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Clinical Trial Results Database

Sponsor
Novartis

Generic Drug Name
BEZ235/dactosilib and BKM120/buparlisib

Trial Indication(s)
Castration-resistant prostate cancer

Protocol Number
CBEZ235D2101

Protocol Title
Phase Ib dose finding study of abiraterone acetate plus BEZ235 or BKM120 in patients with castration-resistant prostate cancer

Clinical Trial Phase
Ib

Phase of Drug Development
Ib

Study Start/End Dates
26-Sep-2012 (first patient first visit, FPFV) to 01-Jul-2015 (last patient last visit, LPLV)

Reason for Termination (If applicable)
Subsequent to maximum tolerated dose (MTD) and/or recommended dose for expansion (RDE) of each combination, it was also planned to conduct dose expansion treatment in each of the combination groups but Novartis decided to stop the study at the dose escalation phase based on the available pharmacokinetic, safety and efficacy data.

Study Design/Methodology
The open-label, multi-center study design consisted of a dose escalation part to evaluate the MTD and a dose expansion part to evaluate the recommended dose expansion of abiratone acetate (AA) in combination with BEZ235 and AA in combination with BKM120 in castration-resistant prostate cancer (CRPC) patients with AA failure.The study consisted of the following periods:

Screening: After signing the informed consent form, the screening assessments were done within 28 days prior to treatment start

Run-in period: In the BEZ235 arm of the dose escalation part, eligible patients were enrolled in a run-in phase to receive AA and prednisone from Cycle 1 Day 1 to Cycle 1 Day 7. Combination treatment with BEZ235 started at Cycle 1 Day 8.

Treatment period: Treatment was organized into cycles of 28 days (except cycle 1 for the BEZ235 arm which was a 35-day cycle). Patients were treated with AA + BKM120 or AA + BEZ235 until disease progression, unacceptable toxicity, death, or other discontinuation criteria were met.

End of treatment: At the time patients discontinued study treatment, a visit was scheduled within 15 days after last dose of study treatment, at which time all of the assessments listed for the End of Treatment visit were performed.

Follow-up period:

- **Safety follow-up:** All patients had safety evaluations for 30 days after the last dose of study treatment.
- **Efficacy follow-up:** Patients who discontinued treatment for reasons other than disease progression underwent tumor assessments every 12 weeks until the start of new anti-cancer therapy, disease progression, death, lost to follow-up, or withdrawn consent to efficacy follow-up.
- **Survival follow-up:** All patients were followed for survival status every three months regardless of treatment discontinuation reason until death, lost to follow-up, or withdrawal of consent to survival follow-up.

Centers

Belgium (2), Canada (1), France (2), United States (2), Spain (2) and United Kingdom (1)

Publication

None

Objectives:

The primary objectives of the study were:

Dose escalation part:

To determine the maximum tolerated dose (MTD) and/or recommended dose for expansion (RDE) of abiraterone acetate (AA) plus BEZ235 (twice a day) and AA plus BKM120 (once a day) in castration resistant prostate cancer (CRPC) patients with AA failure.

The secondary objectives of the study were:

Dose escalation part:

To assess the safety and tolerability of the combinations.

To asses preliminary anti-tumor activity of the combinations.

To characterize pharmacokinetics (PK) of BEZ235, BKM120 and AA and also to investigate potential drug-drug. Interaction between BEZ235 and AA.

Dose expansion part:

For the BEZ235 combination arm, because of the marginal activity, overall safety profile and variable PK observed with BEZ235, the development of the compound in Oncology was terminated. For the BKM120 combination arm, dose escalation was stopped after Cohort 4 due to substantially lower PK exposures of BKM120 in combination with AA compared to the single agent and no clinically meaningful anti-tumor activity. Due to these reasons, the dose expansion part of the study was not conducted for both the combination arms.

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

The investigational drugs were BEZ235 and BKM120. The dose of BEZ235 was 200 mg twice a day. The doses of BKM120 were 60 mg once a day and 100 mg once a day. The mode of administration for both the drugs was oral.

Statistical Methods

The following analysis sets were considered in the data analyses:

Full analysis set (FAS) comprised of all patients who received at least one dose of study treatment. Patients were analyzed according to the starting dose (BEZ235 or BKM120) they received. For efficacy analyses, the FAS was used.

Safety set comprised all patients who received at least one dose of study treatment and had at least one post-baseline safety assessment. Patients were analyzed according to the starting dose (BEZ235 or BKM120) they received. Note: The statement that a patient has no AEs (i.e. ticked 'No' on the AE eCRF page) or the occurrence of a death constituted a valid safety assessment.

Dose determining set consisted of all the patients from safety set who either met the minimum exposure criteria or had sufficient safety evaluations or experience a DLT during Cycle 1.

For BEZ235/AA arm, the minimum exposure criterion was at least 21 of the 28 full daily planned doses of AA between D8 and D35 of Cycle 1 and at least 21 of the 28 full daily planned doses of BEZ235 between D8 and D35 of Cycle 1.

For BKM120/AA arm, the minimum exposure criterion was at least 21 of the 28 full daily planned doses of AA between D1 and D28 (Cycle 1) and at least 21 of the 28 full daily planned doses of BKM120 between D1 and D28 (Cycle 1).

Pharmacokinetic analysis set (PAS) consisted of patients who receive at least one dose of BKM120/BEZ235 or AA and have at least one non-missing and non-zero concentration measurement of BKM120/BEZ235 or AA.

Efficacy analysis: The primary variable was estimation of MTD/RDE of the combination arms and was based upon the estimation of the probability of DLT in Cycle 1. For each combination arm, an adaptive 5-parameter Bayesian logistic regression model (BLRM) with overdose control (EWOC) was used. The BLRMs were fitted on the Cycle 1 DLT data accumulated throughout the dose-escalation to model the dose-toxicity relationship of AA and BEZ235 or AA and BKM120 when given in combination.

The secondary variables were the following efficacy assessments for the BKM120 combination arm using FAS:

PSA progression: Summary statistics (n, minimum, maximum, mean, median, standard deviation (sd)) of PSA at baseline (ng/mL) and change of PSA from baseline at 12 weeks (ng/mL), waterfall plot for best percentage PSA change from baseline were presented. PSA percentage change at 12 weeks and best percentage PSA change were presented for the following criteria : ≤ -50, $(-50,-30]$, $(-30,0]$, $(0,25]$, >25 percent change categories as well as the proportion of patients with PSA decline $\geq 30\%$ at Week 12 or later.

Soft tissue best overall response (radiological): Summary of patients with best overall response (BoR) of Complete response (CR), Partial Response (PR), Non-CR/Non-Progressive Disease (PD), Stable Disease (SD), progressive disease (PD), Unknown (UNK) and Not Assessed were presented. In addition, overall response rate (ORR), defined as the proportion of patients with a best overall response of CR or PR was summarized.

Bone progression: Progressive evaluation in bone per Investigator assessment and derived assessments based on PCWG2 guidelines were listed. The derived assessment categories were summarized ("progressive disease", "no progression", "unknown" and "not assessed").

Safety analysis: All the safety analyses were based on the safety set, and summarized overall and by treatment arm. AEs were coded using the MedDRA terminology. The latest version of MedDRA (version 18.1) prior to database lock was used for reporting. AEs were graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.3.

Specific safety event categories (SEC) consisted of AEs for which there was a specific clinical interest in connection with BEZ235 (or BKM120) treatment (i.e. where BEZ235 (or BKM120) might influence a common mechanism of action responsible for triggering them) or AEs which were similar in nature (although not identical).

The following selected SECs were analyzed for the patients in BEZ235+AA arm: nausea, vomiting, diarrhea, stomatitis and mucosal inflammation, hyperglycemia and hypercholesterolemia, rash and hypersensitivity, pneumonitis, asthenia, fatigue, liver toxicity, QTc prolongation, cardiac dysrhythmias, thrombocytopenia, anemia, lymphopenia, leukopenia, neutropenia, and eosinophilia.

The following selected SECs were analyzed for the patients in BKM120+AA arm: hyperglycemia, mood disorders, hypersensitivity, rash, asthenia, fatigue, nausea, vomiting, diarrhea, pneumonitis, and liver toxicity.

All AEs of patients having at least one AE in that SEC was listed.

Shift tables based on CTC grades, by dose level were provided for liver enzymes (ALT (SGPT), AST (SGOT), total bilirubin), fasting plasma glucose, GGT, lipase, INR laboratory parameters for the BKM120 combination arm only. For BKM120 combination arm, all laboratory parameters collected were also listed.

A listing for vital signs and ECG parameters were produced by dose level, for the BKM120 combination arm only, flagging clinically notable vital sign abnormalities for blood pressure and pulse and ECG values.

ECOG Performance status (PS) was assessed to attempt to quantify the impact of disease on daily life activities of patients. ECOG PS scale was used to assess physical health of patients, ranging from 0 (most active) to 5 (least active). Baseline results were summarized overall and by dose level separately for each combination arm. All data were listed for BKM120 combination arm.

Mood assessment included two self-rating mood questionnaires: GAD-7 Anxiety scale and PHQ-9 Depression scale.

The variable for the analyses of mood were the total scores of the two scales. Analyses were performed based on the Safety set, by dose level for BKM120 combination arm only.

Pharmacokinetics (PK): The pharmacokinetics of BKM120 were analyzed using PAS on Cycle 1 Day 22, based on the full PK profiles collected during the dose escalation part.

Pre-dose concentrations were qualified for analysis if sampled within 3 hours of the scheduled time and if collected before the subsequent dose was administered. In addition, post-dose samples taken from patients who vomited within 4 hours were excluded from the analysis.

Derived PK parameters for BKM120 were summarized and concentrations of BKM120 and AA (from BKM combination arm only) were listed by day and dose level. n(number of non-missing values), m(number of non-zero non-missing values), arithmetic mean, median, SD, coefficient of variation CV (%), minimum, maximum, geometric mean and its CV(%) were present in the summary table. Geometric mean and the geometric CV(%) were derived from

non-zero non-missing concentrations. For Tmax only median, minimum and maximum were presented

Study Population: Key Inclusion/Exclusion Criteria

The patient population consisted of adult males with CRPC who failed AA treatment.

Inclusion criteria:

Patients eligible for this study met all of the following inclusion criteria:

- Adult males (≥ 18 years) with histologically/cytologically confirmed diagnosis of advanced or metastatic CRPC that progressed after AA failure.
- Histologically or cytologically confirmed diagnosis of advanced or metastatic prostate cancer.
- Advanced or metastatic CRPC progression after AA failure.
- Patient with castrate level of testosterone (≤ 50 ng/dL or 1.7 nmol/L) and Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1 or 2, and adequate bone marrow, organ function, and laboratory parameters.
- Patient with ≤ 2 lines of prior chemotherapy including cytotoxic agents (i.e. docetaxel) and discontinuation of all anti-androgen, anti-neoplastic or investigational treatment ≥ 4 weeks (6 weeks for bicalutamide).
- Patient must have documented progressive disease to the previous line of therapy according to prostate cancer working group-2 (PCWG2) criteria.
- Patient who progressed based solely on PSA rising, should have had a sequence of rising values on three consecutive occasions of at least 1 week intervals and should have 5.0 ng/mL minimum level for entry.
- Patient who manifested disease progression per RECIST are eligible independent of prostate specific antigen (PSA).
- Patient with bone only progression according to PCWG2.
- Patients with adequate bone marrow and organ function as defined by the following laboratory values:
    - Absolute Neutrophil Count ≥ 1.0 x 10e9/L
    - Platelets ≥ 100 x 10e9/L (in case of transfusion stable for ≥14 days prior to treatment start)
    - Hemoglobin (Hgb) ≥ 9.0 g/dL (in case of transfusion stable for ≥14 days prior to treatment start)
    - International normalized ratio ≤ 2
    - Serum Creatinine ≤ 1.5 x ULN and creatinine clearance >45 mL/min
    - Potassium, calcium (corrected for serum albumin) and magnesium within normal limits (WNL)
    - Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) equal or below the upper limit of normal range (or <3.0 x ULN in case of liver metastases).
    - Total serum Bilirubin equal or below the upper limit of normal range (or ≤ 1.5 x ULN if liver metastases are present; or total bilirubin ≤ 3.0 x ULN with direct bilirubin within normal range in patients with well documented Gilbert Syndrome which is defined as presence of several episodes of unconjugated hyperbilirubinemia with normal results from CBC count (including normal reticulocyte count and blood

smear), normal liver function test results, and absence of other contributing disease processes at the time of diagnosis.
    - Fasting plasma glucose (FPG) ≤ 120 mg/dL or ≤ 6.7 mmol/L
    - HbA1c ≤ 8%
- Recovery from all treatment-related toxicity to grade ≤ 1 within 4 weeks prior to treatment start with exception of alopecia, organ functions and bone marrow as described above.
- Patient who agreed to use effective contraception during the study and for at least 16 weeks after discontinuation.
- Patient who was able to swallow and retain oral medication.

Exclusion Criteria:

Patients eligible for this study did not meet any of the following inclusion criteria:

- Previous treatment with PI3K pathway inhibitors (e.g. PI3K, AKT, mTOR inhibitor), ketoconazole, CYP17 inhibitors (exception of AA), or enzalutamide.
- Known hypersensitivity and/or contraindication to any of the study medications or their excipients.
- Patient with concurrent malignancy or malignancy within three years of study enrollment (with the exception of adequately treated basal or squamous cell carcinoma, non-melanomatous skin cancer or curatively resected cervical cancer).
- Patient with active uncontrolled or symptomatic CNS metastases.
- Patient who received wide field radiotherapy (including therapeutic radioisotopes such as strontium 89) ≤ 28 days or limited field radiation for palliation ≤ 14 days prior to starting study drug or has not recovered from side effects of such therapy and patient who had major surgery within 14 days prior to starting study drug or has not recovered from major side effects.
- Patient who did not recover to grade 1 or better (except alopecia, bone marrow and organ functions listed above) from related side effects of any prior antineoplastic therapy and patients with inadequately controlled hypertension (e.g. systolic blood pressure ≥ 160 mmHg or diastolic blood pressure ≥ 95 mmHg.
- Inadequately controlled hypertension (e.g. systolic blood pressure ≥ 160 mmHg or diastolic blood pressure ≥ 95 mmHg).
- Patient with active cardiac disease or a history of cardiac dysfunction including any of the following:
    - Severe or unstable angina pectoris within 6 months prior to study entry
    - Symptomatic pericarditis
    - Documented myocardial infarction or arterial thrombotic events within 6 months prior to study entry
    - History of documented congestive heart failure (New York Heart Association functional classification III-IV)
    - Documented cardiomyopathy
- Patient with Left Ventricular Ejection Fraction (LVEF) <50% as determined by Multiple Gated acquisition (MUGA) scan or echocardiogram (ECHO).
- Patient with any of the following cardiac conduction abnormalities.

- Ventricular arrhythmias except for benign premature ventricular contractions.
- Supraventricular and nodal arrhythmias requiring a pacemaker or not controlled with medication.
- Conduction abnormality requiring a pacemaker.
- Other cardiac arrhythmia not controlled with medication.
- Patient who had a QTcF >480 msec on the screening ECG (using the QTcF formula), has a short/long QT syndrome, or history of QT prolongation/Torsades de Pointes.
- Patient was currently receiving treatment with medication that has a known risk to prolong the QT interval or inducing Torsades de Pointes, and the treatment cannot be discontinued or switched to a different medication prior to treatment start.
- Patient was currently receiving increasing or chronic treatment (>5 days) with corticosteroids or another immunosuppressive agent, as chronic administration of corticosteroids (>5 days) can induce CYP3A4.The following corticosteroids were permitted:
  - Prednisone 5 mg twice a day as part of the study treatment
  - Topical applications (e.g., rash), inhaled sprays (e.g., obstructive airways diseases), eye drops or local injections (e.g., intra-articular)
- Patient who was receiving warfarin or other coumarin derived anti-coagulant, for treatment, prophylaxis or otherwise. Therapy with heparin, low molecular weight heparin (LMWH), or fondaparinux is allowed.
- Patient who was receiving treatment with drugs known to be moderate or strong inhibitors or inducers of isoenzyme CYP3A. The patient must have discontinued strong inducers for at least one week and must have discontinued strong inhibitors before the treatment is initiated.
- Patient with impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of study drugs (e.g., ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, or small bowel resection).
- Patient with any other concurrent severe and/or uncontrolled medical condition that would, in the Investigator's judgment contraindicate patient participation in the clinical study (e.g. active or uncontrolled severe infection, chronic pancreatitis, active or symptomatic hepatitis, chronic obstructive or restrictive pulmonary disease including dyspnea at rest, interstitial lung disease, uncontrolled high blood pressure, adrenal insufficiency, etc.).
- Patient with a history of non-compliance to medical regimen or inability to grant consent.
- Patient with a known history of HIV infection (testing not mandatory) infection.
- Patient was concurrently using other approved or investigational antineoplastic agent.
- Patient with a score $\geq$ 12 on the PHQ-9 questionnaire.
- Patient selected a response of "1, 2 or 3" to question number 9 on the PHQ-9 questionnaire regarding potential for suicidal thoughts or ideation (independent of the total score of the PHQ-9).
- Patient with a GAD-7 mood scale score $\geq$ 15.
- Patient with a medically documented history of or active major depressive episode, bipolar disorder (I or II), obsessive-compulsive disorder, schizophrenia, a history of suicidal

attempt or ideation, or homicidal ideation (e.g. risk of doing harm to self or others) or patient has an active severe personality disorder (defined according to DSM- IV-TR). Note: for patients with psychotropic treatments ongoing at baseline, the dose and the schedule was not be modified within the previous 6 weeks prior to start of study drug.

- Patient with ≥ CTCAE grade 3 anxiety.
- Patient consuming Seville oranges, grapefruit, grapefruit hybrids, pummelos and exotic citrus fruits (as well as their juices) during the last 7 days prior to start of treatment. Regular orange juice is permitted.
- Sexually active males not willing to use a condom during the whole course of the study and for 16 weeks after stopping treatment. Male subjects were not to father a child during the study period. A condom was required to be used also by vasectomized men as well as during intercourse with a male partner in order to prevent delivery of the drug via seminal fluid.
- Patient who experienced dose reductions and/or treatment interruptions due to AA related toxicities (i.e. serious AEs, AEs, liver toxicities during AA treatment).

Participant Flow Table

Patient disposition by dose level, BEZ235 combination arm (FAS)

Disposition reason	BEZ235 200 mg twice a day + AA 1000 mg once a day N=18 n (%)
Patients enrolled	
Treated	18 (100.0)
Patients treated	
End of treatment	18 (100.0)
Primary reason for end of treatment	
Adverse event	9 (50.0)
Progressive disease	4 (22.2)
Subject/guardian decision	5 (27.8)
Post Treatment follow-up after End of Treatment	
Not Applicable	7 (38.9)
Patients no longer being followed post treatment	11 (61.1)
Primary reason for discontinuation of post treatment follow-up	
Progressive disease	2 (11.1)
Study terminated by sponsor	1 (5.6)
Subject/guardian decision	1 (5.6)
Death	2 (11.1)
New therapy for study indication	5 (27.8)

Percentage is based on N

Reason for not being treated is from CRF completion page.

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Patient disposition by dose level, BKM120 combination arm (FAS)

Disposition reason	BKM120 60 mg once a day+ AA 1000 mg once a day N=5 n (%)	BKM120 100 mg once a day+ AA 1000 mg once a day N=20 n (%)	All patients N=25 n (%)
Patients enrolled			
Treated	5 (100.0)	20 (100.0)	25 (100.0)
Patients treated			
End of treatment	5 (100.0)	20 (100.0)	25 (100.0)
Primary reason for end of treatment			
Adverse event	0	7 (35.0)	7 (28.0)
Progressive disease	2 (40.0)	10 (50.0)	12 (48.0)
Subject/guardian decision	3 (60.0)	3 (15.0)	6 (24.0)
Post Treatment follow-up after End of Treatment			
Not Applicable	3 (60.0)	14 (70.0)	17 (68.0)
Patients no longer being followed post treatment	2 (40.0)	6 (30.0)	8 (32.0)
Primary reason for discontinuation of post treatment follow-up			
Progressive disease	0	1 (5.0)	1 (4.0)
Study terminated by sponsor	0	1 (5.0)	1 (4.0)
Subject/guardian decision	0	1 (5.0)	1 (4.0)
Death	2 (40.0)	2 (10.0)	4 (16.0)
New therapy for study indication	0	1 (5.0)	1 (4.0)

Percentage is based on N

Reason for not being treated is from CRF completion page.

Baseline Characteristics

Demographics summary by dose level, BEZ235 combination arm

Demographic Variable	BEZ235 200 mg twice a day + AA 1000 mg once a day N=18
Age, n (%)	
< 65 years	4 (22.2)
≥65 years	14 (77.8)
Age (years)	
n	18
Mean	69.3
SD	7.58

Demographic Variable	BEZ235 200 mg twice a day + AA 1000 mg once a day N=18
Median	71.0
Minimum-Maximum	54.0 – 78.0
Race, n (%)	
Caucasian	16 (88.9)
Asian	1 (5.6)
Unknown	1 (5.6)
Ethnicity, n (%)	
Hispanic or Latino	1 (5.6)
East Asian	1 (5.6)
Not reported	6 (33.3)
Unknown	5 (27.8)
Other	5 (27.8)
BSA (m2)	
n	18
Mean	2.0
SD	0.19
Median	2.0
Minimum-Maximum	1.7 – 2.3
BMI (kg/m2)	
n	18
Mean	27.1
SD	3.85
Median	27.3
Minimum-Maximum	20.4 – 34.0
ECOG Performance Status n (%)	
0	6 (33.3)
1	12 (66.7)

Weight and height are taken from last available vital signs evaluation performed on or before the first day of treatment.

BSA: Body surface area is calculated using the Mosteller formula

BSA (m^2) = sqrt(wt(kg)×ht(cm)/3600)

Body Mass Index: BMI (kg/m2) = weight(kg) / (height(m)^2)

BMI and BSA are calculated based on raw data assessments

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Demographics summary by dose level, BKM120 combination arm

Demographic variable	BKM120 60 mg once a day+ AA 1000 mg once a day N=5 n (%)	BKM120 100 mg once a day+ AA 1000 mg once a day N=20 n (%)	All patients N=25 n (%)
Age, n (%)			
<65 years	0	7 (35.0)	7 (28.0)
≥ 65 years	5 (100.0)	13 (65.0)	18 (72.0)
Age (years)			
n	5	20	25
Mean	71.4	66.8	67.7
SD	7.86	7.38	7.55
Median	68.0	67.0	67.0
Minimum-Maximum	65.0 – 84.0	47.0 – 79.0	47.0 – 84.0
Race, n (%)			
Caucasian	5 (100.0)	19 (95.0)	24 (96.0)
Black	0 (0.0)	1 (5.0)	1 (4.0)
Ethnicity, n (%)			
Hispanic/Latino	1 (20.0)	6 (30.0)	7 (28.0)
Mixed ethnicity	1 (20.0)	0 (0.0)	1 (4.0)
Not reported	0 (0.0)	5 (25.0)	5 (20.0)
Unknown	0 (0.0)	2 (10.0)	2 (8.0)
Other	3 (60.0)	7 (35.0)	10 (40.0)
BSA(m^2)			
n	5	20	25
Mean	2.0	2.0	2.0
SD	0.20	0.15	0.16
Median	2.0	2.0	2.0
Minimum-Maximum	1.8 – 2.2	1.7 – 2.3	1.7 – 2.3
BMI (kg/m^2)			
n	5	20	25
Mean	28.4	27.0	27.3
SD	5.92	3.45	3.95
Median	27.9	26.4	27.1
Minimum-Maximum	20.9 - 37.4	22.1 - 34.4	20.9 - 37.4
ECOG performance status, n (%)			
0	1 (20.0)	6 (30.0)	7 (28.0)
1	4 (80.0)	13 (65.0)	17 (68.0)
2	0 (0.0)	1 (5.0)	1 (4.0)

Weight and height are taken from any vital signs evaluation performed on or before the first day of treatment.
Body Mass index: BMI [kg/m2] = weight [kg]/(height[m]**2).
BSA: Body surface area is calculated using the Mosteller formula.
BSA (m2) = Sqrt(wt(kg)×ht(cm)/3600).

Demographic variable	BKM120 60 mg once a day+ AA 1000 mg once a day N=5 n (%)	BKM120 100 mg once a day+ AA 1000 mg once a day N=20 n (%)	All patients N=25 n (%)

BMI and BSA are calculated based on raw data assessments.

Summary of Efficacy

Primary Outcome Result(s)

Due to study termination the MTD was not reached for all three arms.

Secondary Outcome Results

Summary of change in PSA from baseline, by dose level, BKM120 combination arm (FAS)

	Statistics	BKM120 60 mg once a day+ AA 1000 mg once a day N=5	BKM120 100 mg once a day+ AA 1000 mg once a day N=20	All Patients N=25
Baseline (ng/mL)	n	5	20	25
	Mean	174.48	304.87	278.79
	SD	208.105	445.349	408.739
	Median	73.00	87.15	73.00
	Min - Max	0.2 - 510.0	7.0 - 1547.0	0.2 - 1547.0
Change from baseline at 12 weeks (ng/mL)	n	3	13	16
	Mean	350.91	369.62	366.11
	SD	227.548	462.931	422.380
	Median	325.72	161.25	198.62
	Min -Max	137.0 - 590.0	−2.3 - 1210.0	−2.3 - 1210.0
Best change from baseline (ng/mL)	n	5	20	25
	Mean	131.58	39.40	57.84
	SD	159.786	101.924	117.879
	Median	81.02	11.00	13.08
	Min - Max	−0.1 - 410.0	−118.8 - 367.6	−118.8 - 410.0

Baseline is defined as the last non-missing value prior to the first dose.

Change from baseline at 12 week or later: PSA values obtained at least 80 days after treatment start - baseline

Best PSA change is defined as the change from baseline to the lowest PSA value at any time from the start of treatment.

Soft tissue best overall response per local Investigator, by dose level, BKM120 combination arm (FAS)

	BKM120 60 mg once a day+ AA 1000 mg once a day N=5		BKM120 100 mg once a day+ AA 1000 mg once a day N=20	
	n (%)	**95% CI**	**n (%)**	**95% CI**
Patients with measurable disease at baseline	2 (40.0)		12 (60.0)	
Patients with non-measurable disease only at baseline	3 (60.0)		8 (40.0)	
Best overall response				
Complete response (CR)	0		0	
Partial response (PR)	0		0	
Non-CR/Non-PD	2 (40.0)		3 (15.0)	
Stable disease (SD)	0		3 (15.0)	
Progressive disease (PD)	1 (20.0)		8 (40.0)	
Unknown (UNK)	2 (40.0)		6 (30.0)	
Not assessed	0		0	
Overall response rate (ORR:CR+PR)	0	(0.0, 52.2)	0	(0.0, 16.8)

N: The total number of patients in the treatment group. It is the denominator for percentage (%) calculation.
n: Number of patients who are in the corresponding category.
The 95% CI for the frequency distribution of each variable were computed based on the method (Clopper 1934).

PK results- BKM120 combination arm

Summary of BKM120 PK parameters (Cycle 1 Day 22), BKM120 combination arm –PK analysis set

BKM120 dose (mg/day)	Statistics	AUCtau (h*ng/mL)	Cmax (ng/mL)	Tmax (h)
BKM120 60 mg Once a day + AA 1000 mg Once a day (N=5)	n	4	4	4
	Mean (SD)	6830(1030)	599(140)	N/A
	CV% mean	15.1	23.3	N/A
	Geo-mean	6770	588	N/A
	CV% geo-mean	15.1	22.2	N/A
	Median	6730	556	2.00
	[Min; Max]	[5880;7980]	[487;799]	[1.50;2.97]
BKM120 100 mg Once a day + AA 1000 mg Once a day (N=19)	n	12	12	12
	Mean (SD)	15100(3230)	1180(423)	N/A
	CV% mean	21.3	35.9	N/A
	Geo-mean	14800	1110	N/A
	CV% geo-mean	21.6	35.7	N/A
	Median	15700	1000	2.51
	[Min; Max]	[10400;21800]	[651;2040]	[0;6.08]

Patients with at least 7 continuous days of daily dosing of BKM120 prior to the pharmacokinetic assessments are included in the summary statistics.

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Summary of Safety

Safety Results

BEZ combination arm

Adverse events regardless of study treatment relationship by primary system organ class, maximum CTC grade and dose level, BEZ235 combination arm

	BEZ235 200mg bid + AA 1000mg qd N=18	
Primary system organ class	**All grades n (%)**	**Grades 3/4 n (%)**
Any primary system organ class		
-Total	18 (100)	16 (88.9)
Gastrointestinal disorders	18 (100)	6 (33.3)
General disorders and administration site conditions	12 (66.7)	2 (11.1)
Metabolism and nutrition disorders	12 (66.7)	5 (27.8)
Musculoskeletal and connective tissue disorders	11 (61.1)	4 (22.2)
Infections and infestations	9 (50.0)	1 (5.6)
Nervous system disorders	8 (44.4)	2 (11.1)
Investigations	7 (38.9)	3 (16.7)
Psychiatric disorders	7 (38.9)	0
Vascular disorders	5 (27.8)	1 (5.6)
Skin and subcutaneous tissue disorders	4 (22.2)	1 (5.6)
Blood and lymphatic system disorders	3 (16.7)	3 (16.7)
Cardiac disorders	3 (16.7)	0
Renal and urinary disorders	3 (16.7)	0
Respiratory, thoracic and mediastinal disorders	3 (16.7)	1 (5.6)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (11.1)	1 (5.6)
Ear and labyrinth disorders	1 (5.6)	0
Hepatobiliary disorders	1 (5.6)	1 (5.6)
Injury, poisoning and procedural complications	1 (5.6)	0

- Primary system organ classes are sorted in descending frequency, as reported in the All grades 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 during treatment or within 30 days of the last study medication are reported.

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Clinical Trial Results Database

Adverse events (greater than 15%) regardless of study treatment relationship by preferred term, maximum CTC grade and dose level, BEZ235 combination arm (Safety set)

	BEZ235 200 mg twice a day + AA 1000 mg once a day	
	N=18	
Preferred term	All grades n (%)	Grades 3/4 n (%)
Any Preferred term		
-Total	18 (100)	16 (88.9)
Diarrhoea	14 (77.8)	4 (22.2)
Nausea	11 (61.1)	1 (5.6)
Stomatitis	7 (38.9)	1 (5.6)
Fatigue	6 (33.3)	0
Vomiting	6 (33.3)	2 (11.1)
Decreased appetite	5 (27.8)	0
Weight decreased	5 (27.8)	1 (5.6)
Asthenia	4 (22.2)	2 (11.1)
Constipation	4 (22.2)	0
Hyperglycaemia	4 (22.2)	1 (5.6)
Myalgia	4 (22.2)	1 (5.6)
Pain in extremity	4 (22.2)	1 (5.6)
Abdominal pain	3 (16.7)	0
Anaemia	3 (16.7)	2 (11.1)
Bone pain	3 (16.7)	2 (11.1)
Dry mouth	3 (16.7)	0
Dysgeusia	3 (16.7)	0
Hypokalaemia	3 (16.7)	1 (5.6)
Pyrexia	3 (16.7)	0

Preferred terms are sorted in descending frequency, as reported in the All grades 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 during treatment or within 30 days of the last study medication are reported.

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Clinical Trial Results Database

Summary of deaths and treatment-emergent adverse events by dose level, BEZ235 combination arm (Safety set)

	BEZ235 200 mg twice a day + AA 1000 mg once a day
	N=18
Patients with at least one AE	18 (100.0)
Patients with at least one SAE	10 (55.6)
Patients who died	1 (5.6)
Patients who discontinued from study treatment due to AEs	9 (50.0)
Patients who discontinued from study treatment due to SAEs	4 (22.2)
Patients who discontinued from study treatment due to non-serious AEs	5 (27.8)

Only deaths and AEs occurring during treatment or within 30 days of the last study medication are reported.

Serious adverse events regardless of study treatment relationship by preferred term, maximum CTC grade and dose level, BEZ235 combination arm (Safety set)

	BEZ235 200 mg twice a day + AA 1000 mg once a day	
	N=18	
	All grades	Grades 3/4
Preferred term	n (%)	n (%)
Any Preferred term		
-Total	10 (55.6)	10 (55.6)
Vomiting	2 (11.1)	1 (5.6)
Anaemia	1 (5.6)	1 (5.6)
Asthenia	1 (5.6)	1 (5.6)
Bone marrow failure	1 (5.6)	1 (5.6)
Bone pain	1 (5.6)	1 (5.6)
Diarrhoea	1 (5.6)	0
Dyspnoea	1 (5.6)	1 (5.6)
Haemorrhagic transformation stroke	1 (5.6)	1 (5.6)
Hepatic pain	1 (5.6)	1 (5.6)
Metastases to central nervous system	1 (5.6)	1 (5.6)
Nausea	1 (5.6)	0
Pathological fracture	1 (5.6)	1 (5.6)
Pneumocystis jirovecii pneumonia	1 (5.6)	1 (5.6)
Pneumonia	1 (5.6)	0
Pyrexia	1 (5.6)	0
Renal failure	1 (5.6)	0

Preferred term	BEZ235 200 mg twice a day + AA 1000 mg once a day N=18 All grades n (%)	Grades 3/4 n (%)
Spinal cord compression	1 (5.6)	1 (5.6)
Thrombocytopenia	1 (5.6)	1 (5.6)

Preferred terms are sorted within primary system organ class in descending frequency, as reported in the All grades 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 during treatment or within 30 days of the last study medication are reported.

Adverse events leading to treatment permanent discontinuation regardless of study treatment relationship, by preferred term, maximum CTC grade and dose level, BEZ235 combination arm (Safety set)

Preferred term	BEZ235 200 mg twice a day + AA 1000 mg once a day All grades n (%)	Grades 3/4 n (%)
Any Preferred term	N=18	N=18
-Total	9 (50.0)	4 (22.2)
Stomatitis	2 (11.1)	0
Back pain	1 (5.6)	0
Diarrhoea	1 (5.6)	0
Hyperglycaemia	1 (5.6)	1 (5.6)
Pneumocystis jirovecii pneumonia	1 (5.6)	1 (5.6)
Renal failure	1 (5.6)	0
Thrombocytopenia	1 (5.6)	1 (5.6)
Vomiting	1 (5.6)	1 (5.6)

Preferred terms are sorted within primary system organ class in descending frequency, as reported in the All grades 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 during treatment or within 30 days of the last study medication are reported.

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Clinical Trial Results Database

BKM120 combination arm

Adverse events regardless of study treatment relationship by primary system organ class, maximum CTC grade and dose level, BKM120 combination arm (Safety set)

	BKM120 60mg qd + AA 1000mg qd N=5		BKM120 100mg qd + AA 1000mg qd N=20		All patients N=25	
Primary system organ class	All grades n (%)	Grades 3/4 n (%)	All grades n (%)	Grades 3/4 n (%)	All grades n (%)	Grades 3/4 n (%)
Any primary system organ class						
-Total	5 (100)	3 (60.0)	19 (95.0)	12 (60.0)	24 (96.0)	15 (60.0)
Gastrointestinal disorders	3 (60.0)	1 (20.0)	17 (85.0)	1 (5.0)	20 (80.0)	2 (8.0)
General disorders and administration site conditions	4 (80.0)	1 (20.0)	15 (75.0)	4 (20.0)	19 (76.0)	5 (20.0)
Metabolism and nutrition disorders	2 (40.0)	1 (20.0)	16 (80.0)	6 (30.0)	18 (72.0)	7 (28.0)
Nervous system disorders	3 (60.0)	1 (20.0)	10 (50.0)	0	13 (52.0)	1 (4.0)
Musculoskeletal and connective tissue disorders	2 (40.0)	0	10 (50.0)	1 (5.0)	12 (48.0)	1 (4.0)
Investigations	1 (20.0)	0	10 (50.0)	2 (10.0)	11 (44.0)	2 (8.0)
Skin and subcutaneous tissue disorders	1 (20.0)	0	8 (40.0)	2 (10.0)	9 (36.0)	2 (8.0)
Psychiatric disorders	3 (60.0)	0	5 (25.0)	0	8 (32.0)	0
Respiratory, thoracic and mediastinal disorders	2 (40.0)	0	6 (30.0)	2 (10.0)	8 (32.0)	2 (8.0)
Blood and lymphatic system disorders	0	0	6 (30.0)	3 (15.0)	6 (24.0)	3 (12.0)
Infections and infestations	0	0	6 (30.0)	1 (5.0)	6 (24.0)	1 (4.0)
Ear and labyrinth disorders	2 (40.0)	0	1 (5.0)	0	3 (12.0)	0
Eye disorders	1 (20.0)	0	2 (10.0)	0	3 (12.0)	0
Renal and urinary disorders	1 (20.0)	0	2 (10.0)	1 (5.0)	3 (12.0)	1 (4.0)
Reproductive system and breast disorders	0	0	3 (15.0)	0	3 (12.0)	0
Vascular disorders	1 (20.0)	0	2 (10.0)	0	3 (12.0)	0
Cardiac disorders	1 (20.0)	0	1 (5.0)	0	2 (8.0)	0
Injury, poisoning and procedural complications	0	0	2 (10.0)	0	2 (8.0)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	0	1 (5.0)	1 (5.0)	1 (4.0)	1 (4.0)

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Clinical Trial Results Database

Primary system organ class	BKM120 60mg qd + AA 1000mg qd N=5		BKM120 100mg qd + AA 1000mg qd N=20		All patients N=25	
	All grades n (%)	Grades 3/4 n (%)	All grades n (%)	Grades 3/4 n (%)	All grades n (%)	Grades 3/4 n (%)

Primary system organ classes are sorted in descending frequency, as reported in the All grades 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 during treatment or within 30 days of the last study medication are reported.

Adverse events (greater than 10% in all patients) regardless of study treatment relationship by preferred term, maximum CTC grade and dose level, BKM120 combination arm (Safety set)

Preferred term	BKM120 60 mg Once a day + AA 1000 mg Once a day N=5		BKM120 100 mg Once a day + AA 1000 mg Once a day N=20		All patients N=25	
	All grades n (%)	Grades 3/4 n (%)	All grades n (%)	Grades 3/4 n (%)	All grades n (%)	Grades 3/4 n (%)
Any Preferred term						
-Total	5 (100)	3 (60.0)	19 (95.0)	12 (60.0)	24 (96.0)	15 (60.0)
Nausea	3 (60.0)	0	11 (55.0)	0	14 (56.0)	0
Hyperglycaemia	2 (40.0)	1 (20.0)	9 (45.0)	2 (10.0)	11 (44.0)	3 (12.0)
Decreased appetite	1 (20.0)	0	9 (45.0)	1 (5.0)	10 (40.0)	1 (4.0)
Fatigue	3 (60.0)	1 (20.0)	7 (35.0)	0	10 (40.0)	1 (4.0)
Asthenia	2 (40.0)	1 (20.0)	7 (35.0)	1 (5.0)	9 (36.0)	2 (8.0)
Vomiting	2 (40.0)	1 (20.0)	6 (30.0)	0	8 (32.0)	1 (4.0)
Diarrhoea	1 (20.0)	0	6 (30.0)	1 (5.0)	7 (28.0)	1 (4.0)
Anaemia	0	0	6 (30.0)	3 (15.0)	6 (24.0)	3 (12.0)
Hypokalaemia	2 (40.0)	0	4 (20.0)	1 (5.0)	6 (24.0)	1 (4.0)
Arthralgia	2 (40.0)	0	3 (15.0)	0	5 (20.0)	0
Back pain	1 (20.0)	0	4 (20.0)	1 (5.0)	5 (20.0)	1 (4.0)
Weight decreased	0	0	5 (25.0)	1 (5.0)	5 (20.0)	1 (4.0)
Abdominal pain	0	0	4 (20.0)	0	4 (16.0)	0
Dizziness	1 (20.0)	0	3 (15.0)	0	4 (16.0)	0
Neck pain	1 (20.0)	0	3 (15.0)	0	4 (16.0)	0
Rash	0	0	4 (20.0)	1 (5.0)	4 (16.0)	1 (4.0)
Bone pain	0	0	3 (15.0)	0	3 (12.0)	0
Dry skin	0	0	3 (15.0)	0	3 (12.0)	0
Dyspepsia	0	0	3 (15.0)	0	3 (12.0)	0
Headache	1 (20.0)	0	2 (10.0)	0	3 (12.0)	0
Insomnia	2 (40.0)	0	1 (5.0)	0	3 (12.0)	0

	BKM120 60 mg Once a day + AA 1000 mg Once a day		BKM120 100 mg Once a day + AA 1000 mg Once a day		All patients	
	N=5		N=20		N=25	
Preferred term	**All grades n (%)**	**Grades 3/4 n (%)**	**All grades n (%)**	**Grades 3/4 n (%)**	**All grades n (%)**	**Grades 3/4 n (%)**
Musculoskeletal pain	2 (40.0)	0	1 (5.0)	0	3 (12.0)	0
Somnolence	0	0	3 (15.0)	0	3 (12.0)	0

Preferred terms are sorted in descending frequency, as reported in the All grades 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 during treatment or within 30 days of the last study medication are reported.

Summary of deaths and treatment-emergent adverse events by dose level, BKM120 combination arm (Safety set)

	BKM120 60 mg Once a day + AA 1000 mg Once a day	BKM120 100 mg Once a day + AA 1000 mg Once a day	All Patients
	N=5	N=20	N=25
Patients with at least one AE	5 (100.0)	19 (95.0)	24 (96.0)
Patients with at least one SAE	1 (20.0)	7 (35.0)	8 (32.0)
Patients who died	0	1 (5.0)	1 (4.0)
Patients who discontinued from study treatment due to AEs	0	7 (35.0)	7 (28.0)
Patients who discontinued from study treatment due to SAEs	0	2 (10.0)	2 (8.0)
Patients who discontinued from study treatment due to non-serious AEs	0	5 (25.0)	5 (20.0)

Only deaths and AEs occurring during treatment or within 30 days of the last study medication are reported.

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Clinical Trial Results Database

Serious adverse events regardless of study treatment relationship by preferred term, maximum CTC grade and dose level, BKM120 combination arm (Safety set)

	BKM120 60 mg once a day + AA 1000 mg once a day N=5		BKM120 100 mg once a day + AA 1000 mg once a day N=20		All patients N=25	
Preferred term	**All grades n (%)**	**Grades 3/4 n (%)**	**All grades n (%)**	**Grades 3/4 n (%)**	**All grades n (%)**	**Grades 3/4 n (%)**
Any Preferred term						
-Total	1 (20.0)	1 (20.0)	7 (35.0)	7 (35.0)	8 (32.0)	8 (32.0)
Anaemia	0	0	1 (5.0)	1 (5.0)	1 (4.0)	1 (4.0)
Atrial fibrillation	1 (20.0)	0	0	0	1 (4.0)	0
Back pain	0	0	1 (5.0)	1 (5.0)	1 (4.0)	1 (4.0)
Diarrhoea	0	0	1 (5.0)	1 (5.0)	1 (4.0)	1 (4.0)
Gastroenteritis viral	0	0	1 (5.0)	1 (5.0)	1 (4.0)	1 (4.0)
General physical health deterioration	0	0	1 (5.0)	1 (5.0)	1 (4.0)	1 (4.0)
Metastases to spine	0	0	1 (5.0)	1 (5.0)	1 (4.0)	1 (4.0)
Pain	0	0	1 (5.0)	1 (5.0)	1 (4.0)	1 (4.0)
Pneumonitis	0	0	1 (5.0)	1 (5.0)	1 (4.0)	1 (4.0)
Pulmonary embolism	0	0	1 (5.0)	1 (5.0)	1 (4.0)	1 (4.0)
Renal impairment	0	0	1 (5.0)	1 (5.0)	1 (4.0)	1 (4.0)
Spinal cord compression	1 (20.0)	1 (20.0)	0	0	1 (4.0)	1 (4.0)
Venous thrombosis	0	0	1 (5.0)	0	1 (4.0)	0

Preferred terms are sorted within primary system organ class in descending frequency, as reported in the All grades 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 SAEs occurring during treatment or within 30 days of the last study medication are reported.

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Clinical Trial Results Database

Adverse events leading to treatment permanent discontinuation regardless of study treatment relationship, by preferred term, maximum CTC grade and dose level, BKM120 combination arm (Safety set)

	BKM120 60 mg once a day + AA 1000 mg once a day N=5		BKM120 100 mg once a day + AA 1000 mg once a day N=20		All patients N=25	
Preferred term	All grades n (%)	Grades 3/4 n (%)	All grades n (%)	Grades 3/4 n (%)	All grades n (%)	Grades 3/4 n (%)
Any Preferred term						
-Total	0	0	7 (35.0)	3 (15.0)	7 (28.0)	3 (12.0)
Asthenia	0	0	2 (10.0)	1 (5.0)	2 (8.0)	1 (4.0)
Decreased appetite	0	0	2 (10.0)	1 (5.0)	2 (8.0)	1 (4.0)
Hyperglycaemia	0	0	2 (10.0)	0	2 (8.0)	0
Abdominal pain	0	0	1 (5.0)	0	1 (4.0)	0
Depressed mood	0	0	1 (5.0)	0	1 (4.0)	0
Diarrhoea	0	0	1 (5.0)	1 (5.0)	1 (4.0)	1 (4.0)
Hiccups	0	0	1 (5.0)	0	1 (4.0)	0
Nausea	0	0	1 (5.0)	0	1 (4.0)	0
Pneumonitis	0	0	1 (5.0)	1 (5.0)	1 (4.0)	1 (4.0)
Vomiting	0	0	1 (5.0)	0	1 (4.0)	0

Preferred terms are sorted within primary system organ class in descending frequency, as reported in the All grades 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 during treatment or within 30 days of the last study medication are reported.

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Clinical Trial Results Database

Other Relevant Findings

Conclusion:

- The study did not meet its primary objective of establishing the MTD/RDE as it was terminated prematurely.
- Safety of BEZ235 or BKM120 in combination with AA was consistent with previous studies and the expected safety profile of each compound; no new or unexpected findings have been identified.
- PK exposure of BKM120 in combination with AA was approximately 30% lower compared with single agent.
- Preliminary efficacy data suggests that BKM120 in combination with AA has no clinically meaningful anti-tumor activity in CRPC patients who failed prior AA as evidenced in this trial with a limited number of patients enrolled.

Date of Clinical Trial Report

Clinical report published: 13-May-2016