitis	1 (100.0)	0	0	1 (25.0)	0	5 (14.3)	0	0	7 (13.2)
Rash	0	1 (20.0)	0	1 (25.0)	0	5 (14.3)	0	0	7 (13.2)
Abdominal pain upper	0	0	0	1 (25.0)	0	5 (14.3)	0	0	6 (11.3)
Aspartate aminotransferase increased	0	0	0	0	0	5 (14.3)	0	1 (33.3)	6 (11.3)
Dermatitis acneiform	0	1 (20.0)	0	1 (25.0)	0	4 (11.4)	0	0	6 (11.3)
Erythema	0	0	0	1 (25.0)	0	4 (11.4)	0	1 (33.3)	6 (11.3)
Hypophosphataemia	0	0	0	0	0	4 (11.4)	1 (100.0)	1 (33.3)	6 (11.3)
Pain in extremity	0	0	0	2 (50.0)	0	4 (11.4)	0	0	6 (11.3)
Alanine aminotransferase increased	0	0	0	0	0	5 (14.3)	0	0	5 (9.4)
Arthralgia	0	1 (20.0)	0	0	0	4 (11.4)	0	0	5 (9.4)
Blood bilirubin increased	0	0	0	0	0	4 (11.4)	0	1 (33.3)	5 (9.4)

Preferred term	BKM120 40 mg/ Ptx 70 mg N=1 n (%)	BKM120 40 mg/ Ptx 80 mg N=5 n (%)	BKM120 60 mg/ Ptx 80 mg N=3 n (%)	BKM120 80 mg/ Ptx 80 mg N=4 n (%)	BKM120 100 mg/ Ptx 70 mg N=1 n (%)	BKM120 100 mg/ Ptx 80 mg N=35 n (%)	BKM120 120 mg/ Ptx 70 mg N=1 n (%)	BKM120 120 mg/ Ptx 80 mg N=3 n (%)	All BKM120/ Ptx N=53 n (%)
Dizziness	0	0	0	0	0	4 (11.4)	0	1 (33.3)	5 (9.4)
Gastrooesophageal reflux disease	0	0	0	0	0	5 (14.3)	0	0	5 (9.4)
Hypokalaemia	0	0	0	2 (50.0)	0	3 (8.6)	0	0	5 (9.4)
Insomnia	0	0	0	1 (25.0)	0	3 (8.6)	0	1 (33.3)	5 (9.4)
Musculoskeletal pain	0	0	0	0	0	5 (14.3)	0	0	5 (9.4)
Paraesthesia	0	1 (20.0)	0	0	0	4 (11.4)	0	0	5 (9.4)

- Preferred terms are sorted in descending frequency, as reported in the all patients column.
- A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.
- A patient with multiple adverse events is counted only once in the total row.
- Only AEs occurring after C1D1 and within 28 days of the last study treatment are reported.

BKM120 triple-agent combination:

Frequent AEs (greater than or equal to 10%), regardless of study drug relationship, by preferred term and treatment group (Safety set - BKM120/paclitaxel/Trastuzumab)

	BKM120 100 mg/ Ptx 80mg/ Tz N=11	All BKM120/ Ptx/Tz N=11
Preferred term	**All grades n (%)**	**All grades n (%)**
- Total	11 (100.0)	11 (100.0)
Nausea	9 (81.8)	9 (81.8)
Diarrhoea	7 (63.6)	7 (63.6)
Constipation	6 (54.5)	6 (54.5)
Fatigue	6 (54.5)	6 (54.5)
Decreased appetite	5 (45.5)	5 (45.5)
Epistaxis	5 (45.5)	5 (45.5)
Vomiting	5 (45.5)	5 (45.5)
Anaemia	4 (36.4)	4 (36.4)
Asthenia	4 (36.4)	4 (36.4)
Bone pain	4 (36.4)	4 (36.4)
Neurotoxicity	4 (36.4)	4 (36.4)
Neutropenia	4 (36.4)	4 (36.4)
Urinary tract infection	4 (36.4)	4 (36.4)
Anxiety	3 (27.3)	3 (27.3)
Cough	3 (27.3)	3 (27.3)
Dysuria	3 (27.3)	3 (27.3)
Haematoma	3 (27.3)	3 (27.3)
Lipase increased	3 (27.3)	3 (27.3)
Nasopharyngitis	3 (27.3)	3 (27.3)
Rash maculo-papular	3 (27.3)	3 (27.3)
Tremor	3 (27.3)	3 (27.3)
Vertigo	3 (27.3)	3 (27.3)
Abdominal pain	2 (18.2)	2 (18.2)
Alopecia	2 (18.2)	2 (18.2)
Amylase increased	2 (18.2)	2 (18.2)
Back pain	2 (18.2)	2 (18.2)
Dizziness	2 (18.2)	2 (18.2)
Dyspepsia	2 (18.2)	2 (18.2)
Headache	2 (18.2)	2 (18.2)

Preferred term	BKM120 100 mg/ Ptx 80mg/ Tz N=11 All grades n (%)	All BKM120/ Ptx/Tz N=11 All grades n (%)
Hyperglycaemia	2 (18.2)	2 (18.2)
Hypophosphataemia	2 (18.2)	2 (18.2)
Leukopenia	2 (18.2)	2 (18.2)
Myalgia	2 (18.2)	2 (18.2)
Nail toxicity	2 (18.2)	2 (18.2)
Nasal inflammation	2 (18.2)	2 (18.2)
Palpitations	2 (18.2)	2 (18.2)
Peripheral sensory neuropathy	2 (18.2)	2 (18.2)
Rash	2 (18.2)	2 (18.2)
Sinusitis	2 (18.2)	2 (18.2)
Visual acuity reduced	2 (18.2)	2 (18.2)
Weight decreased	2 (18.2)	2 (18.2)

- Preferred terms are sorted in descending frequency of 'All grades' column, as reported in the 'All patients' column.
- A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.
- A patient with multiple adverse events is counted only once in the total row.
- Only AEs occurring after C1D1 and within 28 days of the last study treatment are reported.

Overview of deaths, SAEs and other significant adverse events by treatment arms (Safety set)

	BEZ235				BKM120			
	BEZ235 Dual		BEZ235 Triple		BKM120 Dual		BKM120 Triple	
Category	BEZ235 800 mg/ Ptx 80mg N=26	All BEZ235/ Ptx N=35	BEZ235 400 mg/ Ptx 80mg/ Tz N=6	All BEZ235/ Ptx/Tz N=11	BKM120 100 mg/ Ptx 80mg N=35	All BKM120/ Ptx N=53	BKM120 100 mg/ Ptx 80mg/ Tz N=11	All BKM120/ Ptx/Tz N=11
All deaths	4 (15.4%)	5 (14.3%)	0	0	8 (22.9%)	10 (18.9%)	0	0
On treatment deaths [1]	4 (15.4%)	4 (11.4%)	0	0	5 (14.3%)	7 (13.2%)	0	0
Serious adverse events (SAEs)	15 (57.7%)	19 (54.3%)	2 (33.3%)	3 (27.3%)	13 (37.1%)	22 (41.5%)	6 (54.5%)	6 (54.5%)

	BEZ235				BKM120			
	BEZ235 Dual		BEZ235 Triple		BKM120 Dual		BKM120 Triple	
Category	**BEZ235 800 mg/ Ptx 80mg N=26**	**All BEZ235/ Ptx N=35**	**BEZ235 400 mg/ Ptx 80mg/ Tz N=6**	**All BEZ235/ Ptx/Tz N=11**	**BKM120 100 mg/ Ptx 80mg N=35**	**All BKM120/ Ptx N=53**	**BKM120 100 mg/ Ptx 80mg/ Tz N=11**	**All BKM120/ Ptx/Tz N=11**
Suspected to be treatment-related SAEs	4 (15.4%)	4 (11.4%)	1 (16.7%)	1 (9.1%)	6 (17.1%)	10 (18.9%)	3 (27.3%)	3 (27.3%)
AEs leading to discontinuation	9 (34.6%)	10 (28.6%)	1 (16.7%)	1 (9.1%)	8 (22.9%)	9 (17.0%)	3 (27.3%)	3 (27.3%)
Suspected to be treatment-related AEs leading to discontinuation.	9 (34.6%)	10 (28.6%)	1 (16.7%)	1 (9.1%)	7 (20.0%)	8 (15.1%)	2 (18.2%)	2 (18.2%)
Other significant AEs	26 (100.0%)	35 (100.0%)	6 (100.0%)	11 (100.0%)	34 (97.1%)	52 (98.1%)	11 (100.0%)	11 (100.0%)
At least one grade 3/4 AE	23 (88.5%)	28 (80.0%)	5 (83.3%)	9 (81.8%)	25 (71.4%)	38 (71.7%)	10 (90.9%)	10 (90.9%)
AEs requiring dose interruption and / or reduction	25 (96.2%)	31 (88.6%)	5 (83.3%)	10 (90.9%)	28 (80.0%)	41 (77.4%)	8 (72.7%)	8 (72.7%)
AEs requiring additional therapy	26 (100.0%)	34 (97.1%)	6 (100.0%)	11 (100.0%)	34 (97.1%)	52 (98.1%)	10 (90.9%)	10 (90.9%)

[1] On-treatment deaths are deaths which occurred up to 28 days after the discontinuation of study treatment

Adverse events occurring more than 28 days after the discontinuation of study treatment are not summarized

Other relevant findings

Summary statistics of exposure of trastuzumab study drug by treatment group – All cycles Full analysis set - BEZ235/paclitaxel/trastuzmab

	BEZ235 400 mg/ Ptx 80mg/ Tz N=6	BEZ235 600 mg/ Ptx 80mg/ Tz N=5	All BEZ235/ Ptx/Tz N=11
Duration of study drug exposure (weeks)			
n	6	5	11
Mean	32.3	31.6	32.0
SD	23.44	28.18	24.34
Median	34.2	19.0	19.0

	BEZ235 400 mg/ Ptx 80mg/ Tz N=6	BEZ235 600 mg/ Ptx 80mg/ Tz N=5	All BEZ235/ Ptx/Tz N=11
Minimum	3.0	5.1	3.0
Maximum	56.9	63.0	63.0
Percentage of weeks dosed*			
Mean	93.3	90.9	92.2
SD	10.45	9.56	9.63
Median	100.0	94.6	94.8
Minimum	78.1	75.0	75.0
Maximum	100.0	100.0	100.0

- Duration of study treatment exposure is defined as: date of last exposure to study treatment (including rest period for combination arm) - date of first administration of study treatment +1.

* Denominator is the duration of study treatment exposure.

- Dose intensity across all cycles = (Total dose/weight/Duration of study treatment exposure)*100.

- Relative dose intensity across all cycles = [Actual dose intensity/Planned dose intensity]*100.

Conclusion:

- For BEZ235 in combination with paclitaxel, the MTD was defined as 800 mg for BEZ235 in combination with 80 mg/m2/w PTX.
- For BEZ235 in combination with paclitaxel and trastuzumab, the MTD was defined as BEZ235 400 mg with 80 mg/m_2/w PTX and 2 mg/kg/w Tz.
- For BKM120 in combination with paclitaxel, MTD was declared at 100 mg for BKM120 in combination with 80 mg/m_2/w Ptx.
- For BKM120 in combination with paclitaxel and trastuzumab, MTD was declared at 100 mg for BKM120 in combination with 80 mg/m_2/w Ptx and 2 mg/kg/w Tz.
- For the BEZ235 dual combination arm, the most common AEs regardless of study drug (>30%) were diarrhea, nausea, vomiting, alopecia, asthenia, anemia, fatigue, decreased appetite, and stomatitis.
- For the BEZ235 triple combination arm, the most common AEs regardless of study drug (>30%) were diarrhea, nausea, alopecia, asthenia, cough, vomiting, anemia, headache, stomatitis, decreased appetite, neutropenia, pyrexia, abdominal pain increased aspartate aminotransferase (AST), back pain,, dry eye, epistaxis, nasopharyngitis, neurotoxicity, paronychia, and rash.
- For the BKM120 dual combination arm, the most common AEs regardless of study drug (>30%) were diarrhea, nausea, asthenia, decreased appetite, fatigue, anemia, alopecia, constipation, hyperglycemia and vomiting.
- For the BKM120 triple combination arm, the most common AEs regardless of study drug (>30%) were nausea, diarrhea, constipation, fatigue, decreased appetite, epistaxis,

vomiting, anemia, asthenia, bone pain, neurotoxicity, neutropenia, and urinary tract infection.

- Evidence of activity was observed in all four arms, but it needs to be interpreted with caution due to a long interval from prior taxane or trastuzumab in the majority of patients.
- Biomarker analysis was limited by the small number of analyzed samples. No consistent pharmacodynamics effect was observed. Examples of responses were seen in each arm in patients with and without evidence of PI3K pathway activation.

  In the dual combination, an overexposure was observed for BEZ235 with exposure at the dose of 800 mg, qd corresponding to 1000 mg dose, qd in the first in man trial. However, the variability observed in the data does not allow to draw firm conclusions.
- The pharmacokinetics of paclitaxel was not modified with the co-administration of either BEZ235 or BKM120.
- Trough concentrations of trastuzumab were in the expected range when administered at the dose of 2 mg/kg/w, weekly as triple combination with paclitaxel and BEZ235/BKM120.

Date of Clinical Trial Report

29 June 2015