



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 |
|-----------------------|--------------|

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 |
|------------------|--|

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 |
|-----------------------|---------------|

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] |
| 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 |
| 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 + Dexamethasone | | | |
|---|--|--|--|--|
| 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 |
| End point description: | |
| Overall Response Rate 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 |
| 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 |
|-----------------|------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 21.1 |
|--------------------|------|

Reporting groups

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

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

| | | | |
|-----------------------------|------------------|--|--|
| 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 |
|------|--------------|--------------|
|------|--------------|--------------|

| | | |
|-------------|--|---|
| 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. | - |
|-------------|--|---|

Notes:

Limitations and caveats

None reported