



Clinical trial results:

An Open-label study of Ibrutinib in Combination with Bortezomib and Dexamethasone in Subjects with Relapsed or Relapsed and Refractory Multiple Myeloma

Summary

EudraCT number	2015-005105-36
Trial protocol	CZ DE ES GR PL IT
Global end of trial date	25 October 2018

Results information

Result version number	v1 (current)
This version publication date	08 November 2019
First version publication date	08 November 2019

Trial information

Trial identification

Sponsor protocol code	PCYC-1139-CA
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01744691
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Pharmacyclics Switzerland GmbH
Sponsor organisation address	Mühlentalstrasse 36, Schaffhausen, Switzerland, 8200
Public contact	Clinical Trial information, Pharmacyclics LLC, 140 87740330, info@pcyc.com
Scientific contact	Clinical Trial information, Pharmacyclics LLC, 140 87740330, info@pcyc.com

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	26 November 2018
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	25 October 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to evaluate Progression-Free Survival (PFS) according to International Myeloma Working Group (IMWG) response criteria (Rajkumar 2011) in subjects with relapsed or relapsed and refractory MM.

Protection of trial subjects:

This study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with the International Conference on Harmonisation Harmonized Tripartite Guidelines for Good Clinical Practices and applicable local regulatory requirements.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	20 September 2016
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	Czech Republic: 23
Country: Number of subjects enrolled	Germany: 1
Country: Number of subjects enrolled	Greece: 11
Country: Number of subjects enrolled	Italy: 10
Country: Number of subjects enrolled	Spain: 16
Country: Number of subjects enrolled	Turkey: 13
Worldwide total number of subjects	74
EEA total number of subjects	61

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)	29
From 65 to 84 years	43
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

Key Inclusion Criteria:

- Subjects may have received prior bortezomib treatment but must not be refractory or non-responsive
- Serum monoclonal protein (SPEP) ≥ 1 g/dL
- Urine monoclonal protein (UPEP) ≥ 200 mg by 24 hour urine electrophoresis

Pre-assignment

Screening details:

Seventy four subjects were enrolled and 74 subjects received at least 1 dose of PCI-32765 and constitute the all treated population and the safety analysis set.

Period 1

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

Arms

Arm title	Ibrutinib + Bortezomib + Dexamethasone
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Arm description:

Ibrutinib 840 mg + Bortezomib 1.3 mg/sqm + Dexamethasone

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

Dosage and administration details:

All subjects received ibrutinib 840 mg (6 x 140 mg capsules) orally once daily in combination with 1.3 mg/sqm Bortezomib s.c. on Days 1, 4, 8, 11 during each 21-day cycle (Cycles 1-8) and on Days 1, 8, 22, and 29 on each 42-day cycle (Cycles 9-12) and 20 mg dexamethasone (10 mg in subjects 75 years and older) on Days 1, 2, 4, 5, 8, 9, 11, and 12 during each 21-day cycle (Cycles 1-8) and on Days 1, 2, 8, 9, 22, 23, 29, and 30 on each 42-day cycle (Cycles 9-12) and 40 mg once weekly (20 mg in subjects 75 years and older) during Cycle 13 and beyond. Following implementation of Amendment 4, the dexamethasone dose was reduced to on Days 1, 4, 8, and 11 during each 21-day cycle (Cycles 1-8) and on Days 1, 8, 22, and 29 on each 42-day cycle (Cycles 9-12) and unchanged thereafter.

Number of subjects in period 1	Ibrutinib + Bortezomib + Dexamethasone
Started	74
Completed	64
Not completed	10
Consent withdrawn by subject	10

Baseline characteristics

Reporting groups

Reporting group title	overall study
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Reporting group description:

All subjects received ibrutinib 840 mg (6 x 140 mg capsules) orally once daily in combination with 1.3 mg/sqm Bortezomib s.c. on Days 1, 4, 8, 11 during each 21-day cycle (Cycles 1-8) and on Days 1, 8, 22, and 29 on each 42-day cycle (Cycles 9-12) and 20 mg dexamethasone (10 mg in subjects 75 years and older) on Days 1, 2, 4, 5, 8, 9, 11, and 12 during each 21-day cycle (Cycles 1-8) and on Days 1, 2, 8, 9, 22, 23, 29, and 30 on each 42-day cycle (Cycles 9-12) and 40 mg once weekly (20 mg in subjects 75 years and older) during Cycle 13 and beyond. Following implementation of Amendment 4, the dexamethasone dose was reduced to on Days 1, 4, 8, and 11 during each 21-day cycle (Cycles 1-8) and on Days 1, 8, 22, and 30 on each 42-day cycle (Cycles 9-12) and unchanged thereafter.

Reporting group values	overall study	Total	
Number of subjects	74	74	
Age categorical			
Count of Participants			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	29	29	
From 65-84 years	43	43	
85 years and over	2	2	
Age continuous			
Units: years			
arithmetic mean	65.9		
standard deviation	± 10.14	-	
Gender categorical			
Units: Subjects			
Female	39	39	
Male	35	35	

End points

End points reporting groups

Reporting group title	Ibrutinib + Bortezomib + Dexamethasone
Reporting group description:	
Ibrutinib 840 mg + Bortezomib 1.3 mg/sqm + Dexamethasone	

Primary: Progression free survival

End point title	Progression free survival ^[1]
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End point description:

The primary efficacy endpoint of this study was mPFS. Progression free survival was defined as the time from the date of first dose of study treatment to confirmed disease progression or death from any cause, whichever occurs first.

End point type	Primary
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End point timeframe:

The median time on study for all treated participants was 19.6 (range 0.16+, 24.64) months.

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: This has been a single-arm, open-label study and it is not possible to enter a statistical analysis for a single-arm study in EudraCT.

End point values	Ibrutinib + Bortezomib + Dexamethason e			
Subject group type	Reporting group			
Number of subjects analysed	74			
Units: Month number (confidence interval 95%)				
number (confidence interval 95%)	8.5 (6.2 to 10.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Response Rate

End point title	Overall Response Rate
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End point description:

Overall Response Reate is the proportion of subjects who achieve a PR or better over the course of the study but prior to initiation of subsequent anti-cancer therapy.

End point type	Secondary
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End point timeframe:

The median time on study for all treated participants was 19.6 (range 0.16+, 24.64) months

End point values	Ibrutinib + Bortezomib + Dexamethason e			
Subject group type	Reporting group			
Number of subjects analysed	74			
Units: number (confidence interval 95%)				
number (confidence interval 95%)	56.8 (44.7 to 68.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival at 24 months

End point title	Overall Survival at 24 months
End point description: As the median overall survival has not been reached, the data for the landmark analysis at 24 months are provided.	
End point type	Secondary
End point timeframe: The median time on study for all treated participants was 19.6 (range 0.16+, 24.64) months	

End point values	Ibrutinib + Bortezomib + Dexamethason e			
Subject group type	Reporting group			
Number of subjects analysed	74			
Units: percent				
number (confidence interval 95%)	53.6 (38.0 to 67.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response

End point title	Duration of Response
End point description:	
End point type	Secondary
End point timeframe: The median time on study for all treated participants was 19.6 (range 0.16+, 24.64) months	

End point values	Ibrutinib + Bortezomib + Dexamethason e			
Subject group type	Reporting group			
Number of subjects analysed	74			
Units: months				
number (confidence interval 95%)	9.5 (6.9 to 10.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Progression

End point title	Time to Progression
End point description:	
End point type	Secondary
End point timeframe:	
The median time on study for all treated participants was 19.6 (range 0.16+, 24.64) months	

End point values	Ibrutinib + Bortezomib + Dexamethason e			
Subject group type	Reporting group			
Number of subjects analysed	74			
Units: months				
number (confidence interval 95%)	10.6 (7.8 to 12.0)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose of PCI-32765 to within 30 days of last dose for each participant or until study closure

Adverse event reporting additional description:

Number of participants who had experienced at least one treatment emergent AE

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	21.1
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Reporting groups

Reporting group title	IBRUTINIB (PCI-32765) + BORTEZOMIB + DEXAMETHASONE
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Reporting group description:

All subjects received ibrutinib 840 mg (6 x 140 mg capsules) orally once daily in combination with 1.3 mg/sqm Bortezomib s.c. on Days 1, 4, 8, 11 during each 21-day cycle (Cycles 1-8) and on Days 1, 8, 22, and 29 on each 42-day cycle (Cycles 9-12) and 20 mg dexamethasone (10 mg in subjects 75 years and older) on Days 1, 2, 4, 5, 8, 9, 11, and 12 during each 21-day cycle (Cycles 1-8) and on Days 1, 2, 8, 9, 22, 23, 29, and 30 on each 42-day cycle (Cycles 9-12) and 40 mg once weekly (20 mg in subjects 75 years and older) during Cycle 13 and beyond. Following implementation of Amendment 4, the dexamethasone dose was reduced to on Days 1, 4, 8, and 11 during each 21-day cycle (Cycles 1-8) and on Days 1, 8, 22, and 30 on each 42-day cycle (Cycles 9-12) and unchanged thereafter.

Serious adverse events	IBRUTINIB (PCI-32765) + BORTEZOMIB + DEXAMETHASONE		
Total subjects affected by serious adverse events			
subjects affected / exposed	47 / 74 (63.51%)		
number of deaths (all causes)	27		
number of deaths resulting from adverse events	11		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			
subjects affected / exposed	1 / 74 (1.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Vascular disorders			
Circulatory collapse			
subjects affected / exposed	1 / 74 (1.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
General disorders and administration site conditions			

Asthenia			
subjects affected / exposed	1 / 74 (1.35%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 1		
Death			
subjects affected / exposed	1 / 74 (1.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Pyrexia			
subjects affected / exposed	1 / 74 (1.35%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 1		
Sudden death			
subjects affected / exposed	1 / 74 (1.35%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Respiratory, thoracic and mediastinal disorders			
Aspiration			
subjects affected / exposed	1 / 74 (1.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Dyspnoea			
subjects affected / exposed	1 / 74 (1.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Pneumonitis			
subjects affected / exposed	1 / 74 (1.35%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 1		
Pulmonary alveolar haemorrhage			
subjects affected / exposed	1 / 74 (1.35%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 1		

Pulmonary embolism			
subjects affected / exposed	1 / 74 (1.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Pulmonary toxicity			
subjects affected / exposed	1 / 74 (1.35%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 1		
Respiratory failure			
subjects affected / exposed	1 / 74 (1.35%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 1		
Psychiatric disorders			
Delirium			
subjects affected / exposed	1 / 74 (1.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Investigations			
Weight decreased			
subjects affected / exposed	1 / 74 (1.35%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 1		
Injury, poisoning and procedural complications			
Humerus fracture			
subjects affected / exposed	1 / 74 (1.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Spinal compression fracture			
subjects affected / exposed	1 / 74 (1.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Thoracic vertebral fracture			

subjects affected / exposed	1 / 74 (1.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	3 / 74 (4.05%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 3		
Atrial flutter			
subjects affected / exposed	1 / 74 (1.35%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 1		
Sinus bradycardia			
subjects affected / exposed	1 / 74 (1.35%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 1		
Nervous system disorders			
Cerebral haemorrhage			
subjects affected / exposed	1 / 74 (1.35%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Generalised tonic-clonic seizure			
subjects affected / exposed	1 / 74 (1.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Polyneuropathy			
subjects affected / exposed	1 / 74 (1.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Syncope			
subjects affected / exposed	1 / 74 (1.35%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 1		
Blood and lymphatic system disorders			

Anaemia			
subjects affected / exposed	1 / 74 (1.35%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 1		
Thrombocytopenia			
subjects affected / exposed	2 / 74 (2.70%)		
occurrences causally related to treatment / all	7 / 7		
deaths causally related to treatment / all	0 / 7		
Spontaneous haematoma			
subjects affected / exposed	3 / 74 (4.05%)		
occurrences causally related to treatment / all	2 / 3		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 74 (1.35%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 1		
Gastrointestinal inflammation			
subjects affected / exposed	1 / 74 (1.35%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 1		
Mouth ulceration			
subjects affected / exposed	1 / 74 (1.35%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 1		
Hepatobiliary disorders			
Cholangitis acute			
subjects affected / exposed	1 / 74 (1.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Skin and subcutaneous tissue disorders			
Rash maculo-papular			

subjects affected / exposed	1 / 74 (1.35%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 1		
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	2 / 74 (2.70%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 2		
Renal impairment			
subjects affected / exposed	1 / 74 (1.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Infections and infestations			
Atypical pneumonia			
subjects affected / exposed	1 / 74 (1.35%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 1		
Bacteraemia			
subjects affected / exposed	1 / 74 (1.35%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 1		
Brain abscess			
subjects affected / exposed	1 / 74 (1.35%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 1		
Bronchitis			
subjects affected / exposed	2 / 74 (2.70%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 2		
Bronchitis viral			
subjects affected / exposed	1 / 74 (1.35%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 1		
Bronchopulmonary aspergillosis			

subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 1			
Erysipelas				
subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 1			
Gastroenteritis				
subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Gastrointestinal infection				
subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 1			
Haemophilus bacteraemia				
subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 1			
Haemophilus infection				
subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Herpes simplex				
subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 1			
Infection				
subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 1			
Influenza				

subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Lung infection				
subjects affected / exposed	2 / 74 (2.70%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 2			
Pneumococcal sepsis				
subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 1			
Pneumocystis jirovecii pneumonia				
subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 1			
Pneumonia				
subjects affected / exposed	11 / 74 (14.86%)			
occurrences causally related to treatment / all	4 / 12			
deaths causally related to treatment / all	1 / 2			
Pneumonia bacterial				
subjects affected / exposed	2 / 74 (2.70%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	1 / 2			
Pneumonia escherichia				
subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Pneumonia haemophilus				
subjects affected / exposed	2 / 74 (2.70%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 2			
Pneumonia pneumococcal				

subjects affected / exposed	2 / 74 (2.70%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 2		
Pseudomonal sepsis			
subjects affected / exposed	1 / 74 (1.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Respiratory tract infection			
subjects affected / exposed	1 / 74 (1.35%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 1		
Salmonellosis			
subjects affected / exposed	1 / 74 (1.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Sepsis			
subjects affected / exposed	3 / 74 (4.05%)		
occurrences causally related to treatment / all	1 / 4		
deaths causally related to treatment / all	1 / 3		
Staphylococcal infection			
subjects affected / exposed	1 / 74 (1.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Upper respiratory tract infection			
subjects affected / exposed	2 / 74 (2.70%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 2		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 74 (1.35%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 1		
Hypoglycaemia			

subjects affected / exposed	1 / 74 (1.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Hyponatraemia			
subjects affected / exposed	2 / 74 (2.70%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 2		

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

Non-serious adverse events	IBRUTINIB (PCI-32765) + BORTEZOMIB + DEXAMETHASONE		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	74 / 74 (100.00%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	10 / 74 (13.51%)		
occurrences (all)	14		
Hypotension			
subjects affected / exposed	8 / 74 (10.81%)		
occurrences (all)	9		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	22 / 74 (29.73%)		
occurrences (all)	60		
Fatigue			
subjects affected / exposed	21 / 74 (28.38%)		
occurrences (all)	40		
Oedema peripheral			
subjects affected / exposed	21 / 74 (28.38%)		
occurrences (all)	29		
Pain			
subjects affected / exposed	3 / 74 (4.05%)		
occurrences (all)	3		
Peripheral swelling			

<p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Pyrexia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>5 / 74 (6.76%)</p> <p>6</p> <p>13 / 74 (17.57%)</p> <p>18</p>		
<p>Respiratory, thoracic and mediastinal disorders</p> <p>Cough</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Dyspnoea</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Epistaxis</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Oropharyngeal pain</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Productive cough</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>15 / 74 (20.27%)</p> <p>20</p> <p>8 / 74 (10.81%)</p> <p>11</p> <p>7 / 74 (9.46%)</p> <p>8</p> <p>5 / 74 (6.76%)</p> <p>6</p> <p>4 / 74 (5.41%)</p> <p>4</p>		
<p>Psychiatric disorders</p> <p>Depression</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Insomnia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>3 / 74 (4.05%)</p> <p>3</p> <p>6 / 74 (8.11%)</p> <p>6</p>		
<p>Investigations</p> <p>Blood creatinine increased</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Platelet count decreased</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Weight decreased</p>	<p>4 / 74 (5.41%)</p> <p>6</p> <p>4 / 74 (5.41%)</p> <p>16</p>		

subjects affected / exposed occurrences (all)	4 / 74 (5.41%) 5		
Cardiac disorders Atrial fibrillation subjects affected / exposed occurrences (all)	6 / 74 (8.11%) 7		
Nervous system disorders Dizziness subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all) Neuropathy peripheral subjects affected / exposed occurrences (all) Peripheral sensorimotor neuropathy subjects affected / exposed occurrences (all) Peripheral sensory neuropathy subjects affected / exposed occurrences (all) Polyneuropathy subjects affected / exposed occurrences (all) Somnolence subjects affected / exposed occurrences (all) Syncope subjects affected / exposed occurrences (all)	5 / 74 (6.76%) 6 6 / 74 (8.11%) 6 4 / 74 (5.41%) 6 5 / 74 (6.76%) 14 18 / 74 (24.32%) 19 5 / 74 (6.76%) 10 4 / 74 (5.41%) 6 4 / 74 (5.41%) 4		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all) Lymphopenia	28 / 74 (37.84%) 66		

subjects affected / exposed	11 / 74 (14.86%)		
occurrences (all)	50		
Thrombocytopenia			
subjects affected / exposed	45 / 74 (60.81%)		
occurrences (all)	293		
Neutropenia			
subjects affected / exposed	10 / 74 (13.51%)		
occurrences (all)	20		
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	3 / 74 (4.05%)		
occurrences (all)	4		
Eye disorders			
Lacrimation increased			
subjects affected / exposed	4 / 74 (5.41%)		
occurrences (all)	5		
Vision blurred			
subjects affected / exposed	4 / 74 (5.41%)		
occurrences (all)	4		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	5 / 74 (6.76%)		
occurrences (all)	8		
Abdominal pain upper			
subjects affected / exposed	6 / 74 (8.11%)		
occurrences (all)	7		
Constipation			
subjects affected / exposed	10 / 74 (13.51%)		
occurrences (all)	17		
Diarrhoea			
subjects affected / exposed	40 / 74 (54.05%)		
occurrences (all)	119		
Dyspepsia			
subjects affected / exposed	5 / 74 (6.76%)		
occurrences (all)	5		
Mouth haemorrhage			

subjects affected / exposed occurrences (all)	3 / 74 (4.05%) 3		
Nausea subjects affected / exposed occurrences (all)	18 / 74 (24.32%) 24		
Stomatitis subjects affected / exposed occurrences (all)	4 / 74 (5.41%) 5		
Vomiting subjects affected / exposed occurrences (all)	11 / 74 (14.86%) 13		
Hepatobiliary disorders Hepatic function abnormal subjects affected / exposed occurrences (all)	6 / 74 (8.11%) 22		
Skin and subcutaneous tissue disorders Dermatitis allergic subjects affected / exposed occurrences (all)	5 / 74 (6.76%) 6		
Rash maculo-papular subjects affected / exposed occurrences (all)	10 / 74 (13.51%) 15		
Renal and urinary disorders Renal impairment subjects affected / exposed occurrences (all)	3 / 74 (4.05%) 6		
Endocrine disorders Cushingoid subjects affected / exposed occurrences (all)	4 / 74 (5.41%) 5		
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all)	15 / 74 (20.27%) 19		
Bone pain			

subjects affected / exposed	4 / 74 (5.41%)		
occurrences (all)	5		
Muscle spasms			
subjects affected / exposed	5 / 74 (6.76%)		
occurrences (all)	7		
Musculoskeletal chest pain			
subjects affected / exposed	3 / 74 (4.05%)		
occurrences (all)	4		
Musculoskeletal pain			
subjects affected / exposed	3 / 74 (4.05%)		
occurrences (all)	3		
Myalgia			
subjects affected / exposed	5 / 74 (6.76%)		
occurrences (all)	6		
Pain in extremity			
subjects affected / exposed	6 / 74 (8.11%)		
occurrences (all)	8		
Infections and infestations			
Bronchitis			
subjects affected / exposed	9 / 74 (12.16%)		
occurrences (all)	11		
Conjunctivitis			
subjects affected / exposed	10 / 74 (13.51%)		
occurrences (all)	11		
Herpes zoster			
subjects affected / exposed	3 / 74 (4.05%)		
occurrences (all)	4		
Infection			
subjects affected / exposed	3 / 74 (4.05%)		
occurrences (all)	3		
Influenza			
subjects affected / exposed	3 / 74 (4.05%)		
occurrences (all)	3		
Nasopharyngitis			
subjects affected / exposed	10 / 74 (13.51%)		
occurrences (all)	17		

Oral candidiasis			
subjects affected / exposed	4 / 74 (5.41%)		
occurrences (all)	4		
Pharyngitis			
subjects affected / exposed	3 / 74 (4.05%)		
occurrences (all)	3		
Pneumonia			
subjects affected / exposed	5 / 74 (6.76%)		
occurrences (all)	5		
Respiratory tract infection			
subjects affected / exposed	7 / 74 (9.46%)		
occurrences (all)	11		
Tonsillitis			
subjects affected / exposed	3 / 74 (4.05%)		
occurrences (all)	3		
Upper respiratory tract infection			
subjects affected / exposed	19 / 74 (25.68%)		
occurrences (all)	29		
Urinary tract infection			
subjects affected / exposed	8 / 74 (10.81%)		
occurrences (all)	9		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	10 / 74 (13.51%)		
occurrences (all)	11		
Hyperuricaemia			
subjects affected / exposed	3 / 74 (4.05%)		
occurrences (all)	3		
Hypocalcaemia			
subjects affected / exposed	11 / 74 (14.86%)		
occurrences (all)	16		
Hypomagnesaemia			
subjects affected / exposed	4 / 74 (5.41%)		
occurrences (all)	4		
Hypokalaemia			

subjects affected / exposed	13 / 74 (17.57%)		
occurrences (all)	22		
Hyponatraemia			
subjects affected / exposed	5 / 74 (6.76%)		
occurrences (all)	10		
Hypophosphataemia			
subjects affected / exposed	4 / 74 (5.41%)		
occurrences (all)	8		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 February 2016	<ul style="list-style-type: none">• Modify inclusion criteria to allow subjects with IgA, IgD, IgE or IgM multiple myeloma to enroll in the study with SPEP \geq 0.5 g/dL.• Removal of local analysis of FISH at Screening and clarification of biomarker testing.• Added option for low-dose whole-body CT scan to be performed instead of skeletal survey based upon methods that could be used to clarify presence of bone disease for the diagnosis of multiple myeloma.• Provided updated text regarding risks associated with ibrutinib for second primary malignancies.• Provided updated information regarding hepatic impairment.• Provided updated results on safety and efficacy for the Phase 1 part of PCYC-1119-CA (Study 1119).• Clarification added for dose reductions due to toxicity for dexamethasone for subjects >75 years of age.• Modified timing of collection of bone marrow aspirate samples at time of CR from every 3 months after confirmed CR to every 12 months after confirmed CR as MRD assessment more often than once a year is not needed.
08 December 2016	<ul style="list-style-type: none">• Include changes to clarify requirements for mid-cycle visits in the case of bortezomib discontinuation prior to protocol-scheduled completion• Include changes to clarify cycles and some test requirements for efficacy assessments• Update safety language per ibrutinib Investigator's Brochure Version 10
18 January 2017	<ul style="list-style-type: none">• Update of risk and dose modification language for ibrutinib• Update the exclusion criteria regarding treatment free interval for recent prior monoclonal antibody use from <6 weeks to <2 weeks (exclusion criteria #3).• Update reporting instructions for special reporting situations, adverse events and pregnancies and clarification regarding safety analysis.
12 May 2017	<ul style="list-style-type: none">• Provide an update on the current safety status of the study and outcome of recent Sponsor Safety review• Modify inclusion criteria to only enroll subjects with 2 or 3 prior lines of therapy• Update inclusion criteria for absolute neutrophil count• Modify the treatment schedule of dexamethasone to only administer dexamethasone on the day of bortezomib administration• Modify dose reduction guidelines of bortezomib to be in line with current clinical practice• Include clarification that interim analysis will include analysis of the enrollment distribution to reassess the initial hypothesis based on the actual subject population enrolled.• Implement a formal internal safety review committee to review safety data• Update protocol language per the current ibrutinib protocol template.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
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12 May 2017	On this date, enrollment of subjects was put on hold for the implementation of safety measures based on the observation of an increased incidence of serious and fatal infections in treated subjects. Risk minimization mainly included a reduction of the dexamethasone dose (effectively halving the dose in treatment cycles 1-12) and strengthening of infection prophylaxis. Subjects already enrolled were allowed to continue treatment with the reduced dose of dexamethasone. As significantly reduced number of serious and no fatal infections were observed in the following 6 months leading to approval of restarting enrollment by regulatory authorities and ethics committees. However, an evaluation of the efficacy data performed at the same time indicated that the primary endpoint of achieving a mPFS of >12 months was unlikely to be achieved following inclusion of additional subjects. As a result, the study was terminated and enrolment was not restarted.	-
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Notes:

Limitations and caveats

None reported