



Clinical trial results:

A Phase II Study of Oral Panobinostat in Adult Patients with Relapsed/Refractory Classical Hodgkins lymphoma after Failure of High-dose Chemotherapy with Autologous Stem Cell Transfusion and a Gemcitabine- or Vinorelbine- or Vinblastine-Containing Treatment Regimen

Summary

EudraCT number	2008-003016-35
Trial protocol	ES DE FR BE GB IT
Global end of trial date	12 August 2013

Results information

Result version number	v1
This version publication date	13 July 2016
First version publication date	29 July 2015

Trial information

Trial identification

Sponsor protocol code	CLBH589E2214
-----------------------	--------------

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00742027
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	CH-4002 , Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111,
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111,

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	12 August 2013
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	12 August 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of oral panobinostat in patients with refractory/relapsed classical HL who have received prior treatment with high dose chemotherapy and autologous stem cell transplant. Safety of panobinostat will also be assessed. Other markers that may correlate with efficacy or safety will be explored.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	16 September 2008
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 13
Country: Number of subjects enrolled	United Kingdom: 6
Country: Number of subjects enrolled	Belgium: 4
Country: Number of subjects enrolled	France: 10
Country: Number of subjects enrolled	Germany: 11
Country: Number of subjects enrolled	Italy: 10
Country: Number of subjects enrolled	Australia: 7
Country: Number of subjects enrolled	Brazil: 12
Country: Number of subjects enrolled	Israel: 12
Country: Number of subjects enrolled	Malaysia: 5
Country: Number of subjects enrolled	New Zealand: 4
Country: Number of subjects enrolled	Singapore: 2
Country: Number of subjects enrolled	United States: 33
Worldwide total number of subjects	129
EEA total number of subjects	54

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)	123
From 65 to 84 years	6
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 102 patients were to be enrolled and treated in the study. 129 patients were enrolled and analyzed.

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	Panobinostat
-----------	--------------

Arm description:

All patients were treated with a starting dose of 40 mg of oral panobinostat given 3 x week (i.e. days 1, 3 and 5) every week, on a 21-day cycle.

Arm type	Experimental
Investigational medicinal product name	Panobinostat
Investigational medicinal product code	
Other name	LBH589
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Oral panobinostat was supplied as 5 mg or 20 mg hard gelatin capsules and was given on a flat scale of mg on a given day.

Number of subjects in period 1	Panobinostat
Started	129
Completed	1
Not completed	128
Adverse event, serious fatal	1
Consent withdrawn by subject	12
Adverse event, non-fatal	25
Administrative problems	1
'New cancer therapy '	11
Lost to follow-up	1
'Disease progression '	76
Protocol deviation	1

Baseline characteristics

Reporting groups

Reporting group title	Panobinostat
-----------------------	--------------

Reporting group description:

All patients were treated with a starting dose of 40 mg of oral panobinostat given 3 x week (i.e. days 1, 3 and 5) every week, on a 21-day cycle.

Reporting group values	Panobinostat	Total	
Number of subjects	129	129	
Age categorical			
Units: Subjects			
< 65	123	123	
≥ 65	6	6	
Age continuous			
Units: years			
arithmetic mean	34.7		
standard deviation	± 12.24	-	
Gender categorical			
Units: Subjects			
Female	63	63	
Male	66	66	

End points

End points reporting groups

Reporting group title	Panobinostat
Reporting group description:	
All patients were treated with a starting dose of 40 mg of oral panobinostat given 3 x week (i.e. days 1, 3 and 5) every week, on a 21-day cycle.	

Primary: Objective response rate to therapy with oral panobinostat in patients with refractory/relapsed classical Hodgkin Lymphoma (HL)

End point title	Objective response rate to therapy with oral panobinostat in patients with refractory/relapsed classical Hodgkin Lymphoma (HL) ^[1]
-----------------	---

End point description:

Objective Response defined by RECIST criteria: Partial response (PR) must have $\geq 30\%$ decrease in the sum of the longest diameter of all target lesions, from the baseline sum. Complete response (CR) must have disappearance of all target and non-target lesions. For CR or PR, tumor measurements must be confirmed by 2nd assessments within 4 weeks. Progression = 20% increase in the sum of the longest diameter of all target lesions, from the smallest sum of longest diameter of all target lesions recorded at or after baseline; or a new lesion; or progression of non-target lesions. This is a single arm study and as such there were no comparison statistics performed.

End point type	Primary
----------------	---------

End point timeframe:

32 weeks from start of treatment; cut-off date 11-Jun-2010

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: No planned statistical analysis was planned for this outcome measure

End point values	Panobinostat			
Subject group type	Reporting group			
Number of subjects analysed	129			
Units: Percentage of participants				
number (not applicable)				
Complete response	3.9			
Partial response	23.3			
Stable disease	55			
Progressive disease	10.9			
Unknown	7			

Statistical analyses

No statistical analyses for this end point

Secondary: Response rate based on central review of CT scan/MRI

End point title	Response rate based on central review of CT scan/MRI
-----------------	--

End point description:

Best overall disease response recorded from the start of treatment until progression/recurrence or the start of new cancer therapy.

End point type	Secondary
End point timeframe:	
From start of treatment until progression/recurrence or start of a new cancer therapy up to Data cut-off 11Jun2010	

End point values	Panobinostat			
Subject group type	Reporting group			
Number of subjects analysed	129			
Units: Percentage of participants				
number (not applicable)				
Complete response	0.8			
Partial response	20.9			
Stable disease	56.6			
Progressive disease	15.5			
Unknown	6.2			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to overall disease response in responders

End point title	Time to overall disease response in responders
End point description:	
Time to overall disease response (CR or PR) is defined as the time from the date of randomization / start of treatment to the date of first documented disease response (PR or CR).	
End point type	Secondary
End point timeframe:	
From start of treatment up to Data cut-off 11Jun2010	

End point values	Panobinostat			
Subject group type	Reporting group			
Number of subjects analysed	35 ^[2]			
Units: weeks				
median (confidence interval 95%)	9.9 (6 to 12.1)			

Notes:

[2] - Number of responders

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of overall disease response

End point title	Duration of overall disease response
-----------------	--------------------------------------

End point description:

Duration of overall response (CR or PR) is defined as the time from the date of first documented disease response (CR or PR) to the date of first documented progression or death due to lymphoma. If a patient has not had an event, duration of overall response is censored at the date of the last adequate assessment.

End point type	Secondary
----------------	-----------

End point timeframe:

From start of treatment up to Data cut-off 11Jun2010

End point values	Panobinostat			
Subject group type	Reporting group			
Number of subjects analysed	35 ^[3]			
Units: weeks				
median (confidence interval 95%)	30.1 (17.4 to 35.9)			

Notes:

[3] - Number of responders

Statistical analyses

No statistical analyses for this end point

Secondary: Progression free survival (PFS)

End point title	Progression free survival (PFS)
-----------------	---------------------------------

End point description:

Progression-free survival (PFS) is defined as the time from the date of randomization/start of treatment to the date of event defined as the first documented progression or death due to any cause. If a patient has not had an event, progression-free survival is censored at the date of the last adequate assessment.

End point type	Secondary
----------------	-----------

End point timeframe:

From start of treatment up to database lock 14Feb2014

End point values	Panobinostat			
Subject group type	Reporting group			
Number of subjects analysed	129			
Units: months				
median (confidence interval 95%)	6.1 (5.4 to 8.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival

End point title	Overall survival
End point description:	
Overall survival (OS) is the duration from date of randomization to date of death from any cause	
End point type	Secondary
End point timeframe:	
Baseline to date of death from any cause; with a cut-off / DBL of 14-Feb-2014	

End point values	Panobinostat			
Subject group type	Reporting group			
Number of subjects analysed	129			
Units: months				
median (full range (min-max))	34.9 (0.7 to 53)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All Adverse events are reported in this record from First Patient First Treatment until Last Patient Last Visit.

Adverse event reporting additional description:

Consistent with EudraCT disclosure specifications, Novartis has reported under the Serious adverse events field "number of deaths resulting from adverse events" all those deaths, resulting from serious adverse events that are deemed to be causally related to treatment by the investigator.

Assessment type	Systematic
-----------------	------------

Dictionary used

Dictionary name	MedDRA
Dictionary version	13.0

Reporting groups

Reporting group title	Panobinostat 40mg, 3 x week, q week
-----------------------	-------------------------------------

Reporting group description:

Panobinostat 40mg, 3 x week, q week

Serious adverse events	Panobinostat 40mg, 3 x week, q week		
Total subjects affected by serious adverse events			
subjects affected / exposed	51 / 129 (39.53%)		
number of deaths (all causes)	3		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasm skin			
subjects affected / exposed	1 / 129 (0.78%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Cervicitis human papilloma virus			
subjects affected / exposed	1 / 129 (0.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Neuroendocrine carcinoma of the skin			
subjects affected / exposed	1 / 129 (0.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	2 / 129 (1.55%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Hypotension			
subjects affected / exposed	3 / 129 (2.33%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Multi-organ failure			
subjects affected / exposed	1 / 129 (0.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pyrexia			
subjects affected / exposed	2 / 129 (1.55%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	4 / 129 (3.10%)		
occurrences causally related to treatment / all	1 / 4		
deaths causally related to treatment / all	0 / 0		
Pleural effusion			
subjects affected / exposed	1 / 129 (0.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lung disorder			
subjects affected / exposed	1 / 129 (0.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary embolism			

subjects affected / exposed	1 / 129 (0.78%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Confusional state			
subjects affected / exposed	1 / 129 (0.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Depression			
subjects affected / exposed	1 / 129 (0.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Mental status changes			
subjects affected / exposed	1 / 129 (0.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	3 / 129 (2.33%)		
occurrences causally related to treatment / all	2 / 3		
deaths causally related to treatment / all	0 / 0		
Pericardial effusion			
subjects affected / exposed	1 / 129 (0.78%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Sinus tachycardia			
subjects affected / exposed	1 / 129 (0.78%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Ventricular hypokinesia			
subjects affected / exposed	1 / 129 (0.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			

Dizziness				
subjects affected / exposed	1 / 129 (0.78%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Intracranial venous sinus thrombosis				
subjects affected / exposed	1 / 129 (0.78%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Headache				
subjects affected / exposed	1 / 129 (0.78%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nerve root compression				
subjects affected / exposed	1 / 129 (0.78%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lethargy				
subjects affected / exposed	1 / 129 (0.78%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Neuralgia				
subjects affected / exposed	1 / 129 (0.78%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Peripheral nerve lesion				
subjects affected / exposed	1 / 129 (0.78%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Syncope				
subjects affected / exposed	1 / 129 (0.78%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Posterior reversible encephalopathy syndrome				

subjects affected / exposed	1 / 129 (0.78%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	5 / 129 (3.88%)		
occurrences causally related to treatment / all	6 / 6		
deaths causally related to treatment / all	0 / 0		
Febrile neutropenia			
subjects affected / exposed	1 / 129 (0.78%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Haemorrhagic disorder			
subjects affected / exposed	1 / 129 (0.78%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Idiopathic thrombocytopenic purpura			
subjects affected / exposed	1 / 129 (0.78%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Neutropenia			
subjects affected / exposed	2 / 129 (1.55%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Thrombocytopenia			
subjects affected / exposed	12 / 129 (9.30%)		
occurrences causally related to treatment / all	12 / 12		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 129 (0.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Colitis			

subjects affected / exposed	1 / 129 (0.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			
subjects affected / exposed	2 / 129 (1.55%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Gastritis			
subjects affected / exposed	1 / 129 (0.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nausea			
subjects affected / exposed	1 / 129 (0.78%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Upper gastrointestinal haemorrhage			
subjects affected / exposed	1 / 129 (0.78%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	2 / 129 (1.55%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	1 / 129 (0.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cholelithiasis			
subjects affected / exposed	1 / 129 (0.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			

Renal failure acute			
subjects affected / exposed	1 / 129 (0.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urethral haemorrhage			
subjects affected / exposed	1 / 129 (0.78%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 129 (0.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bronchopneumonia			
subjects affected / exposed	1 / 129 (0.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cellulitis			
subjects affected / exposed	1 / 129 (0.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Dengue fever			
subjects affected / exposed	1 / 129 (0.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Device related infection			
subjects affected / exposed	2 / 129 (1.55%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Device related sepsis			
subjects affected / exposed	1 / 129 (0.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infection			

subjects affected / exposed	1 / 129 (0.78%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lower respiratory tract infection				
subjects affected / exposed	2 / 129 (1.55%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Necrotising ulcerative gingivostomatitis				
subjects affected / exposed	1 / 129 (0.78%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Neutropenic sepsis				
subjects affected / exposed	1 / 129 (0.78%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Oropharyngeal candidiasis				
subjects affected / exposed	1 / 129 (0.78%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumocystis jirovecii pneumonia				
subjects affected / exposed	1 / 129 (0.78%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	5 / 129 (3.88%)			
occurrences causally related to treatment / all	1 / 5			
deaths causally related to treatment / all	0 / 0			
Pneumonia pneumococcal				
subjects affected / exposed	1 / 129 (0.78%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Sepsis				

subjects affected / exposed	4 / 129 (3.10%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Septic shock			
subjects affected / exposed	1 / 129 (0.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Sinusitis			
subjects affected / exposed	1 / 129 (0.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Cachexia			
subjects affected / exposed	1 / 129 (0.78%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Dehydration			
subjects affected / exposed	2 / 129 (1.55%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Decreased appetite			
subjects affected / exposed	1 / 129 (0.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Panobinostat 40mg, 3 x week, q week		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	129 / 129 (100.00%)		
General disorders and administration site conditions			
Asthenia			

subjects affected / exposed	24 / 129 (18.60%)		
occurrences (all)	33		
Chills			
subjects affected / exposed	8 / 129 (6.20%)		
occurrences (all)	8		
Fatigue			
subjects affected / exposed	60 / 129 (46.51%)		
occurrences (all)	93		
Non-cardiac chest pain			
subjects affected / exposed	10 / 129 (7.75%)		
occurrences (all)	11		
Oedema peripheral			
subjects affected / exposed	17 / 129 (13.18%)		
occurrences (all)	19		
Pyrexia			
subjects affected / exposed	56 / 129 (43.41%)		
occurrences (all)	95		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	36 / 129 (27.91%)		
occurrences (all)	46		
Dyspnoea			
subjects affected / exposed	23 / 129 (17.83%)		
occurrences (all)	26		
Epistaxis			
subjects affected / exposed	15 / 129 (11.63%)		
occurrences (all)	30		
Oropharyngeal pain			
subjects affected / exposed	10 / 129 (7.75%)		
occurrences (all)	11		
Productive cough			
subjects affected / exposed	10 / 129 (7.75%)		
occurrences (all)	13		
Wheezing			

subjects affected / exposed occurrences (all)	7 / 129 (5.43%) 8		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	16 / 129 (12.40%)		
occurrences (all)	18		
Depression			
subjects affected / exposed	11 / 129 (8.53%)		
occurrences (all)	11		
Insomnia			
subjects affected / exposed	12 / 129 (9.30%)		
occurrences (all)	12		
Investigations			
Blood alkaline phosphatase increased			
subjects affected / exposed	7 / 129 (5.43%)		
occurrences (all)	11		
Blood creatinine increased			
subjects affected / exposed	10 / 129 (7.75%)		
occurrences (all)	26		
Weight decreased			
subjects affected / exposed	16 / 129 (12.40%)		
occurrences (all)	19		
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	7 / 129 (5.43%)		
occurrences (all)	7		
Cardiac disorders			
Sinus tachycardia			
subjects affected / exposed	7 / 129 (5.43%)		
occurrences (all)	8		
Tachycardia			
subjects affected / exposed	8 / 129 (6.20%)		
occurrences (all)	8		
Nervous system disorders			
Dizziness			

subjects affected / exposed	8 / 129 (6.20%)		
occurrences (all)	10		
Dysgeusia			
subjects affected / exposed	21 / 129 (16.28%)		
occurrences (all)	29		
Headache			
subjects affected / exposed	27 / 129 (20.93%)		
occurrences (all)	42		
Lethargy			
subjects affected / exposed	9 / 129 (6.98%)		
occurrences (all)	13		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	52 / 129 (40.31%)		
occurrences (all)	120		
Leukopenia			
subjects affected / exposed	16 / 129 (12.40%)		
occurrences (all)	29		
Neutropenia			
subjects affected / exposed	36 / 129 (27.91%)		
occurrences (all)	113		
Thrombocytopenia			
subjects affected / exposed	109 / 129 (84.50%)		
occurrences (all)	360		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	17 / 129 (13.18%)		
occurrences (all)	32		
Abdominal pain upper			
subjects affected / exposed	21 / 129 (16.28%)		
occurrences (all)	26		
Constipation			
subjects affected / exposed	25 / 129 (19.38%)		
occurrences (all)	33		
Diarrhoea			

subjects affected / exposed	96 / 129 (74.42%)		
occurrences (all)	219		
Dry mouth			
subjects affected / exposed	14 / 129 (10.85%)		
occurrences (all)	17		
Dyspepsia			
subjects affected / exposed	12 / 129 (9.30%)		
occurrences (all)	18		
Nausea			
subjects affected / exposed	87 / 129 (67.44%)		
occurrences (all)	158		
Stomatitis			
subjects affected / exposed	9 / 129 (6.98%)		
occurrences (all)	12		
Vomiting			
subjects affected / exposed	55 / 129 (42.64%)		
occurrences (all)	103		
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	8 / 129 (6.20%)		
occurrences (all)	8		
Dry skin			
subjects affected / exposed	13 / 129 (10.08%)		
occurrences (all)	18		
Petechiae			
subjects affected / exposed	12 / 129 (9.30%)		
occurrences (all)	13		
Pruritus			
subjects affected / exposed	21 / 129 (16.28%)		
occurrences (all)	26		
Rash			
subjects affected / exposed	11 / 129 (8.53%)		
occurrences (all)	11		
Endocrine disorders			
Hypothyroidism			

subjects affected / exposed	20 / 129 (15.50%)		
occurrences (all)	22		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	8 / 129 (6.20%)		
occurrences (all)	14		
Back pain			
subjects affected / exposed	24 / 129 (18.60%)		
occurrences (all)	35		
Bone pain			
subjects affected / exposed	10 / 129 (7.75%)		
occurrences (all)	13		
Muscle spasms			
subjects affected / exposed	30 / 129 (23.26%)		
occurrences (all)	39		
Musculoskeletal chest pain			
subjects affected / exposed	13 / 129 (10.08%)		
occurrences (all)	13		
Myalgia			
subjects affected / exposed	14 / 129 (10.85%)		
occurrences (all)	19		
Pain in extremity			
subjects affected / exposed	7 / 129 (5.43%)		
occurrences (all)	7		
Infections and infestations			
Influenza			
subjects affected / exposed	8 / 129 (6.20%)		
occurrences (all)	10		
Lower respiratory tract infection			
subjects affected / exposed	7 / 129 (5.43%)		
occurrences (all)	9		
Nasopharyngitis			
subjects affected / exposed	12 / 129 (9.30%)		
occurrences (all)	17		
Sinusitis			

subjects affected / exposed occurrences (all)	9 / 129 (6.98%) 20		
Upper respiratory tract infection subjects affected / exposed occurrences (all)	19 / 129 (14.73%) 27		
Urinary tract infection subjects affected / exposed occurrences (all)	7 / 129 (5.43%) 12		
Metabolism and nutrition disorders			
Decreased appetite subjects affected / exposed occurrences (all)	48 / 129 (37.21%) 61		
Dehydration subjects affected / exposed occurrences (all)	7 / 129 (5.43%) 8		
Hypokalaemia subjects affected / exposed occurrences (all)	19 / 129 (14.73%) 49		
Hypomagnesaemia subjects affected / exposed occurrences (all)	7 / 129 (5.43%) 9		
Hypophosphataemia subjects affected / exposed occurrences (all)	8 / 129 (6.20%) 46		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 March 2009	<ul style="list-style-type: none">• Removal of requirement for patients to have prior exposure to gemcitabine, vinblastine, or vinorelbine.• Dosing with panobinostat without regard to food was permitted.• Clarification was provided regarding response assessment in the study, stating that a 4 week post response confirmatory scan was not required.• Clarified that there would be no enrollment hold between stage 1 to 2, in light of additional safety and efficacy data.• All references to the Data Monitoring Committee were changed to Steering Committee to accurately identify the name of the committee and their role in the study since some of the committee members are clinical investigators on the study.
04 August 2009	<ul style="list-style-type: none">• Provided additional guidance on dose modifications: For patients who do not tolerate every week (qw) dosing, dose modification will allow changing the drug administration schedule to an every other week (qow) dosing in addition to decreasing the dose. For patients who have been tolerating reduced doses, dose re-escalation may also be allowable to seek maximal clinical benefit from panobinostat.• Starting dose remained unchanged at 40 mg 3×week, every week to allow for maximum dose intensity upfront to combat tumor burden.• For those patients who become intolerant to this every week dosing schedule, changing to an every other week dosing schedule was permitted. Preliminary data from and ongoing Study E2214 showed that the every other week schedule may be better tolerated and was anticipated to help patients sustain continued exposure and therefore potentially achieve maximal benefit from panobinostat. Dose intensity below 30 mg, 3 x week, every week or 20 mg, 3 x week, every week were not permitted as the plasma concentrations at lower dose intensity may not have maintained the histone acetylation for prolonged period of time and thus could possibly be subtherapeutic.
22 August 2011	<ul style="list-style-type: none">• Provided instructions on continuation of treatment and on necessary safety investigations for ongoing patients.• No further efficacy data captured other than documentation of the date of disease progression as assessed by investigator and death on study, as applicable. Laboratory and other safety assessments reduced to that which is appropriate to adequately monitor and protect patient safety. Patients had their data further summarized and/or listed as applicable in a subsequent extension report once these patients had either completed or discontinued the study.• Section added to provide updated data from Study E2214 interim analysis• Updated the study design, assessments and central review• Indicated completeness of enrollment as of 30-Oct-2009 in section on population• Clarified requirements for ECG monitoring• Updates on study duration and follow up requirements• Updates to reflect current program guidance for co-administration of CYP2D6 substrates• Updates to reflect current program guidance for co-administration of CYP3A4/5 inducers and inhibitors• Updated the pregnancy guidance for panobinostat• Updated the section on supportive analyses

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported