Sponsor

Novartis

Generic Drug Name

Panobinostat

Trial Indication

Multiple Myeloma

Protocol Number

CLBH589B2207

Protocol Title

A phase Ib, multi-center, open-label, dose-escalation study of oral LBH589 and iv bortezomib in adult patients with multiple myeloma

Clinical Trial Phase

Phase Ib

Phase of Drug Development

Phase III

Study Start/End Dates

18-Oct-2007 to 07-Oct-2013

Study Design/Methodology

This was a phase Ib study in which escalating doses of oral panobinostat and bortezomib were administered to patients with relapsed or relapsed and refractory multiple myeloma. Each cohort consisted of a minimum of six patients and dose escalation was to end when at least 12 maximum tolerated dose-evaluable patients had been enrolled at the given dose level. The maximum tolerated dose-level cohort was to be expanded to a total of 22 patients treated, in order to assess safety and tolerability at maximum tolerated dose.

A 10 mg dose of panobinostat and 1.0 mg/m^2 of bortezomib were considered to be safe and appropriate for the commencement of the dose-escalation phase. In this phase, dexamethasone was added to the study treatment from Cycle 2 onward at the Investigator's discretion; as the addition of 20 mg of dexamethasone on the day of and the day after each bortezomib dose was associated with improved responses.

After implementation of Amendment 2 to the protocol, the dose expansion phase was opened to enroll 12 to 15 patients to collect safety, tolerability and pharmacokinetic data of panobinostat and bortezomib with dexamethasone at the recommended dose with a different dosing regimen (non-continuous 20 mg panobinostat thrice in a week with 2 weeks on/1 week off schedule, with 1.3 mg/m^2 bortezomib on D1, D4, D8 and D11, plus 20 mg dexamethasone on each day of and each day after bortezomib dosing). The cycle length was 3 weeks. After 8 cycles of treatment, patients were to discontinue bortezomib/dexamethasone, and continue on panobinostat only, until disease progression, unacceptable toxicity, patient refusal and/or at Investigator's own discretion.

Centers

Australia- 2 centers, Canada- 2 centers, Germany- 6 centers, Italy- 2 centers, Spain- 2 centers, and the USA – 5 centers

Publication

San-Miguel JF, Richardson PG, Guenther A, et al (2013) Phase Ib study of panobinostat and bortezomib in relapsed or relapsed and refractory multiple myeloma. J Clin Oncol; 31(29): 3696-703

Objectives:

Primary Objective:

- To determine the maximum tolerated dose of panobinostat and bortezomib when administered in combination

Secondary objectives:

- To characterize the safety and tolerability of the study treatment on dose escalation and expansion phase
- To characterize the pharmacokinetic profile of bortezomib in combination with panobinostat in the dose escalation phase
- To evaluate the pharmacokinetic profile of panobinostat with and without bortezomib in the dose escalation phase
- To evaluate the pharmacokinetic of bortezomib and panobinostat with and without dexamethasone in the dose expansion phase
- To assess the preliminary efficacy of the study treatment on dose escalation and expansion phases

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

Panobinostat was supplied as hard gelatin capsules at dose strengths of 5 mg or 20 mg and administered orally at escalating dose for three days per week every week (Days 1, 3, 5, 8, 10, 12, 15, 17, 19 in a 21 day cycle) in the dose escalation phase and three days per week on

"2 weeks on/1 week off" schedule, i.e. on Days: 1, 3, 5, 8, 10, 12, with Days 13-21 being treatment holiday, in the dose expansion phase.

Bortezomib (Velcade®) was administered in the dose escalation phase at escalating doses as a 3 to 5 seconds bolus iv injection starting at 1.0 mg/m^2, twice weekly for two weeks (Days 1, 4, 8 and 11) followed by a 10-day treatment holiday (Days 12-21). In the dose expansion phase, the dosage was 1.3 mg/m^2 using the same schedule.

Dexamethasone was sourced locally, and administered at a dose of 20 mg orally. In the dose escalation phase, investigators could administer dexamethasone from Cycle 2 onwards four times weekly for two weeks (Days 1, 2, 4, 5, 8, 9, 11, and 12) and continued onwards if required. In the dose expansion phase, dexamethasone was administered from Cycle 2 day 1, four times weekly for two weeks (Days 1, 2, 4, 5, 8, 9, 11 and 12) with Days 13-21 being treatment holiday.

Statistical Methods

Estimation of the maximum tolerated dose was performed based on incidence of dose limiting toxicities. An adaptive Bayesian logistic regression model with overdose control and dose escalation criteria were used for the dose escalation.

The maximum tolerated dose was defined as the dose level with the highest probability of target dosing in which the posterior probability of the chance of excessive and unacceptable toxicity was less than 25% with at least 12 patients required to be treated at that dose level. The final recommended dose level was based on considerations of the maximum tolerated dose estimated by the 6-parameter logistic model, and on an overall assessment of safety taking into consideration tolerability data from subsequent cycles at all different dose levels tested.

Evidence of anti-multiple myeloma activity of panobinostat in combination with bortezomib was evaluated using best overall response based on the International Uniform Response Criteria for multiple myeloma by the International Myeloma Working Group and the Guidelines for the Uniform Reporting of Clinical Trials: Report of the 2008 International Myeloma Workshop Consensus Panel I. The overall response rate defined as percent of patients with best overall response≥ partial response was presented in the dose escalation and expansion phases. Also, the two-sided 95% confidence interval using the exact method of response rate was calculated for dose escalation phase and the expansion phase. Efficacy analysis was repeated on the dose escalation and expansion phases in following subgroups:

- Bortezomib refractory population
- Population refractory to the last line of therapy received prior to study entry

The assessment of safety was based mainly on the frequency of adverse events and on the number of laboratory values outside of lab normal ranges. Other safety data (e.g., electrocardiogram, vital signs, etc.) were considered as appropriate. All safety data were listed.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion criteria

- Patients with a diagnosis of active multiple myeloma according to the International Myeloma Working Group criteria, and deemed by the investigator as requiring treatment.
- Patients who had received at least one prior line of therapy, including patients with relapsed as well as relapsed-refractory multiple myeloma. One prior line of therapy may consist of induction followed by autologous stem cell transplantation.
- Patients who were suitable (according to their local product information and applicable health authority recommendations) for treatment with bortezomib. Note: patients previously treated with bortezomib were eligible to participate in the study.
- Patients enrolled in the dose expansion phase were to have measurable M component at entry according to the International Myeloma Working Group criteria including at least one of the following:
  - Serum M-protein by sPEP ≥ 1 g/dL (>10g/L)
  - For patients with IgA M-protein whose sPEP was not providing sufficiently precise quantification due to confounded migration of M-protein with serum beta globulins, a quantification by nephelometry / turbidometry was permitted and to show serum M-protein ≥ 1 g/dL
  - Urine M-protein by uPEP ≥ 200 mg/24 h
  - Serum free light chain assay: Involved free light chain level ≥ 100 mg/L, provided serum free light chain ratio was abnormal. (abnormal if free light chain ratio is <0.26 or >1.65)
- Adults ≥ 18 years old
- Eastern Cooperative Oncology Group Performance Status ≤ 2
- Life expectancy >12 weeks
- Patients with following laboratory values:
  - Absolute Neutrophil Count ≥ 1.5 x 10^9/L
  - Platelets ≥ 100 x 10^9/L
  - Calculated creatinine clearance ≥ 30 mL/min
  - Aspartate aminotransferase and alanine aminotransferase ≤ 2.5 x upper limit of normal
  - Serum bilirubin ≤ 1.5 x upper limit of normal
  - Serum potassium, magnesium, phosphorous, within normal limits for institution
  - Total calcium (corrected for serum albumin) or ionized calcium equal to lower normal limits for institution or greater (≥ lower limit of normal) but not higher than common terminology criteria for adverse events grade 1

  Note: Potassium, calcium, magnesium, and/or phosphorous supplements was given to correct values that are < lower limit of normal.

- Baseline multiple uptake gated acquisition or echocardiography must demonstrate left ventricular ejection fraction ≥ the lower limit of the institutional normal
- All patients (dose-escalation and dose-expansion patients) were willing to undergo a mandatory bone marrow aspirate sampling at baseline (for cytology) and another later in the study if the patient eventually goes on to experience a complete remission or partial response. For patients who joined the study at the dose-expansion phase, they must also give consent to have an extra volume of sample taken for exploratory biomarker testing. (Note: One extra bone aspirate sample at C2D1 was optional as per the protocol).
- Patient was able to sign informed consent and to comply with the protocol
- Patient was able to swallow capsules

Exclusion criteria:

- Patients with prior exposure to a histone deacetylase inhibitor used in the treatment of multiple myeloma
- Patients with refractory multiple myeloma (i.e. patients refractory to all prior therapies) who under all prior previous lines of therapy had :
  - either never reached a response better than stable disease
  - or whose disease progressed from any best response while still under therapy
  - or whose disease progressed within 60 days of last dose of therapy
- Patients who had prior allogeneic stem cell transplantation and showed evidence of active graft-versus-host disease or of graft-versus-host disease requiring immunosuppressive therapy.
- Patient who had grade 1 peripheral neuropathy with pain or grade ≥ 2 peripheral neuropathy on clinical examination within 14 days before first study treatment
- Patients with impaired cardiac function or clinically significant cardiac diseases, including any one of the following:
  - Congenital long QT syndrome
  - History or presence of sustained ventricular tachyarrhythmia. (Patients with a history of atrial arrhythmia were eligible but had to be discussed with the Sponsor prior to enrollment)
  - Any history of ventricular fibrillation or torsade de pointes
  - Bradycardia defined as heart rate < 50 beats per minute. Patients with pacemakers were eligible if heart rate ≥ 50 beats per minute.
  - Screening electrocardiogram with a QTc > 450 msec
  - Right bundle branch block + left anterior hemiblock (bifascicular block)
  - Myocardial infarction or unstable angina ≤ 6 months prior to starting study drug
  - Other clinically significant heart disease (e.g., Congestive heart failure New York Heart Association class III or IV, uncontrolled hypertension, history of labile hypertension, or history of poor compliance with an antihypertensive regimen)

- Patients with impaired gastrointestinal function or gastrointestinal disease that might significantly alter the absorption of panobinostat
- Patient with unresolved diarrhea ≥ common terminology criteria for adverse events grade 2
- Patients with other concurrent severe and/or uncontrolled medical conditions (e.g., uncontrolled diabetes, active or uncontrolled infection, acute diffuse pulmonary disease, pericardial disease, uncontrolled thyroid dysfunction) including abnormal laboratory values, that could cause unacceptable safety risks or compromise compliance with the protocol
- Patients using medications that had relative risk of prolonging the QT interval or inducing torsade de pointes if treatment could not be discontinued or switched to a different medication prior to starting study drug
- Patients who needed valproic acid for any medical condition during the study or within 5 days prior to the first panobinostat treatment.
- Patients who had received targeted agents within 2 weeks or within 5 half-lives of the agent and active metabolites (whichever was longer) and who had not recovered from side effects of those therapies.
- Patients who had received either immunotherapy within ≤ 8 weeks; chemotherapy within ≤ 4 weeks; or radiation therapy to >30% of marrow-bearing bone within ≤ 2 weeks prior to starting study treatment; or who had not yet recovered from side effects of such therapies.
- Patients who had received steroids (e.g. dexamethasone) ≤ 2 weeks prior to starting study treatment or who had not recovered from side effects of such therapy. Concomitant therapy medications that included corticosteroids were allowed if patients received <10 mg of prednisone or equivalent as indicated for other medical conditions, or up to 100 mg of hydrocortisone as pre-medication for administration of certain medications or blood products while enrolled in this study.
- Patients who had undergone major surgery ≤ 4 weeks prior to starting study drug or who had not recovered from side effects of such therapy.
- Women who were pregnant or breast feeding or women of childbearing potential not willing to use a double method of contraception during the study and for 3 months after treatment. One of these methods of contraception must be a barrier method. Women of child bearing potential were defined as women who had not undergone a hysterectomy or who had not been naturally postmenopausal for at least 12 consecutive months (i.e., who had menses any time in the preceding 12 consecutive months). Women of childbearing potential must had a negative serum pregnancy test within 7 days of the first administration of oral panobinostat.
- Male patients whose sexual partners were women of child bearing potential not using a double method of contraception during the study and for 3 months after treatment. One of these methods of contraception must be a condom.

- Patients with a prior malignancy within the last 3 years (except for basal or squamous cell carcinoma, or in situ cancer of the cervix).
- Patients with any significant history of non-compliance to medical regimens or unwilling or unable to comply with the instructions given to him/her by the study staff.
- Patients who had shown intolerance to bortezomib or to dexamethasone or components of these drugs or has any contraindication to one or the other drug, following locally applicable prescribing information.

Participant Flow Table

Patient disposition by cohort in dose escalation phase - Full Analysis Set

	PAN 10 mg + BTZ 1.0 mg/m^2 N=7 n (%)	PAN 20 mg + BTZ 1.0 mg/m^2 N=7 n (%)	PAN 20 mg + BTZ 1.3 mg/m^2 (MTD) N=17 n (%)	PAN 30 mg + BTZ 1.3 mg/m^2 N=7 n (%)	PAN 25 mg + BTZ 1.3 mg/m^2 N=9 n (%)	All Patients (Dose Escalation Phase) N=47 n (%)
Patients enrolled[1]	7 (100.0)	7 (100.0)	17 (100.0)	7 (100.0)	9 (100.0)	47 (100.0)
Patients discontinued treatment[2]	7 (100.0)	7 (100.0)	17 (100.0)	7 (100.0)	9 (100.0)	47 (100.0)
Primary reason for end of treatment						
Abnormal laboratory value(s)	1 (14.3)	0	0	0	0	1 (2.1)
Administrative problems	1 (14.3)	1 (14.3)	2 (11.8)	0	1 (11.1)	5 (10.6)
Adverse Event(s)	1 (14.3)	2 (28.6)	8 (47.1)	4 (57.1)	3 (33.3)	18 (38.3)
Disease progression	3 (42.9)	4 (57.1)	5 (29.4)	2 (28.6)	4 (44.4)	18 (38.3)
Subject withdrew consent	1 (14.3)	0	2 (11.8)	1 (14.3)	1 (11.1)	5 (10.6)

[1]Treated with at least one dose of study treatment
[2]Patient completed End of Treatment CRF page

Patient disposition in dose expansion phase - Full Analysis Set

	PAN 20 mg (2 weeks on/1 week off) + BTZ 1.3 mg/m^2 + DEX 20 mg N=15 n (%)
Patients enrolled[1]	15 (100.0)
Patients discontinued treatment[2]	15 (100.0)
Primary reason for end of treatment	
Administrative problems	1 (6.7)
Adverse Event(s)	5 (33.3)
Death[3]	1 (6.7)
Disease progression	6 (40.0)

	PAN 20 mg (2 weeks on/1 week off) + BTZ 1.3 mg/m^2 + DEX 20 mg N=15 n (%)
Subject withdrew consent	2 (13.3)

[1]Treated with at least one dose of study treatment

[2]Patient completed End of Treatment CRF page

[3]Includes only those patients for whom death was reported as the primary reason for discontinuation of treatment.

Baseline Characteristics

Demographic summary by cohort in dose escalation phase – Full analysis set

Demographics variable	PAN 10 mg + BTZ 1.0 mg/m^2 N=7	PAN 20 mg + BTZ 1.0 mg/m^2 N=7	(MTD) PAN 20 mg + BTZ 1.3 mg/m^2 N=17	PAN 30 mg + BTZ 1.3 mg/m^2 N=7	PAN 25 mg + BTZ 1.3 mg/m^2 N=9	All Patients (Dose Escalation Phase) N=47
Sex - n (%)						
Female	3 (42.9)	1 (14.3)	6 (35.3)	3 (42.9)	2 (22.2)	15 (31.9)
Male	4 (57.1)	6 (85.7)	11 (64.7)	4 (57.1)	7 (77.8)	32 (68.1)
Age (Years)						
Mean	61.1	57.6	64.4	60.0	60.3	61.4
Median	62.0	54.0	63.0	61.0	62.0	62.0
SD	10.67	10.49	8.80	7.16	8.62	9.04
Minimum - Maximum	47.0 - 73.0	46.0 - 78.0	46.0 - 83.0	48.0 - 71.0	49.0 - 73.0	46.0 - 83.0
Age category - n (%)						
<65 years	4 (57.1)	6 (85.7)	10 (58.8)	6 (85.7)	6 (66.7)	32 (68.1)
≥65 years	3 (42.9)	1 (14.3)	7 (41.2)	1 (14.3)	3 (33.3)	15 (31.9)
Race - n (%)						
Caucasian	7 (100.0)	7 (100.0)	17 (100.0)	7 (100.0)	9 (100.0)	47 (100.0)
Ethnicity - n (%)						
Hispanic/Latino	3 (42.9)	1 (14.3)	5 (29.4)	3 (42.9)	2 (22.2)	14 (29.8)
Other	4 (57.1)	6 (85.7)	12 (70.6)	4 (57.1)	7 (77.8)	33 (70.2)
ECOG performance status - n (%)						
0	3 (42.9)	5 (71.4)	6 (35.3)	5 (71.4)	3 (33.3)	22 (46.8)
1	4 (57.1)	2 (28.6)	11 (64.7)	2 (28.6)	6 (66.7)	25 (53.2)
Weight (kg)						
Mean	75.6	75.6	73.5	83.3	72.8	75.5
Median	75.5	73.4	72.0	85.2	71.9	72.2
SD	20.36	8.84	14.54	23.17	10.57	15.47

Demographics variable	PAN 10 mg + BTZ 1.0 mg/m^2 N=7	PAN 20 mg + BTZ 1.0 mg/m^2 N=7	(MTD) PAN 20 mg + BTZ 1.3 mg/m^2 N=17	PAN 30 mg + BTZ 1.3 mg/m^2 N=7	PAN 25 mg + BTZ 1.3 mg/m^2 N=9	All Patients (Dose Escalation Phase) N=47
Minimum - Maximum	45.1 - 104.0	65.0 - 89.0	50.0 - 102.0	53.9 - 119.5	60.0 - 90.0	45.1 - 119.5
Height (cm)						
n	7	7	16	7	9	46
Mean	164.7	171.1	166.2	170.6	169.6	168.0
Median	163.0	173.0	167.0	173.0	168.0	168.0
SD	10.00	10.68	8.92	13.66	9.42	10.08
Minimum - Maximum	150.0 - 178.0	154.0 - 182.0	145.0 - 182.0	150.0 - 187.0	153.0 - 180.0	145.0 - 187.0
Body surface area (m^2)						
n	7	7	16	7	9	46
Mean	1.9	1.9	1.8	2.0	1.9	1.9
Median	1.9	1.8	1.9	2.0	1.8	1.9
SD	0.29	0.15	0.22	0.35	0.16	0.23
Minimum - Maximum	1.4 - 2.3	1.8 - 2.1	1.4 - 2.2	1.5 - 2.5	1.7 - 2.1	1.4 - 2.5

SD = standard deviation
ECOG = Eastern Cooperative Oncology Group
Body Surface Area: BSA[m^2] = 234.94*(height[cm]**0.422)*(weight[kg]**0.515)/10000

Demographic summary in dose expansion phase – Full analysis set

Demographics variable	PAN 20 mg (2 weeks on/1 week off) + BTZ 1.3 mg/m^2 + Dex 20 mg N=15
Sex -n (%)	
Female	4 (26.7)
Male	11 (73.3)
Age (Years)	
Mean	60.8
Median	62.0
SD	6.32
Minimum - Maximum	48.0 - 71.0
Age category -n (%)	
<65 years	12 (80.0)
≥65 years	3 (20.0)
Race -n (%)	
Black	1 (6.7)

Demographics variable	PAN 20 mg (2 weeks on/1 week off) + BTZ 1.3 mg/m^2 + Dex 20 mg N=15
Caucasian	14 (93.3)
Ethnicity -n (%)	
Hispanic/Latino	2 (13.3)
Other	13 (86.7)
ECOG performance status -n (%)	
0	12 (80.0)
1	3 (20.0)
Weight (kg)	
Mean	77.1
Median	76.8
SD	16.56
Minimum - Maximum	50.0 - 109.5
Height (cm)	
Mean	170.4
Median	172.0
SD	10.52
Minimum - Maximum	150.0 - 183.0
Body surface area (m^2)	
Mean	1.9
Median	1.9
SD	0.24
Minimum - Maximum	1.5 - 2.3

Summary of Efficacy

Primary Outcome Result

Refer to Safety Result section for primary outcome result.

Secondary Outcome Result(s)

Best overall response rates by cohort in dose escalation phase – Full analysis set

	PAN 10 mg + BTZ 1.0 mg/m^2 N=7 n (%)	PAN 20 mg + BTZ 1.0 mg/m^2 N=7 n (%)	(MTD) PAN 20 mg + BTZ 1.3 mg/m^2 N=17 n (%)	PAN 30 mg + BTZ 1.3 mg/m^2 N=7 n (%)	PAN 25 mg + BTZ 1.3 mg/m^2 N=9 n (%)	All Patients (Dose Escalation Phase) N=47 n (%)

Stringent Complete response (sCR)	0	0	1 (5.9)	1 (14.3)	0	2 (4.3)
Complete Response (CR)	0	0	2 (11.8)	0	0	2 (4.3)
Very Good Partial Response (VGPR)	1 (14.3)	0	2 (11.8)	0	0	3 (6.4)
Partial Response (PR)	0	2 (28.6)	4 (23.5)	3 (42.9)	5 (55.6)	14 (29.8)
Minor Response (MR)	0	1 (14.3)	3 (17.6)	0	0	4 (8.5)
Stable Disease (SD)	3 (42.9)	2 (28.6)	2 (11.8)	0	1 (11.1)	8 (17.0)
Clinical Relapse (CRel)	0	0	0	0	0	0
Progressive Disease (PD)	2 (28.6)	1 (14.3)	0	1 (14.3)	1 (11.1)	5 (10.6)
Unknown	1 (14.3)	1 (14.3)	3 (17.6)	2 (28.6)	2 (22.2)	9 (19.1)
Response rate (sCR, CR, VGPR, PR)	1 (14.3)	2 (28.6)	9 (52.9)	4 (57.1)	5 (55.6)	21 (44.7)
95% Confidence interval[1]	(0.4, 57.9)	(3.7, 71.0)	(27.8, 77.0)	(18.4, 90.1)	(21.2, 86.3)	(30.2, 59.9)

[1]The confidence interval is calculated in terms of the Clopper-Pearson method

Best overall response rates in dose expansion phase – Full analysis set

	PAN 20 mg (2 weeks on/1 week off) + BTZ 1.3 mg/m^2 + Dex 20 mg **N=15** **n (%)**
Stringent Complete response (sCR)	0
Complete Response (CR)	0
Very Good Partial Response (VGPR)	3 (20.0)
Partial Response (PR)	8 (53.3)
Minor Response (MR)	2 (13.3)
Stable Disease (SD)	1 (6.7)
Clinical Relapse (CRel)	0
Progressive Disease (PD)	1 (6.7)
Unknown	0
Response rate (sCR, CR, VGPR, PR)	11 (73.3)
95% Confidence interval [1]	(44.9%, 92.2%)

[1]The confidence interval is calculated in terms of the Clopper-Pearson method.

Best overall response rates as per Investigator's assessment by cohort for bortezomib refractory patients in dose escalation phase - Full analysis set

	PAN 10 mg + BTZ 1.0 mg/m^2 N=7			PAN 20 mg + BTZ 1.0 mg/m^2 N=7			(MTD) PAN 20 mg + BTZ 1.3 mg/m^2 N=17			PAN 30 mg + BTZ 1.3 mg/m^2 N=7			PAN 25 mg + BTZ 1.3 mg/m^2 N=9			All Patients (Dose Escalation Phase) N=47		
	Total	n	(%)	Total	n	(%)	Total	n	(%)	Total	N	(%)	Total	n	(%)	Total	n	(%)
Stringent Complete response (sCR)	4	0	0	5	0	0	4	0	0	0	0	0	2	0	0	15	0	0
Complete Response (CR)	4	0	0	5	0	0	4	0	0	0	0	0	2	0	0	15	0	0
Very Good Partial Response (VGPR)	4	0	0	5	0	0	4	0	0	0	0	0	2	0	0	15	0	0
Partial Response (PR)	4	0	0	5	1	20.0	4	0	0	0	0	0	2	2	100.0	15	3	20.0
Minor Response (MR)	4	0	0	5	1	20.0	4	1	25.0	0	0	0	2	0	0	15	2	13.3
Stable Disease (SD)	4	2	50.0	5	2	40.0	4	1	25.0	0	0	0	2	0	0	15	5	33.3
Clinical Relapse (CRel)	4	0	0	5	0	0	4	0	0	0	0	0	2	0	0	15	0	0
Progressive Disease (PD)	4	1	25.0	5	1	20.0	4	0	0	0	0	0	2	0	0	15	2	13.3
Unknown	4	1	25.0	5	0	0.0	4	2	50.0	0	0	0	2	0	0	15	3	20.0

N: number of patients of the full analysis set;

Total is the subset of the full analysis set including patients refractory to bortezomib by progressing or not responding to bortezomib in the most recent prior line of therapy containing bortezomib (whether last line prior to study entry or not).

Percentages are based on Total

Best overall response rates as per Investigator's assessment for bortezomib refractory patients in dose expansion phase – Full analysis set

	PAN 20 mg (2 weeks on/1 week off) + BTZ 1.3 mg/m^2 + Dex 20 mg N=15		
	Total	**n**	**(%)**
Stringent Complete response (sCR)	4	0	0
Complete Response (CR)	4	0	0
Very Good Partial Response (VGPR)	4	0	0
Partial Response (PR)	4	2	50.0
Minor Response (MR)	4	1	25.0
Stable Disease (SD)	4	0	0
Clinical Relapse (CRel)	4	0	0
Progressive Disease (PD)	4	1	25.0
Unknown	4	0	0

N: number of patients of the full analysis set;

Total is the subset of the full analysis set including patients refractory to bortezomib by progressing or not responding to bortezomib in the most recent prior line of therapy containing bortezomib (whether last line prior to study entry or not)

Percentages are based on Total

Summary of Safety

Safety Results

Posterior probabilities of dose limiting toxicity based on the Bayesian logistic regression model by dose level of panobinostat and bortezomib – Maximum tolerated dose determining set

Drug dose			**Proportion of patients with DLT**			**Posterior Probability of DLT**					
						Next dose level					
PAN (mg)	**BTZ (mg/m^2)**	**Cohort#**	**Total**	**n**	**%**	**PAN (mg)**	**BTZ (mg/m^2)**	**Mean (95% CI)**	**Under-dosing (%)[1]**	**Target toxicity (%)[2]**	**Unacceptable or excessive toxicity (%)[3]**
10	1.0	1	6	0	0	10	1	14 (4 ; 33)	79.4	18.8	1.8
						20	1	21 (6 ; 46)	54.3	36.8	8.9
						20	1.3	28 (9 ; 58)	29.9	45.2	25
20	1.0	2	5	0	0	20	1	16 (5 ; 33)	74.6	23.7	1.7
						20	1.3	22 (7 ; 44)	47.8	42.6	9.5

Drug dose			Proportion of patients with DLT			Posterior Probability of DLT					
						Next dose level					
PAN (mg)	BTZ (mg/m^2)	Cohort[#]	Total	n	%	PAN (mg)	BTZ (mg/m^2)	Mean (95% CI)	Under-dosing (%)[1]	Target toxicity (%)[2]	Unacceptable or excessive toxicity (%)[3]
						25	1.3	26 (10 ; 51)	31.7	49.9	18.4
20	1.3	3	6	0	0	20	1.3	17 (6 ; 33)	72	26.4	1.6
						25	1.3	21 (8 ; 40)	53	41.4	5.6
						30	1.3	26 (11 ; 55)	31.5	50.9	17.6
30	1.3	4	6	4	66.7	20	1.3	21 (7 ; 39)	48.5	45.4	6.1
						25	1.3	28 (12 ; 49)	19.6	57.9	22.5
						30	1.3	39 (18 ; 71)	4.3	39	56.6
25	1.3	5	6	2	33.3	20	1.3	22 (8 ; 39)	43.5	50.7	5.8
						25	1.3	29 (14 ; 48)	13.4	62.8	23.8
						30	1.3	40 (20 ; 70)	2.5	37.6	59.9
20	1.3	6	9	3	33.3	20	1.3	25 (12 ; 40)	25.8	66	8.3
						25	1.3	32 (18 ; 49)	5.4	62.9	31.8
						30	1.3	41 (22 ; 68)	1.1	35.6	63.2

Total: number of evaluable patients (included in MTD determining set).
n: Number of patients with at least one DLT.
Percentage is based on Total
[1]Under dosing: DLT rate under 20%.
[2]Targeted toxicity: DLT rate >= 20% and <35%
[3]Excessive or unacceptable toxicity: DLT rate >= 35%
The maximum next dose level is determined if the probability of unacceptable or excessive toxicity is not exceeding 25%.
[#]Cohort 3 and 6 were later pooled as MTD Cohort for presentation of data in the CSR.

Adverse events regardless of study treatment relationship by primary system organ class in dose escalation phase − Safety set

Primary system organ class	PAN 10 mg + BTZ 1.0 mg/m^2 N=7 n (%)	PAN 20 mg + BTZ 1.0 mg/m^2 N=7 n (%)	PAN 20 mg + BTZ 1.3 mg/m^2 (MTD) N=17 n (%)	PAN 30 mg + BTZ 1.3 mg/m^2 N=7 n (%)	PAN 25 mg + BTZ 1.3 mg/m^2 N=9 n (%)	All Patients (Dose Escalation Phase) N=47 n (%)
Any primary system organ class	7 (100.0)	7 (100.0)	17 (100.0)	7 (100.0)	9 (100.0)	47 (100.0)
Blood and lymphatic system disorders	6 (85.7)	6 (85.7)	17 (100.0)	7 (100.0)	9 (100.0)	45 (95.7)
General disorders and administration site conditions	6 (85.7)	6 (85.7)	14 (82.4)	7 (100.0)	8 (88.9)	41 (87.2)
Gastrointestinal disorders	7 (100.0)	2 (28.6)	17 (100.0)	7 (100.0)	7 (77.8)	40 (85.1)
Metabolism and nutrition disorders	5 (71.4)	5 (71.4)	12 (70.6)	5 (71.4)	6 (66.7)	33 (70.2)
Infections and infestations	5 (71.4)	1 (14.3)	13 (76.5)	6 (85.7)	6 (66.7)	31 (66.0)
Nervous system disorders	2 (28.6)	1 (14.3)	13 (76.5)	6 (85.7)	5 (55.6)	27 (57.4)
Respiratory, thoracic and mediastinal disorders	4 (57.1)	2 (28.6)	8 (47.1)	6 (85.7)	4 (44.4)	24 (51.1)
Musculoskeletal and connective tissue disorders	5 (71.4)	3 (42.9)	9 (52.9)	3 (42.9)	3 (33.3)	23 (48.9)
Investigations	1 (14.3)	2 (28.6)	9 (52.9)	4 (57.1)	6 (66.7)	22 (46.8)
Vascular disorders	0	1 (14.3)	7 (41.2)	5 (71.4)	4 (44.4)	17 (36.2)
Psychiatric disorders	2 (28.6)	3 (42.9)	5 (29.4)	2 (28.6)	4 (44.4)	16 (34.0)
Skin and subcutaneous tissue disorders	1 (14.3)	2 (28.6)	8 (47.1)	2 (28.6)	2 (22.2)	15 (31.9)
Renal and urinary disorders	0	1 (14.3)	5 (29.4)	2 (28.6)	5 (55.6)	13 (27.7)
Cardiac disorders	3 (42.9)	0	4 (23.5)	1 (14.3)	1 (11.1)	9 (19.1)
Eye disorders	1 (14.3)	0	3 (17.6)	1 (14.3)	3 (33.3)	8 (17.0)
Injury, poisoning and procedural complications	1 (14.3)	0	3 (17.6)	1 (14.3)	3 (33.3)	8 (17.0)
Endocrine disorders	0	0	3 (17.6)	2 (28.6)	1 (11.1)	6 (12.8)
Hepatobiliary disorders	0	0	1 (5.9)	0	1 (11.1)	2 (4.3)
Reproductive system and breast disorders	0	0	1 (5.9)	1 (14.3)	0	2 (4.3)
Ear and labyrinth disorders	0	0	0	0	1 (11.1)	1 (2.1)

Primary system organ classes are sorted in descending frequency, as reported in the “All patients” column

A patient with multiple adverse events within a primary system organ class is counted only once

Adverse events regardless of study treatment relationship by primary system organ class in dose expansion phase – Safety set

Primary system organ class	PAN 20 mg (2 weeks on/1 week off) + BTZ 1.3 mg/m^2 + DEX 20 mg N=15 n (%)
Any primary system organ class	15 (100.0)
Gastrointestinal disorders	14 (93.3)
General disorders and administration site conditions	14 (93.3)
Infections and infestations	13 (86.7)
Nervous system disorders	13 (86.7)
Respiratory, thoracic and mediastinal disorders	13 (86.7)
Metabolism and nutrition disorders	12 (80.0)
Musculoskeletal and connective tissue disorders	12 (80.0)
Blood and lymphatic system disorders	11 (73.3)
Investigations	7 (46.7)
Psychiatric disorders	7 (46.7)
Skin and subcutaneous tissue disorders	7 (46.7)
Vascular disorders	7 (46.7)
Eye disorders	5 (33.3)
Injury, poisoning and procedural complications	4 (26.7)
Renal and urinary disorders	3 (20.0)
Cardiac disorders	2 (13.3)
Ear and labyrinth disorders	1 (6.7)
Endocrine disorders	1 (6.7)
Immune system disorders	1 (6.7)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (6.7)
Reproductive system and breast disorders	1 (6.7)

Primary system organ classes are sorted in descending frequency
A patient with multiple adverse events within a primary system organ class is counted only once

Frequent AEs (at least 10%) regardless of study treatment relationship by preferred term in dose escalation phase - Safety set

Preferred term	PAN 10 mg + BTZ 1.0 mg/m^2 N=7 n (%)	PAN 20 mg + BTZ 1.0 mg/m^2 N=7 n (%)	(MTD) PAN 20 mg + BTZ 1.3 mg/m^2 N=17 n (%)	PAN 30 mg + BTZ 1.3 mg/m^2 N=7 n (%)	PAN 25 mg + BTZ 1.3 mg/m^2 N=9 n (%)	All Patients (Dose Escalation Phase) N=47 n (%)
-Any preferred term	7 (100)	7 (100)	17 (100)	7 (100)	9 (100)	47 (100)
Thrombocytopenia	6 (85.7)	6 (85.7)	16 (94.1)	7 (100)	9 (100)	44 (93.6)

Preferred term	PAN 10 mg + BTZ 1.0 mg/m^2 N=7 n (%)	PAN 20 mg + BTZ 1.0 mg/m^2 N=7 n (%)	(MTD) PAN 20 mg + BTZ 1.3 mg/m^2 N=17 n (%)	PAN 30 mg + BTZ 1.3 mg/m^2 N=7 n (%)	PAN 25 mg + BTZ 1.3 mg/m^2 N=9 n (%)	All Patients (Dose Escalation Phase) N=47 n (%)
Neutropenia	4 (57.1)	4 (57.1)	15 (88.2)	7 (100)	7 (77.8)	37 (78.7)
Diarrhoea	3 (42.9)	2 (28.6)	14 (82.4)	7 (100)	6 (66.7)	32 (68.1)
Anaemia	3 (42.9)	6 (85.7)	10 (58.8)	5 (71.4)	5 (55.6)	29 (61.7)
Nausea	3 (42.9)	1 (14.3)	13 (76.5)	5 (71.4)	6 (66.7)	28 (59.6)
Pyrexia	3 (42.9)	3 (42.9)	8 (47.1)	5 (71.4)	6 (66.7)	25 (53.2)
Fatigue	4 (57.1)	4 (57.1)	7 (41.2)	4 (57.1)	3 (33.3)	22 (46.8)
Asthenia	1 (14.3)	1 (14.3)	8 (47.1)	5 (71.4)	5 (55.6)	20 (42.6)
Decreased appetite	0	2 (28.6)	10 (58.8)	3 (42.9)	5 (55.6)	20 (42.6)
Vomiting	1 (14.3)	1 (14.3)	7 (41.2)	4 (57.1)	5 (55.6)	18 (38.3)
Dizziness	1 (14.3)	0	7 (41.2)	3 (42.9)	2 (22.2)	13 (27.7)
Hypokalaemia	3 (42.9)	0	5 (29.4)	2 (28.6)	3 (33.3)	13 (27.7)
Hyperglycaemia	1 (14.3)	0	4 (23.5)	3 (42.9)	3 (33.3)	11 (23.4)
Respiratory tract infection	0	0	5 (29.4)	3 (42.9)	3 (33.3)	11 (23.4)
Constipation	4 (57.1)	0	3 (17.6)	1 (14.3)	2 (22.2)	10 (21.3)
Dyspnoea	2 (28.6)	0	3 (17.6)	3 (42.9)	2 (22.2)	10 (21.3)
Leukopenia	0	0	6 (35.3)	3 (42.9)	1 (11.1)	10 (21.3)
Cough	1 (14.3)	1 (14.3)	5 (29.4)	1 (14.3)	1 (11.1)	9 (19.1)
Oedema peripheral	0	2 (28.6)	4 (23.5)	1 (14.3)	2 (22.2)	9 (19.1)
Blood creatinine increased	0	1 (14.3)	3 (17.6)	1 (14.3)	3 (33.3)	8 (17.0)
Headache	2 (28.6)	0	3 (17.6)	3 (42.9)	0	8 (17.0)
Neuropathy peripheral	0	0	4 (23.5)	1 (14.3)	3 (33.3)	8 (17.0)
Weight decreased	1 (14.3)	0	3 (17.6)	1 (14.3)	3 (33.3)	8 (17.0)
Arthralgia	1 (14.3)	1 (14.3)	2 (11.8)	1 (14.3)	2 (22.2)	7 (14.9)
Dysgeusia	1 (14.3)	1 (14.3)	3 (17.6)	0	2 (22.2)	7 (14.9)
Epistaxis	1 (14.3)	0	3 (17.6)	2 (28.6)	1 (11.1)	7 (14.9)
Hypertension	0	1 (14.3)	2 (11.8)	3 (42.9)	1 (11.1)	7 (14.9)
Hypotension	0	0	3 (17.6)	2 (28.6)	2 (22.2)	7 (14.9)
Insomnia	1 (14.3)	2 (28.6)	2 (11.8)	0	2 (22.2)	7 (14.9)
Rash	0	1 (14.3)	4 (23.5)	1 (14.3)	1 (11.1)	7 (14.9)
Back pain	2 (28.6)	0	2 (11.8)	1 (14.3)	1 (11.1)	6 (12.8)
Bone pain	1 (14.3)	0	2 (11.8)	1 (14.3)	2 (22.2)	6 (12.8)
Chills	1 (14.3)	0	3 (17.6)	1 (14.3)	1 (11.1)	6 (12.8)
Dyspepsia	2 (28.6)	1 (14.3)	1 (5.9)	2 (28.6)	0	6 (12.8)

Preferred term	PAN 10 mg + BTZ 1.0 mg/m^2 N=7 n (%)	PAN 20 mg + BTZ 1.0 mg/m^2 N=7 n (%)	(MTD) PAN 20 mg + BTZ 1.3 mg/m^2 N=17 n (%)	PAN 30 mg + BTZ 1.3 mg/m^2 N=7 n (%)	PAN 25 mg + BTZ 1.3 mg/m^2 N=9 n (%)	All Patients (Dose Escalation Phase) N=47 n (%)
Flatulence	0	0	5 (29.4)	0	1 (11.1)	6 (12.8)
Hypothyroidism	0	0	3 (17.6)	2 (28.6)	1 (11.1)	6 (12.8)
Lymphopenia	0	0	3 (17.6)	2 (28.6)	1 (11.1)	6 (12.8)
Nasopharyngitis	0	1 (14.3)	3 (17.6)	0	2 (22.2)	6 (12.8)
Pain in extremity	2 (28.6)	1 (14.3)	3 (17.6)	0	0	6 (12.8)
Paraesthesia	0	0	2 (11.8)	2 (28.6)	2 (22.2)	6 (12.8)
Renal failure	0	0	3 (17.6)	1 (14.3)	2 (22.2)	6 (12.8)
Urinary tract infection	2 (28.6)	0	2 (11.8)	1 (14.3)	1 (11.1)	6 (12.8)
Abdominal pain upper	0	0	4 (23.5)	0	1 (11.1)	5 (10.6)
Blood urea increased	0	0	2 (11.8)	2 (28.6)	1 (11.1)	5 (10.6)
C-reactive protein increased	0	0	3 (17.6)	0	2 (22.2)	5 (10.6)
Hypoalbuminaemia	0	1 (14.3)	1 (5.9)	1 (14.3)	2 (22.2)	5 (10.6)
Hypocalcaemia	0	0	1 (5.9)	1 (14.3)	3 (33.3)	5 (10.6)
Hypomagnesaemia	1 (14.3)	1 (14.3)	1 (5.9)	0	2 (22.2)	5 (10.6)
Hyponatraemia	0	0	3 (17.6)	1 (14.3)	1 (11.1)	5 (10.6)
Orthostatic hypotension	0	0	2 (11.8)	1 (14.3)	2 (22.2)	5 (10.6)

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.

Frequent grade 3/4 AEs (at least 5%) regardless of study treatment relationship by preferred term in dose escalation phase - Safety set

Preferred term	PAN 10 mg + BTZ 1.0 mg/m^2 N=7 n (%)	PAN 20 mg + BTZ 1.0 mg/m^2 N=7 n (%)	(MTD) PAN 20 mg + BTZ 1.3 mg/m^2 N=17 n (%)	PAN 30 mg + BTZ 1.3 mg/m^2 N=7 n (%)	PAN 25 mg + BTZ 1.3 mg/m^2 N=9 n (%)	All Patients (Dose Escalation Phase) N=47 n (%)
Any preferred term	6 (85.7)	6 (85.7)	17 (100.0)	7 (100)	9 (100)	45 (95.7)
Thrombocytopenia	6 (85.7)	6 (85.7)	14 (82.4)	7 (100)	7 (77.8)	40 (85.1)
Neutropenia	2 (28.6)	3 (42.9)	11 (64.7)	7 (100)	7 (77.8)	30 (63.8)
Asthenia	0	1 (14.3)	4 (23.5)	5 (71.4)	4 (44.4)	14 (29.8)
Anaemia	1 (14.3)	4 (57.1)	2 (11.8)	1 (14.3)	2 (22.2)	10 (21.3)
Leukopenia	0	0	5 (29.4)	2 (28.6)	1 (11.1)	8 (17.0)
Diarrhoea	0	0	4 (23.5)	1 (14.3)	2 (22.2)	7 (14.9)

Preferred term	PAN 10 mg + BTZ 1.0 mg/m^2 N=7 n (%)	PAN 20 mg + BTZ 1.0 mg/m^2 N=7 n (%)	(MTD) PAN 20 mg + BTZ 1.3 mg/m^2 N=17 n (%)	PAN 30 mg + BTZ 1.3 mg/m^2 N=7 n (%)	PAN 25 mg + BTZ 1.3 mg/m^2 N=9 n (%)	All Patients (Dose Escalation Phase) N=47 n (%)
Hypokalaemia	1 (14.3)	0	1 (5.9)	2 (28.6)	1 (11.1)	5 (10.6)
Fatigue	0	0	2 (11.8)	2 (28.6)	0	4 (8.5)
Hyperglycaemia	0	0	2 (11.8)	0	2 (22.2)	4 (8.5)
Lymphopenia	0	0	1 (5.9)	2 (28.6)	1 (11.1)	4 (8.5)
Respiratory tract infection	0	0	3 (17.6)	0	1 (11.1)	4 (8.5)
Hypoalbuminaemia	0	1 (14.3)	0	1 (14.3)	1 (11.1)	3 (6.4)
Hyponatraemia	0	0	2 (11.8)	1 (14.3)	0	3 (6.4)
Hypophosphataemia	1 (14.3)	0	0	0	2 (22.2)	3 (6.4)
Pneumonia	0	0	0	1 (14.3)	2 (22.2)	3 (6.4)
Respiratory failure	0	1 (14.3)	1 (5.9)	1 (14.3)	0	3 (6.4)
Vomiting	0	0	2 (11.8)	1 (14.3)	0	3 (6.4)

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.

Frequent AEs (at least 20%) regardless of study treatment relationship by preferred term and CTC grade in dose expansion phase - Safety set

	PAN 20 mg (2 weeks on/1 week off) + BTZ 1.3 mg/m^2 + Dex 20 mg N=15	
Preferred term	Any grade n (%)	Grade 3/4 n (%)
-Any preferred term	15 (100)	13 (86.7)
Diarrhoea	13 (86.7)	3 (20.0)
Fatigue	11 (73.3)	3 (20.0)
Thrombocytopenia	11 (73.3)	10 (66.7)
Nausea	10 (66.7)	0
Neutropenia	9 (60.0)	7 (46.7)
Constipation	8 (53.3)	0
Decreased appetite	8 (53.3)	0
Abdominal pain	7 (46.7)	1 (6.7)
Asthenia	7 (46.7)	2 (13.3)
Dizziness	7 (46.7)	2 (13.3)
Neuropathy peripheral	7 (46.7)	1 (6.7)
Vomiting	7 (46.7)	0

Preferred term	PAN 20 mg (2 weeks on/1 week off) + BTZ 1.3 mg/m^2 + Dex 20 mg N=15 Any grade n (%)	Grade 3/4 n (%)
Abdominal discomfort	6 (40.0)	1 (6.7)
Cough	6 (40.0)	0
Dysgeusia	6 (40.0)	0
Leukopenia	6 (40.0)	3 (20.0)
Pyrexia	6 (40.0)	0
Anaemia	5 (33.3)	1 (6.7)
Hypokalaemia	5 (33.3)	2 (13.3)
Hypophosphataemia	5 (33.3)	4 (26.7)
Lymphopenia	5 (33.3)	5 (33.3)
Weight decreased	5 (33.3)	1 (6.7)
Abdominal pain upper	4 (26.7)	0
Arthralgia	4 (26.7)	1 (6.7)
Dehydration	4 (26.7)	1 (6.7)
Dyspnoea	4 (26.7)	1 (6.7)
Hypocalcaemia	4 (26.7)	0
Insomnia	4 (26.7)	2 (13.3)
Myalgia	4 (26.7)	0
Oedema peripheral	4 (26.7)	0
Pain in extremity	4 (26.7)	0
Upper respiratory tract infection	4 (26.7)	0
Back pain	3 (20.0)	0
Blood creatinine increased	3 (20.0)	0
Dysphonia	3 (20.0)	0
Hypoalbuminaemia	3 (20.0)	0
Hyponatraemia	3 (20.0)	1 (6.7)
Hypotension	3 (20.0)	0
Oropharyngeal pain	3 (20.0)	0
Peripheral sensory neuropathy	3 (20.0)	0
Rash	3 (20.0)	0
Respiratory tract infection	3 (20.0)	1 (6.7)
Rhinorrhoea	3 (20.0)	0

Preferred terms are sorted in descending frequency as reported in the “Any grade” column.
A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.

Summary of adverse events in dose escalation phase – Safety set

Category	PAN 10 mg + BTZ 1.0 mg/m^2 N=7 n (%)	PAN 20 mg + BTZ 1.0 mg/m^2 N=7 n (%)	(MTD) PAN 20 mg + BTZ 1.3 mg/m^2 N=17 n (%)	PAN 30 mg + BTZ 1.3 mg/m^2 N=7 n (%)	PAN 25 mg + BTZ 1.3 mg/m^2 N=9 n (%)	All Patients (Dose Escalation Phase) N=47 n (%)
Adverse events[1]	7 (100)	7 (100)	17 (100)	7 (100)	9 (100)	47 (100)
Suspected to be treatment related	6 (85.7)	5 (71.4)	17 (100)	7 (100)	9 (100)	44 (93.6)
Grade 3 or 4 adverse events	6 (85.7)	6 (85.7)	17 (100)	7 (100)	9 (100)	45 (95.7)
Suspected to be treatment related	5 (71.4)	5 (71.4)	16 (94.1)	7 (100)	8 (88.9)	41 (87.2)
Serious adverse events	4 (57.1)	2 (28.6)	13 (76.5)	3 (42.9)	7 (77.8)	29 (61.7)
AEs leading to treatment discontinuation	1 (14.3)	2 (28.6)	8 (47.1)	4 (57.1)	3 (33.3)	18 (38.3)
All deaths						
On-treatment deaths[2]	1 (14.3)	1 (14.3)	0	0	0	2 (4.3)
Other significant adverse events						
AEs requiring dose adjustment or interruption	4 (57.1)	4 (57.1)	13 (76.5)	6 (85.7)	8 (88.9)	35 (74.5)
AEs requiring hospitalization	4 (57.1)	1 (14.3)	10 (58.8)	3 (42.9)	7 (77.8)	25 (53.2)
Clinically notable AEs (CNAE)[3]	6 (85.7)	6 (85.7)	17 (100)	7 (100)	9 (100)	45 (95.7)
Grade 3/4 CNAEs[3]	6 (85.7)	6 (85.7)	16 (94.1)	7 (100)	8 (88.9)	43 (91.5)

[1]Adverse events occurring more than 28 days after the discontinuation of study treatment are not summarized.
[2]Deaths occurring more than 28 days after the discontinuation of study treatment are not summarized.
[3]Clinically notable adverse events are the events for which there is a specific clinical interest in connection with PAN or events which are similar in nature.

Summary of adverse events in dose expansion phase – Safety set

Category	PAN 20 mg (2 weeks on/ one week off) + BTZ 1.3 mg/m^2 + Dex 20 mg N=15 n (%)
Adverse events[1]	15 (100)
Suspected to be treatment related	15 (100)
Grade 3 or 4 adverse events	13 (86.7)
Suspected to be treatment related	11 (73.3)
Serious adverse events	6 (40.0)
AEs leading to study treatment discontinuation	5 (33.3)
All deaths	
On-treatment deaths[2]	2 (13.3)
Other significant adverse events	
AEs requiring dose adjustment or interruption	11 (73.3)
AEs requiring hospitalization	5 (33.3)
Clinically notable AEs[3]	15 (100)
Grade 3/4 clinically notable adverse events[3]	13 (86.7)

[1]Adverse events occurring more than 28 days after the discontinuation of study treatment are not summarized.
[2]Deaths occurring more than 28 days after the discontinuation of study treatment are not summarized.
[3]Clinically notable adverse events are the events for which there is a specific clinical interest in connection with PAN or events which are similar in nature.

Other Relevant Findings

Summary statistics of panobinostat pharmacokinetic parameters on Cycle 1 Day 8 and Cycle 1 Day 15 in dose escalation phase, by cohort - PK set-panobinostat

Cohort PK Parameter (unit)	Cycle 1 Day 8		Cycle 1 Day 15	
PAN 10 mg + BTZ 1.0 mg/m^2 (N=4)				
AUC(0-48) (ng.h/mL)	4	27.8 (38.6)	4	25.5 (39.0)
Cmax (ng/mL)	4	3.5 (10.8)	4	4.8 (68.8)
Tmax (h)	4	2.0 [1.0;2.0]	4	1.0 [0.5;2.8]
T1/2 (h)	4	7.4 (90.0)	4	6.2 (68.1)
C(last) (ng/mL)	4	0.7 (24.8)	4	0.8 (18.2)
T(last) (h)	4	16.0 [8.0;24.5]	4	8.0 [7.8;24.1]
CL/F (L/h)	4	358.4 (55.3)	4	418.5 (54.7)
Vz/F (L)	4	3815.5 (28.3)	4	3722.4 (11.4)
PAN 20 mg + BTZ 1.0 mg/m^2 (N=6)				
AUC(0-48) (ng.h/mL)	6	111.4 (95.6)	4	82.6 (61.4)
Cmax (ng/mL)	6	10.8 (125.5)	4	7.6 (50.6)

Cohort PK Parameter (unit)	Cycle 1 Day 8		Cycle 1 Day 15	
Tmax (h)	6	2.4 [1.0;3.0]	4	2.0 [1.0;3.9]
T1/2 (h)	5	13.8 (3.3)	4	14.4 (56.7)
C(last) (ng/mL)	6	1.3 (63.1)	4	1.1 (159.4)
T(last) (h)	6	24.5 [22.8;48.0]	4	48.0 [23.5;49.8]
CL/F (L/h)	5	150.6 (108.5)	4	191.9 (74.5)
Vz/F (L)	5	2990.8 (113.1)	4	3989.3 (105.9)
PAN 20 mg + BTZ 1.3 mg/m^2 (MTD) (N=16)				
AUC(0-48) (ng.h/mL)	15	107.8 (64.6)	14	91.9 (91.9)
Cmax (ng/mL)	15	15.8 (63.2)	14	12.2 (103.3)
Tmax (h)	15	1.0 [0.1;6.0]	14	1.8 [0.5;3.0]
T1/2 (h)	15	13.2 (65.6)	14	14.1 (62.3)
C(last) (ng/mL)	15	0.9 (31.8)	14	0.8 (44.2)
T(last) (h)	15	46.0 [8.0;48.8]	14	47.0 [8.0;51.1]
CL/F (L/h)	15	167.1 (71.8)	14	193.3 (103.7)
Vz/F (L)	15	3175.2 (54.0)	14	3930.0 (56.6)
PAN 30 mg + BTZ 1.3 mg/m^2 (N=6)				
AUC(0-48) (ng.h/mL)	5	134.6 (38.4)	4	171.3 (85.7)
Cmax (ng/mL)	5	14.5 (74.8)	4	19.8 (109.6)
Tmax (h)	5	1.0 [1.0;3.0]	4	1.8 [0.5;3.5]
T1/2 (h)	5	18.7 (41.4)	4	14.9 (23.4)
C(last) (ng/mL)	5	1.1 (61.1)	4	0.9 (53.6)
T(last) (h)	5	47.1 [24.0;48.0]	4	47.7 [46.8;48.2]
CL/F (L/h)	5	184.0 (34.2)	4	156.2 (81.1)
Vz/F (L)	5	4962.7 (58.2)	4	3360.5 (106.2)
PAN 25 mg + BTZ 1.3 mg/m^2 (N=8)				
AUC(0-48) (ng.h/mL)	7	134.7 (36.9)	7	95.1 (142.4)
Cmax (ng/mL)	7	18.0 (47.6)	7	12.0 (105.4)
Tmax (h)	7	2.0 [0.5;3.0]	7	2.0 [0.9;6.0]
T1/2 (h)	7	15.1 (26.4)	7	10.8 (60.5)
C(last) (ng/mL)	7	1.0 (26.0)	7	1.0 (51.6)
T(last) (h)	7	46.5 [23.9;49.2]	7	46.3 [5.3;48.8]
CL/F (L/h)	7	166.3 (40.6)	7	245.5 (166.0)
Vz/F (L)	7	3624.2 (31.2)	7	3833.6 (81.9)

Values are n, median (range) for Tmax and Tlast, and n, geometric mean (CV% geometric mean) for all other parameters, where n is the number of subjects with non-missing values.
CV% geometric mean = sqrt (exp (variance for log transformed data)-1)*100.

Summary statistics of bortezomib pharmacokinetic parameters on Cycle 1 Day 8 in dose escalation phase, by cohort - PK set - bortezomib

Cycle 1 Day 8 Parameter (unit)	PAN 10 mg + BTZ 1.0 mg/m^2 N=4	PAN 20 mg + BTZ 1.0 mg/m^2 N=7	(MTD) PAN 20 mg + BTZ 1.3 mg/m^2 N=14	PAN 30 mg + BTZ 1.3 mg/m^2 N=5	PAN 25 mg + BTZ 1.3 mg/m^2 N=4
AUC(0-inf) (ng.h/mL)	4 160.4 (59.1)	7 256.2 (48.7)	14 247.3 (59.9)	5 192.9 (37.8)	4 196.9 (74.8)
AUC(0-tlast) (ng.h/mL)	4 79.0 (27.2)	7 132.6 (58.6)	14 155.4 (49.7)	5 109.0 (16.8)	4 123.3 (45.5)
AUC(0-24) (ng.h/mL)	4 55.9 (29.3)	7 95.9 (74.1)	14 117.2 (58.8)	5 77.1 (16.4)	4 88.6 (38.9)
AUC(0-48) (ng.h/mL)	4 79.4 (26.8)	7 132.6 (59.0)	14 158.2 (51.6)	5 109.7 (16.8)	4 123.9 (44.5)
Cmax (ng/mL)	4 72.7 (49.5)	7 179.5 (223.3)	14 157.9 (65.5)	5 76.8 (43.1)	4 101.9 (26.5)
Tmax (h)	4 0.1 [0.1;0.2]	7 0.1 [0.0;0.1]	14 0.1 [0.0;1.3]	5 0.1 [0.1;0.1]	4 0.1 [0.1;0.1]
C(last) (ng/mL)	4 0.9 (36.5)	7 1.1 (35.1)	14 1.3 (55.1)	5 1.2 (25.7)	4 1.2 (73.3)
T(last) (h)	4 47.5 [47.0;48.1]	7 48.0 [46.8;49.0]	14 47.9 [24.0;49.0]	5 47.3 [46.5;48.0]	4 47.4 [46.3;49.2]

Values are n, median (range) for Tmax and Tlast, and n, geometric mean (CV% geometric mean) for all other parameters, where n is the number of subjects with non-missing values.
CV% geometric mean = sqrt (exp (variance for log transformed data)-1)*100.

Summary statistics of panobinostat PK parameters on Cycle 1 Day 8 (combination with bortezomib) and Cycle 2 Day 8 (combination with bortezomib and dexamethasone) in dose expansion phase - PK set - panobinostat

Cohort PK Parameter (unit)	Cycle 1 Day 8		Cycle 2 Day 8	
PAN 20 mg (2 weeks on/ 1 week off) + BTZ 1.3 mg/m^2 + Dex 20 mg (N=15)				
AUC(0-24) (ng.h/mL)	15	61.8 (60.9)	12	47.5 (76.8)
Cmax (ng/mL)	15	9.5 (60.4)	12	8.1 (90.3)
Tmax (h)	15	2.0 [0.5;3.0]	12	1.0 [0.5;6.3]
T1/2 (h)	15	13.3 (34.7)	12	15.9 (29.2)
C(last) (ng/mL)	15	0.8 (52.5)	12	0.7 (81.2)
T(last) (h)	15	28.0 [23.9;47.7]	12	28.0 [25.6;28.5]
CL/F (L/h)	15	241.5 (60.8)	12	285.2 (79.4)
Vz/F (L)	15	4632.6 (71.5)	12	6539.0 (81.0)

Values are n, median (range) for Tmax and Tlast, and n, geometric mean (CV% geometric mean) for all other parameters, where n is the number of subjects with non-missing values.
CV% geometric mean = sqrt (exp (variance for log transformed data)-1)*100.

Summary statistics of bortezomib PK parameters on Cycle 1 Day 8 (combination with panobinostat) and Cycle 2 Day 8 (combination with panobinostat and dexamethasone) in dose expansion phase - PK set - bortezomib

Cohort PK Parameter (unit)	Cycle 1 Day 8		Cycle 2 Day 8	
PAN 20 mg (2 weeks on/ 1 week off) + BTZ 1.3 mg/m^2 + Dex 20 mg (N=15)				
AUC(0-24) (ng.h/mL)	15	91.7 (87.5)	12	94.3 (40.0)
Cmax (ng/mL)	15	107.9 (114.6)	12	81.4 (87.7)
Tmax (h)	15	0.1 [0.1;0.5]	12	0.1 [0.1;1.0]
C(last) (ng/mL)	15	1.4 (52.1)	12	2.1 (92.2)
T(last) (h)	15	28.1 [23.9;47.7]	12	28.0 [25.9;28.5]

Values are n, median (range) for Tmax and Tlast, and n, geometric mean (CV% geometric mean) for all other parameters, where n is the number of subjects with non-missing values.
CV% geometric mean = sqrt (exp (variance for log transformed data)-1)*100.

Conclusion:

- In the dose escalation phase, PAN 20 mg + BTZ 1.3 mg/m^2 dose level (Cohort 3 + Cohort 6) was considered as maximum tolerated dose and as the recommended dose in this study based on Bayesian logistic model integrated with information from clinical assessment. This dose level was carried forward in the dose expansion phase of the study with introduction of 1 week of treatment holiday for panobinostat similar to that of bortezomib. The non-continuous dose was introduced in order to manage thrombocytopenia. Dexamethasone was introduced as per evidence from preclinical data showing synergy with bortezomib and panobinostat for treatment of multiple myeloma, as

well as per evolution of medical practice (PAN 20 mg [TIW 2 weeks on/1 week off] + BTZ 1.3 mg/m^2 + Dex 20 mg).

- In the dose expansion phase there was notably lower incidence of hematological adverse events, as compared to the maximum tolerated dose cohort of dose escalation phase. Modification of panobinostat dosing schedule, with one week treatment holiday per cycle led to an acceleration of platelet recovery, resulting in lower dose adjustments/interruptions. Thus, a longer median duration of study treatment was also observed. The safety profile of panobinostat in combination with bortezomib and dexamethasone was consistent with that of studies in this indication and as expected for this population of multiple myeloma patients with at least one prior line of therapy. No new safety issues were observed in this study.
- In the dose escalation phase, panobinostat exposure ($AUC_{0\text{-}24h}$ and C_{max}) appears to increase with increase in dose of panobinostat; however it is not affected by changes in bortezomib dose. In the dose expansion phase, an approximately 20% reduction of panobinostat exposure in combination with bortezomib was observed when dexamethasone was added to the treatment regimen and this was consistent with the recognized low induction probability of CYP450 3A4 by dexamethasone.
- The analysis of this study (in terms of response rate) confirmed the highly encouraging evidence of the efficacy of panobinostat as multiple myeloma treatment option, in combination with bortezomib and dexamethasone. Several patients had continued best overall responses for a long period of time, which included two complete responses and two very good partial responses.
- No unexpected new safety concerns were identified during the study and the safety profile of panobinostat in combination with bortezomib and dexamethasone was consistent with that of studies in this indication and as expected for this population of multiple myeloma patients with at least one prior line of therapy.

Date of Clinical Trial Report

Interim clinical trial report: 30-Aug-2013

Final clinical trial report: 02-Aug-2014

Date of Initial Inclusion on Novartis Clinical Trial Results website

3-Sep-2014

Date of Latest Update

Reason for Update