Clinical trial results:
A Phase I/IIa trial of VTD-panobinostat treatment and panobinostat maintenance in relapsed and relapsed/refractory multiple myeloma patients

Summary

EudraCT number	2012-000842-36
Trial protocol	GB
Global end of trial date	15 February 2016

Results information

Result version number	v1 (current)
This version publication date	16 May 2018
First version publication date	16 May 2018

Trial information

Trial identification

Sponsor protocol code	HM12/10174

Additional study identifiers

ISRCTN number	ISRCTN59395590
ClinicalTrials.gov id (NCT number)	NCT02145715
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University of Leeds
Sponsor organisation address	Leeds, Leeds, United Kingdom,
Public contact	CTRU, University of Leeds CTRU, 0044 01133431478, l.m.flanagan@leeds.ac.uk
Scientific contact	CTRU, University of Leeds CTRU, 0044 01133431478, medctco@leeds.ac.uk

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	15 February 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 February 2016
Global end of trial reached?	Yes
Global end of trial date	15 February 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

During the dose escalation phase, the purpose of the study is to determine the maximum tolerated dose (MTD) of panobinostat, administered in combination with VTD, in subjects with relapsed and relapsed/refractory multiple myeloma.

In the dose expansion phase the purpose of the study is to estimate the response rate (partial response or better) within 16 cycles of VTD-pano at the RD identified in the dose escalation phase.

Protection of trial subjects:

N/A

Background therapy:

There are no comparators for this trial all participants received the trial drug.

Evidence for comparator: -

Actual start date of recruitment	01 October 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 57
Worldwide total number of subjects	57
EEA total number of subjects	57

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	37
From 65 to 84 years	20

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were recruited to the trial from January 2013 until October 2014 from NHS hospitals across the UK

Pre-assignment

Screening details:

Relapsed/refractory myeloma with 1-4 prior lines of treatment. Adults.

Pre-assignment period milestones

Number of subjects started	57
Number of subjects completed	

Period 1

Period 1 title	Overall Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Safety Population

Arm description:

The safety population includes all participants who have received at least one dose of any trial treatment. Only patients for whom written informed consent was not received are excluded.

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

Dosage and administration details:

20mg/15mg/10mg Days 1, 3, 5, 8, 10 and 12

Investigational medicinal product name	Bortezomib
Investigational medicinal product code	
Other name	Velcade
Pharmaceutical forms	Powder for concentrate for solution for injection/infusion
Routes of administration	Subcutaneous use

Dosage and administration details:

1.3 mg/m2 Days 1 and 8

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

Dosage and administration details:

100 mg od. days 1-21
50mg given to patients with peripheral neuropathy at baseline

Investigational medicinal product name	Dexamethasone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

20mg Days 1, 2, 8 and 9

Number of subjects in period 1	Safety Population
Started	57
Completed	57

Baseline characteristics

Reporting groups	
Reporting group title	Overall Trial

Reporting group description: -

Reporting group values	Overall Trial	Total	
Number of subjects	57	57	
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	59.8		
standard deviation	± 9.19	-	
Gender categorical Units: Subjects			
Female	23	23	
Male	34	34	
ECOG perfomance Status Units: Subjects			
Zero	26	26	
One	26	26	
Two	3	3	
Missing	2	2	
ISS Units: Subjects			
One	32	32	
Two	16	16	
Three	6	6	
Missing	3	3	
Number of previous lines of Treatment Units: Subjects			
One	43	43	
Two	6	6	
Three	5	5	
Four	3	3	
Previous Velcade Units: Subjects			
No	19	19	
Yes	38	38	
Previous Treatment with IMiD Units: Subjects			
Yes	34	34	
No	23	23	
Previous autologous stem cell transplantation			
Whether a patient has received a ASCT prior to entry to the trial			
Units: Subjects			

Yes	36	36	
No	21	21	

Time from diagnosis to registration			
Calculation includes partial dates, missing day and months were set to 15 and 06 respectively			
Units: months			
median	33		
inter-quartile range (Q1-Q3)	26 to 59	-	

Subject analysis sets

Subject analysis set title	RD ITT
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The ITT population is defined by participants registered to receive to the 20mg recommended Panobinostat dose, (RD) , who receive at least one cycle of experimental treatment defined as 1 dose of panobinostat.

Reporting group values	RD ITT		
Number of subjects	46		
Age categorical			
Units: Subjects			

Age continuous			
Units: years			
arithmetic mean	59.3		
standard deviation	± 9.19		
Gender categorical			
Units: Subjects			
Female	19		
Male	27		
ECOG perfomance Status			
Units: Subjects			
Zero	22		
One	21		
Two	2		
Missing	1		
ISS			
Units: Subjects			
One	28		
Two	13		
Three	3		
Missing	2		
Number of previous lines of Treatment			
Units: Subjects			
One	37		
Two	5		
Three	1		
Four	3		
Previous Velcade			
Units: Subjects			

No	13		
Yes	33		
Previous Treatment with IMiD Units: Subjects			
Yes	24		
No	22		
Previous autologous stem cell transplantation			
Whether a patient has received a ASCT prior to entry to the trial			
Units: Subjects			
Yes	27		
No	19		
Time from diagnosis to registration			
Calculation includes partial dates, missing day and months were set to 15 and 06 respectively			
Units: months			
median	31		
inter-quartile range (Q1-Q3)	26 to 54		

End points

End points reporting groups

Reporting group title	Safety Population

Reporting group description:

The safety population includes all participants who have received at least one dose of any trial treatment. Only patients for whom written informed consent was not received are excluded.

Subject analysis set title	RD ITT
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The ITT population is defined by participants registered to receive to the 20mg recommended Panobinostat dose, (RD) , who receive at least one cycle of experimental treatment defined as 1 dose of panobinostat.

Primary: DLT

End point title	DLT[1]

End point description:

DLT was defined as any of the following events:
- Total bilirubin ≥ Grade 3 according to NCI CTCAE Version 4 which fails to return to Grade 1 within 7 days. In participants with Gilbert's Syndrome with grade 1-2 hyperbilirubinemia at screening, total bilirubin need only return to ≤ Grade 2 (within 7 days).
- Any other non haematological toxicity ≥ Grade 3 according to NCI CTCAE Version 4 which fails to return to ≤ Grade 1 or baseline within 7 days. Nausea, vomiting, diarrhoea and electrolyte imbalances will be considered DLTs only if they remain ≥ Grade 3 severity despite adequate supportive care measures.
- Grade 4 neutropenia lasting 7 days or Grade 4 neutropenia with sepsis.
- Any grade 4 thrombocytopenia which fails to return to Grade 2 within 7 days.
- Prolongation of QTc ≥ Grade 3 according to NCI CTCAE Version 4.0
- Treatment Related Death

End point type	Primary

End point timeframe:

Dose limiting toxicity (DLT) was assessed during the first treatment cycle up to the administration of cycle 2 day 1.

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Single arm trial; endpoint used to make escalation decisions with no formal analysis conducted

End point values	Safety Population			
Subject group type	Reporting group			
Number of subjects analysed	15[2]			
Units: Subjects				
10mg DLT	0			
10mg No DLT	6			
15mg DLT	0			
15mg No DLT	3			
20mg DLT	1			
20mg No DLT	5			

Notes:

[2] - 15 Participants evaluable for endpoint in escalation phase. Registered Panobinostat dose given

Statistical analyses

No statistical analyses for this end point

Primary: Overall Response >=PR

End point title	Overall Response >=PR[3]

End point description:

Proportion of participants achieving at least a partial response within 16 cycles of VTD-pano are analysed using the local response assessment. Response to treatment was assessed after a participant has received each cycle of treatment, following the Modified IWG Uniform Response Criteria. A participant who achieved at least a partial response within 16 cycles of treatment but subsequently progressed (within 16 cycles) or stopped treatment (within 16 cycles), is classed as achieving at least a partial response within 16 cycles of treatment.

End point type	Primary

End point timeframe:

Within 16 cycles of treatment

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Single arm trial; data used to estimate response rate with no formal analysis conducted as no comparator arm

End point values	RD ITT			
Subject group type	Subject analysis set			
Number of subjects analysed	46			
Units: Subjects				
Not acheived	4			
PR or greater acheived	42			

Statistical analyses

No statistical analyses for this end point

Primary: Overall response rate

End point title	Overall response rate[4]

End point description:

Percentage of participants achieving at least a partial response within 16 cycles of VTD-pano are analysed using the local response assessment. Response to treatment was assessed after a participant has received each cycle of treatment, following the Modified IWG Uniform Response Criteria. A participant who achieved at least a partial response within 16 cycles of treatment but subsequently progressed (within 16 cycles) or stopped treatment (within 16 cycles), is classed as achieving at least a partial response within 16 cycles of treatment.

End point type	Primary

End point timeframe:

Within 16 cycles

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Single arm trial; parameter estimate with no formal analysis conducted as no comparator arm

End point values	RD ITT			
Subject group type	Subject analysis set			
Number of subjects analysed				
Units: percent				
number (confidence interval 80%)	91 (83.4 to 96.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Response

End point title	Maximum Response

End point description:

Maximum response is defined as the proportion of participants achieving each of the response categories; Complete Response (CR), Very Good Partial Response (VGPR), Partial Response (PR), Minimal Response (MR) or Stable Disease (SD) as their maximum response within sixteen cycles of treatment. Response assessments for a given cycle were taken at the beginning of the subsequent cycle of treatment or separately at the end of treatment if no further cycles of treatment were received.

End point type	Secondary

End point timeframe:

Within 16 Cycles of treatment

End point values	RD ITT			
Subject group type	Subject analysis set			
Number of subjects analysed	46			
Units: Subjects				
CR	3			
VGPR	18			
PR	21			
MR	2			
SD	2			

Statistical analyses

No statistical analyses for this end point

Secondary: Median Time to Maximum response

End point title	Median Time to Maximum response

End point description:

Time to maximum response is defined as the time from registration until the participant achieves any of the categories CR, VGPR, PR, MR or SD as their maximum response.

Time to maximum response is calculated using the Kaplan Meier method. Median time to maximum response is presented, with corresponding 95% confidence intervals.

End point type	Secondary

End point timeframe:

Within 16 cycles of treatment

End point values	RD ITT			
Subject group type	Subject analysis set			
Number of subjects analysed	46			
Units: Months				
number (confidence interval 95%)	2.46 (1.91 to 3.52)			

Statistical analyses

No statistical analyses for this end point

Secondary: Median Progression free survival

End point title	Median Progression free survival

End point description:

Progression-free survival is defined as the time from registration to first documented evidence of disease progression or death. Participants who, at the time of analysis, have not progressed or died are censored at the last date they were known to be alive and progression free. Patients who go on to receive a stem cell transplant are censored at the date of stem cell harvest if a harvest was carried out or infusion if not.
Calculated using the Kaplan Meier method

End point type	Secondary

End point timeframe:

Median follow up of 15months.

End point values	RD ITT			
Subject group type	Subject analysis set			
Number of subjects analysed	46			
Units: Months				
number (confidence interval 95%)	15.6 (13.4 to 20.47)			

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion progression free at 12 months

End point title	Proportion progression free at 12 months

End point description:

Progression-free survival is defined as the time from registration to first documented evidence of disease progression or death. Participants who, at the time of analysis, have not progressed or died are

censored at the last date they were known to be alive and progression free. Patients who go on to receive a stem cell transplant are censored at the date of stem cell harvest if a harvest was carried out or infusion if not.
Calculated using the Kaplan Meier method

End point type	Secondary

End point timeframe:

12 months

End point values	RD ITT			
Subject group type	Subject analysis set			
Number of subjects analysed	46			
Units: Percentage				
number (confidence interval 95%)	75.4 (56.7 to 86.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Panobinostat dose

End point title	Mean Panobinostat dose

End point description:

Calculated as mean dose over all cycles recieved

End point type	Secondary

End point timeframe:

16 cycles of treatment

End point values	RD ITT			
Subject group type	Subject analysis set			
Number of subjects analysed	46			
Units: mg				
arithmetic mean (standard error)	17.2 (± 0.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Panobinostat dose reduction

End point title	Panobinostat dose reduction

End point description:

Participant required at least 1 dose reduction of panobinostat during therapy. Binary Yes/No

End point type	Secondary

End point timeframe:

16 Cycles of treatment

End point values	RD ITT			
Subject group type	Subject analysis set			
Number of subjects analysed	46			
Units: Subjects				
Yes	19			
No	27			

Statistical analyses

No statistical analyses for this end point

Secondary: Thalidomide dose reduction

End point title	Thalidomide dose reduction

End point description:

Participants requiring at least one dose reduction of thalidomide. Binary Yes/No

End point type	Secondary

End point timeframe:

16 cycles

End point values	RD ITT			
Subject group type	Subject analysis set			
Number of subjects analysed	46			
Units: Subjects				
Yes	20			
No	26			

Statistical analyses

No statistical analyses for this end point

Secondary: Bortezomib dose reduction

End point title	Bortezomib dose reduction

End point description:

Participants who received at least 1 dose reduction during therapy. Binary Yes/No

End point type	Secondary

End point timeframe:

16 cycles

End point values	RD ITT			
Subject group type	Subject analysis set			
Number of subjects analysed	46			
Units: Subjects				
Yes	5			
No	41			

Statistical analyses

No statistical analyses for this end point

Secondary: Dexamethasone dose reduction

End point title	Dexamethasone dose reduction

End point description:

Number of participants requiring at least one dose reduction of dexamethasone within 1 cycle of treatment.

End point type	Secondary

End point timeframe:

Within 16 cycles

End point values	RD ITT			
Subject group type	Subject analysis set			
Number of subjects analysed	46			
Units: Subjects				
Yes	6			
No	40			

Statistical analyses

No statistical analyses for this end point

Secondary: Participants proceeding to Maintenance

End point title	Participants proceeding to Maintenance

End point description:

Upon Completion of 16 cycles of initial therapy participants were eligible for maintenance therapy

End point type	Secondary

End point timeframe:

16 cycles

End point values	Safety Population			
Subject group type	Reporting group			
Number of subjects analysed	57			
Units: Subjects				
Maintenance	15			
No maintenance	42			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Panobinostat dose maintenance

End point title	Mean Panobinostat dose maintenance

End point description:

The mean dose of panobinostat received during maintenance therapy. Four participants of the 15 patients proceeding to maintenance had not completed maintenance at the time of analysis.

End point type	Secondary

End point timeframe:

1-year Maintenance therapy

End point values	Safety Population			
Subject group type	Reporting group			
Number of subjects analysed	15			
Units: mg				
arithmetic mean (standard error)	16.5 (± 0.18)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All AEs occurring for all participants from the time of consent until 30 days post cessation of trial therapy

Assessment type	Systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	4.0

Reporting groups

Reporting group title	Safety Population

Reporting group description:

The safety population includes all participants who have received at least one dose of any trial treatment. Only patients for whom written informed consent was not received are excluded.

Serious adverse events	Safety Population		
Total subjects affected by serious adverse events			
subjects affected / exposed	27 / 57 (47.37%)		
number of deaths (all causes)	6		
number of deaths resulting from adverse events	3		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other, specify			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Thromboembolic event			
subjects affected / exposed	2 / 57 (3.51%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 1		
General disorders and administration site conditions			
Fever			
subjects affected / exposed	8 / 57 (14.04%)		
occurrences causally related to treatment / all	0 / 8		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			

Dyspnea			
subjects affected / exposed	2 / 57 (3.51%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Confusion			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Investigations			
Creatinine increased			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Electrocardiogram QT corrected interval prolonged			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Fracture			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Spinal fracture			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Sinus bradycardia			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Depressed level of consciousness			

subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Facial muscle weakness			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Transient ischemic attacks			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	4 / 57 (7.02%)		
occurrences causally related to treatment / all	3 / 4		
deaths causally related to treatment / all	0 / 0		
Hemolysis			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Hemolytic uremic syndrome			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Diarrhea			
subjects affected / exposed	2 / 57 (3.51%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Esophageal perforation			

subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	2 / 57 (3.51%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bone pain			
subjects affected / exposed	2 / 57 (3.51%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Lung infection			
subjects affected / exposed	5 / 57 (8.77%)		
occurrences causally related to treatment / all	0 / 6		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 4 %

Non-serious adverse events	Safety Population		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	57 / 57 (100.00%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	5 / 57 (8.77%)		
occurrences (all)	5		
Hypotension			
subjects affected / exposed	6 / 57 (10.53%)		
occurrences (all)	8		
General disorders and administration site conditions			
Edema limbs			
subjects affected / exposed	23 / 57 (40.35%)		
occurrences (all)	43		
Fever			
subjects affected / exposed	11 / 57 (19.30%)		
occurrences (all)	15		
Fatigue			
subjects affected / exposed	51 / 57 (89.47%)		
occurrences (all)	94		
Localized edema			
subjects affected / exposed	5 / 57 (8.77%)		
occurrences (all)	6		
Malaise			
subjects affected / exposed	3 / 57 (5.26%)		
occurrences (all)	3		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	15 / 57 (26.32%)		
occurrences (all)	16		
Dyspnea			
subjects affected / exposed	20 / 57 (35.09%)		
occurrences (all)	31		
Epistaxis			
subjects affected / exposed	3 / 57 (5.26%)		
occurrences (all)	3		

Hiccups			
subjects affected / exposed	4 / 57 (7.02%)		
occurrences (all)	4		
Productive cough			
subjects affected / exposed	5 / 57 (8.77%)		
occurrences (all)	5		
Sore throat			
subjects affected / exposed	4 / 57 (7.02%)		
occurrences (all)	4		
Psychiatric disorders			
Agitation			
subjects affected / exposed	6 / 57 (10.53%)		
occurrences (all)	7		
Depression			
subjects affected / exposed	5 / 57 (8.77%)		
occurrences (all)	9		
Insomnia			
subjects affected / exposed	8 / 57 (14.04%)		
occurrences (all)	9		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	8 / 57 (14.04%)		
occurrences (all)	25		
Alkaline phosphatase increased			
subjects affected / exposed	4 / 57 (7.02%)		
occurrences (all)	6		
Aspartate aminotransferase increased			
subjects affected / exposed	3 / 57 (5.26%)		
occurrences (all)	7		
Creatinine increased			
subjects affected / exposed	16 / 57 (28.07%)		
occurrences (all)	31		
Electrocardiogram QT corrected interval prolonged			
subjects affected / exposed	4 / 57 (7.02%)		
occurrences (all)	5		
Investigations - Other, specify			

subjects affected / exposed	5 / 57 (8.77%)		
occurrences (all)	5		
Neutrophil count decreased			
subjects affected / exposed	22 / 57 (38.60%)		
occurrences (all)	66		
Platelet count decreased			
subjects affected / exposed	20 / 57 (35.09%)		
occurrences (all)	65		
Weight loss			
subjects affected / exposed	8 / 57 (14.04%)		
occurrences (all)	9		
White blood cell decreased			
subjects affected / exposed	7 / 57 (12.28%)		
occurrences (all)	15		
Cardiac disorders			
Cardiac disorders - Other, specify			
subjects affected / exposed	6 / 57 (10.53%)		
occurrences (all)	13		
Palpitations			
subjects affected / exposed	3 / 57 (5.26%)		
occurrences (all)	4		
Sinus bradycardia			
subjects affected / exposed	9 / 57 (15.79%)		
occurrences (all)	12		
Nervous system disorders			
Dizziness			
subjects affected / exposed	18 / 57 (31.58%)		
occurrences (all)	32		
Dysgeusia			
subjects affected / exposed	11 / 57 (19.30%)		
occurrences (all)	14		
Headache			
subjects affected / exposed	4 / 57 (7.02%)		
occurrences (all)	4		
Peripheral sensory neuropathy			

subjects affected / exposed	44 / 57 (77.19%)		
occurrences (all)	83		
Somnolence			
subjects affected / exposed	19 / 57 (33.33%)		
occurrences (all)	26		
Tremor			
subjects affected / exposed	22 / 57 (38.60%)		
occurrences (all)	32		
Syncope			
subjects affected / exposed	4 / 57 (7.02%)		
occurrences (all)	4		
Blood and lymphatic system disorders			
Anemia			
subjects affected / exposed	21 / 57 (36.84%)		
occurrences (all)	53		
Eye disorders			
Blurred vision			
subjects affected / exposed	4 / 57 (7.02%)		
occurrences (all)	4		
Dry eye			
subjects affected / exposed	4 / 57 (7.02%)		
occurrences (all)	5		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	9 / 57 (15.79%)		
occurrences (all)	9		
Constipation			
subjects affected / exposed	36 / 57 (63.16%)		
occurrences (all)	59		
Diarrhea			
subjects affected / exposed	38 / 57 (66.67%)		
occurrences (all)	110		
Dry mouth			
subjects affected / exposed	3 / 57 (5.26%)		
occurrences (all)	3		
Dyspepsia			

subjects affected / exposed	6 / 57 (10.53%)		
occurrences (all)	7		
Gastrointestinal disorders - Other, specify			
subjects affected / exposed	3 / 57 (5.26%)		
occurrences (all)	6		
Mucositis oral			
subjects affected / exposed	3 / 57 (5.26%)		
occurrences (all)	3		
Nausea			
subjects affected / exposed	27 / 57 (47.37%)		
occurrences (all)	34		
Vomiting			
subjects affected / exposed	10 / 57 (17.54%)		
occurrences (all)	14		
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	6 / 57 (10.53%)		
occurrences (all)	7		
Hyperhidrosis			
subjects affected / exposed	3 / 57 (5.26%)		
occurrences (all)	3		
Pruritus			
subjects affected / exposed	3 / 57 (5.26%)		
occurrences (all)	3		
Rash maculo-papular			
subjects affected / exposed	14 / 57 (24.56%)		
occurrences (all)	19		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	5 / 57 (8.77%)		
occurrences (all)	8		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	4 / 57 (7.02%)		
occurrences (all)	7		
Back pain			

subjects affected / exposed	25 / 57 (43.86%)		
occurrences (all)	36		
Bone pain			
subjects affected / exposed	35 / 57 (61.40%)		
occurrences (all)	60		
Generalized muscle weakness			
subjects affected / exposed	3 / 57 (5.26%)		
occurrences (all)	4		
Myalgia			
subjects affected / exposed	15 / 57 (26.32%)		
occurrences (all)	19		
Infections and infestations			
Infections and infestations - Other, specify			
subjects affected / exposed	3 / 57 (5.26%)		
occurrences (all)	4		
Lung infection			
subjects affected / exposed	5 / 57 (8.77%)		
occurrences (all)	5		
Skin infection			
subjects affected / exposed	5 / 57 (8.77%)		
occurrences (all)	5		
Upper respiratory infection			
subjects affected / exposed	25 / 57 (43.86%)		
occurrences (all)	41		
Metabolism and nutrition disorders			
Anorexia			
subjects affected / exposed	16 / 57 (28.07%)		
occurrences (all)	16		
Hyperglycemia			
subjects affected / exposed	5 / 57 (8.77%)		
occurrences (all)	12		
Hypermagnesemia			
subjects affected / exposed	3 / 57 (5.26%)		
occurrences (all)	3		
Hypernatremia			

subjects affected / exposed	3 / 57 (5.26%)		
occurrences (all)	3		
Hypoalbuminemia			
subjects affected / exposed	3 / 57 (5.26%)		
occurrences (all)	4		
Hypocalcemia			
subjects affected / exposed	12 / 57 (21.05%)		
occurrences (all)	18		
Hypomagnesemia			
subjects affected / exposed	7 / 57 (12.28%)		
occurrences (all)	12		
Hyponatremia			
subjects affected / exposed	4 / 57 (7.02%)		
occurrences (all)	6		
Hypophosphatemia			
subjects affected / exposed	19 / 57 (33.33%)		
occurrences (all)	63		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 December 2012	Substantial amendment relating to the CTA. Novartis has been included as the company responsible for the final certification of the IMP in the community. The responsibility is now with St Mary's Pharmaceutical Unit (SMPU). A copy of SMPUs manufacturers authorisation is enclosed.
07 August 2013	Clarified contraception for use in the trial. Excluded patients with diffuse infiltrative pulmonary disease Excluded growth factors and platelet support to meet eligibility criteria Clarified the informed consent process Added panobinostat, dexamethasone and thalidomide administration information for clarification Added dose delay periods for clarity Added that parameters outlined in the eligibility criteria need to be met to proceed with treatment.
03 February 2014	Clarification of parameters to start treatment at each cycle. Clarification that toxicities must have resolved to start treatment. Dose modifications for neutropenia amended. Wording for anaemia and grade 3 & 4 non haematological toxicities clarified.
12 August 2014	Clarification of laboratory values to continue treatment and dose reductions. Reporting of SARs and SUSARs until the end of the trial not 30 days after the end of treatment Pregnancy testing requirements clarified. Reporting to the sponsor clarified. Breastfeeding excluded.
18 December 2014	Sample size and analysis population amended in the expansion phase as this was incorrect. Frequency of analyses amended in line with the design.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/27843120