



## Clinical trial results:

### **Efficacy of first line Dexamethasone, Rituximab and Cyclophosphamide (DRC) +/- Bortezomib for patients with Waldenström's Macroglobulinemia**

#### **Summary**

|                          |                   |
|--------------------------|-------------------|
| EudraCT number           | 2013-000506-37    |
| Trial protocol           | CZ IT PT SE GR ES |
| Global end of trial date | 17 April 2024     |

#### **Results information**

|                                   |  |
|-----------------------------------|--|
| Result version number             | v1 (current)   |
| This version publication date     | 26 April 2025  |
| First version publication date    | 26 April 2025  |
| Summary attachment (see zip file) | ECWM-1_Summary of Results_08.04.2025 (ECWM-1_Sum of clin study results_final_1.0_20250408.pdf) |

#### **Trial information**

##### **Trial identification**

|                       |        |
|-----------------------|--------|
| Sponsor protocol code | ECWM-1 |
|-----------------------|--------|

##### **Additional study identifiers**

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT01788020 |
| WHO universal trial number (UTN)   | -           |

Notes:

##### **Sponsors**

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | University Hospital Ulm  |
| Sponsor organisation address | Albert-Einstein-Allee 23, Ulm, Germany, 89081  |
| Public contact               | Prof. Dr. Christian Buske, University Hospital Ulm , +49 731 500 65800, christian.buske@uni-ulm.de |
| Scientific contact           | Prof. Dr. Christian Buske, University Hospital Ulm , +49 731 500 65800, christian.buske@uni-ulm.de |

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                       | 08 April 2025 |
| Is this the analysis of the primary completion data? | Yes           |
| Primary completion date                              | 17 April 2024 |
| Global end of trial reached?                         | Yes           |
| Global end of trial date                             | 17 April 2024 |
| Was the trial ended prematurely?                     | No            |

Notes:

## General information about the trial

Main objective of the trial:

The primary objective of the trial is to evaluate whether the addition of Bortezomib to the combination regimen Dexamethasone/Rituximab/Cyclophosphamide (B-DRC) improves PFS compared to DRC alone.

Protection of trial subjects:

In this study safety was assessed by evaluating the following: reported adverse events, clinical laboratory test results, vital signs measurements, chest X-ray/CT, physical examination findings, monitoring of concomitant therapy. For each safety parameter, all findings were recorded in the CRF.

Background therapy:

-

Evidence for comparator:

-

|   |                  |
|---|------------------|
| Actual start date of recruitment                          | 16 December 2013 |
| Long term follow-up planned                               | No               |
| Independent data monitoring committee (IDMC) involvement? | Yes              |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |             |
|--------------------------------------|-------------|
| Country: Number of subjects enrolled | Portugal: 2 |
| Country: Number of subjects enrolled | Spain: 4    |
| Country: Number of subjects enrolled | Sweden: 5   |
| Country: Number of subjects enrolled | Czechia: 7  |
| Country: Number of subjects enrolled | France: 110 |
| Country: Number of subjects enrolled | Germany: 48 |
| Country: Number of subjects enrolled | Greece: 26  |
| Worldwide total number of subjects   | 202         |
| EEA total number of subjects         | 202         |

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)                     | 74  |
| From 65 to 84 years                      | 127 |
| 85 years and over                        | 1   |

## Subject disposition

### Recruitment

Recruitment details:

First patient in: 28-Jan-2014

Date of early recruitment termination: 21-SEP-2018

Last patient last treatment: 17-APR-2019

Last patient completed Follow Up time: 16-APR-2024

### Pre-assignment

Screening details:

Clinicopathological diagnosis of WM as defined by consensus panel one of the Second International Workshop on WM and in need of treatment.

### Period 1

|                              |                                   |
|------------------------------|-----------------------------------|
| Period 1 title               | Treatment period (overall period) |
| Is this the baseline period? | Yes                               |
| Allocation method            | Randomised - controlled           |
| Blinding used                | Not blinded                       |

### Arms

|                              |       |
|------------------------------|-------|
| Are arms mutually exclusive? | Yes   |
| <b>Arm title</b>             | arm A |

Arm description:

induction standard arm (DRC)

|  |                        |
|--|------------------------|
| Arm type                               | Active comparator      |
| Investigational medicinal product name | Dexamethasone          |
| Investigational medicinal product code |                        |
| Other name                             |                        |
| Pharmaceutical forms                   | Capsule, soft + tablet |
| Routes of administration               | Oral use               |

Dosage and administration details:

20 mg p.o., Cycle 1-6, Day 1

|  |                                       |
|--|---------------------------------------|
| Investigational medicinal product name | Rituximab IV                          |
| Investigational medicinal product code |                                       |
| Other name                             | MabThera IV                           |
| Pharmaceutical forms                   | Concentrate for solution for infusion |
| Routes of administration               | Intravenous use                       |

Dosage and administration details:

375 mg/m<sup>2</sup>, Cycle 1 Day 1

|  |                  |
|--|------------------|
| Investigational medicinal product name | Cyclophosphamide |
| Investigational medicinal product code |                  |
| Other name                             |                  |
| Pharmaceutical forms                   | Tablet           |
| Routes of administration               | Oral use         |

Dosage and administration details:

100 mg/m<sup>2</sup> twice daily, Cycle 1-6, Day 1-5

|  |                        |
|--|------------------------|
| Investigational medicinal product name | Rituximab SC           |
| Investigational medicinal product code |                        |
| Other name                             | MabThera SC            |
| Pharmaceutical forms                   | Solution for injection |
| Routes of administration               | Solution for injection |

Dosage and administration details:  
1400 mg absolute SC, cycle 2-6, day 1

|                  |       |
|------------------|-------|
| <b>Arm title</b> | arm B |
|------------------|-------|

Arm description:

induction experimental arm (DRC +B)

|  |                                   |
|--|-----------------------------------|
| Arm type                               | Experimental                      |
| Investigational medicinal product name | Bortezomib                        |
| Investigational medicinal product code |                                   |
| Other name                             | Velcade                           |
| Pharmaceutical forms                   | Powder for solution for injection |
| Routes of administration               | Intravenous use, Subcutaneous use |

Dosage and administration details:

1.6 mg/m<sup>2</sup> Cycle 1-6, Day 1, 8 and 15

|  |                                       |
|--|---------------------------------------|
| Investigational medicinal product name | Rituximab IV                          |
| Investigational medicinal product code |                                       |
| Other name                             | MabThera IV                           |
| Pharmaceutical forms                   | Concentrate for solution for infusion |
| Routes of administration               | Intravenous use                       |

Dosage and administration details:

375 mg/m<sup>2</sup>, Cycle 1 Day 1

|  |                        |
|--|------------------------|
| Investigational medicinal product name | Rituximab SC           |
| Investigational medicinal product code |                        |
| Other name                             | MabThera SC            |
| Pharmaceutical forms                   | Solution for injection |
| Routes of administration               | Solution for injection |

Dosage and administration details:

1400 mg absolute SC, cycle 2-6, day 1

|  |                        |
|--|------------------------|
| Investigational medicinal product name | Dexamethasone          |
| Investigational medicinal product code |                        |
| Other name                             |                        |
| Pharmaceutical forms                   | Capsule, soft + tablet |
| Routes of administration               | Oral use               |

Dosage and administration details:

20 mg p.o., Cycle 1-6, Day 1

|  |                  |
|--|------------------|
| Investigational medicinal product name | Cyclophosphamide |
| Investigational medicinal product code |                  |
| Other name                             |                  |
| Pharmaceutical forms                   | Tablet           |
| Routes of administration               | Oral use         |

Dosage and administration details:

100 mg/m<sup>2</sup> twice daily, Cycle 1-6, Day 1-5

| <b>Number of subjects in period 1</b>  | arm A | arm B |
|--|-------|-------|
| Started                                | 100   | 102   |
| Completed                              | 82    | 89    |
| Not completed                          | 18    | 13    |
| Adverse event, serious fatal           | 2     | 2     |
| Consent withdrawn by subject           | 5     | 5     |
| Screening failure                      | 3     | 1     |
| missing of relevant values             | 2     | -     |
| Progression during treatment           | 2     | 1     |
| Adverse event, non-fatal               | 4     | 2     |
| Additional malignancy during follow up | -     | 2     |

## Baseline characteristics

---

### Reporting groups

|                       |       |
|-----------------------|-------|
| Reporting group title | arm A |
|-----------------------|-------|

Reporting group description:  
induction standard arm (DRC)

|                       |       |
|-----------------------|-------|
| Reporting group title | arm B |
|-----------------------|-------|

Reporting group description:  
induction experimental arm (DRC +B)

---

| <b>Reporting group values</b>         | arm A | arm B | Total |
|---------------------------------------|-------|-------|-------|
| Number of subjects                    | 100   | 102   | 202   |
| Age categorical<br>Units: Subjects    |       |       |       |
| Adults (18-64 years)                  | 36    | 38    | 74    |
| From 65-84 years                      | 64    | 63    | 127   |
| 85 years and over                     | 0     | 1     | 1     |
| Gender categorical<br>Units: Subjects |       |       |       |
| Female                                | 33    | 34    | 67    |
| Male                                  | 67    | 68    | 135   |

## End points

### End points reporting groups

|   |                    |
|---|--------------------|
| Reporting group title   | arm A              |
| Reporting group description:<br>induction standard arm (DRC)  |                    |
| Reporting group title   | arm B              |
| Reporting group description:<br>induction experimental arm (DRC +B)   |                    |
| Subject analysis set title  | ITT population     |
| Subject analysis set type   | Intention-to-treat |
| Subject analysis set description:   |                    |
| The intention-to-treat (ITT) population includes all patients randomized for induction regardless of study drug being received or not or other protocol violations.<br>According to the ITT, patients from the ITT population were analysed based on assigned treatment group per induction randomization. Patients without staging during induction were excluded for the evaluation of remission rates. |                    |
| Subject analysis set title  | Safety population  |
| Subject analysis set type   | Safety analysis    |
| Subject analysis set description:   |                    |
| For safety analyses, patients who started treatment were evaluated according to the treatment actually received (as treated).   |                    |

### Primary: Progression free survival (PFS)

|   |                                 |
|---|---------------------------------|
| End point title   | Progression free survival (PFS) |
| End point description:  |                                 |
| End point type  | Primary                         |
| End point timeframe:  |                                 |
| From date of inclusion to the following events: the date of progression and the date of death if it occurred earlier. In the absence of progression and death, PFS duration is censored at the stopping date or the date of last follow-up. |                                 |

| End point values            | arm A           | arm B           |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 100             | 102             |  |  |
| Units: month                |                 |                 |  |  |
| number (not applicable)     | 50.1            | 60.0            |  |  |

### Statistical analyses

|                            |                      |
|----------------------------|----------------------|
| Statistical analysis title | Primary analysis PFS |
| Comparison groups          | arm B v arm A        |

|   |                   |
|---|-------------------|
| Number of subjects included in analysis | 202               |
| Analysis specification                  | Pre-specified     |
| Analysis type                           | superiority       |
| P-value                                 | = 0.64            |
| Method                                  | Logrank           |
| Parameter estimate                      | Hazard ratio (HR) |
| Point estimate                          | 0.914             |
| Confidence interval                     |                   |
| level                                   | 95 %              |
| sides                                   | 2-sided           |
| lower limit                             | 0.629             |
| upper limit                             | 1.329             |

### Secondary: Remission duration (RD)

|  |                         |
|--|-------------------------|
| End point title  | Remission duration (RD) |
| End point description:   |                         |
| End point type   | Secondary               |
| End point timeframe:   |                         |
| Calculated in patients with response (CR, VGPR, PR, MR) from end of induction to the date of progression, relapse or death from any cause. Patients alive without progression and relapse is censored at the latest tumor assessment date. |                         |

| End point values            | arm A           | arm B           |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 100             | 102             |  |  |
| Units: month                |                 |                 |  |  |
| number (not applicable)     | 43.5            | 51.1            |  |  |

### Statistical analyses

|   |                    |
|---|--------------------|
| <b>Statistical analysis title</b>       | remission duration |
| Comparison groups                       | arm A v arm B      |
| Number of subjects included in analysis | 202                |
| Analysis specification                  | Pre-specified      |
| Analysis type                           | superiority        |
| P-value                                 | = 0.64             |
| Method                                  | Logrank            |

### Secondary: Time to next treatment (TNT)

|                 |                              |
|-----------------|------------------------------|
| End point title | Time to next treatment (TNT) |
|-----------------|------------------------------|

End point description:

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

End point timeframe:

Time to next treatment (TNT) is defined as the time of randomization to start of new anti-cancer therapy. Patients alive without new anti-cancer therapy are censored at the latest tumor assessment date.

| <b>End point values</b>     | arm A           | arm B           |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 100             | 102             |  |  |
| Units: month                |                 |                 |  |  |
| number (not applicable)     | 67.5            | 68.8            |  |  |

### Statistical analyses

|   |                        |
|---|------------------------|
| <b>Statistical analysis title</b>       | time to next treatment |
| Comparison groups                       | arm B v arm A          |
| Number of subjects included in analysis | 202                    |
| Analysis specification                  | Post-hoc               |
| Analysis type                           | superiority            |
| P-value                                 | = 0.98                 |
| Method                                  | Logrank                |

### Secondary: Cumulative incidence of first response

|                 |  |
|-----------------|--|
| End point title | Cumulative incidence of first response |
|-----------------|--|

End point description:

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

End point timeframe:

4-months cumulative incidence

| <b>End point values</b>          | arm A           | arm B           |  |  |
|----------------------------------|-----------------|-----------------|--|--|
| Subject group type               | Reporting group | Reporting group |  |  |
| Number of subjects analysed      | 100             | 102             |  |  |
| Units: %                         |                 |                 |  |  |
| number (confidence interval 95%) | 61 (52 to 70)   | 73 (64 to 81)   |  |  |

## Statistical analyses

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | cumulative incidence of first response |
| Comparison groups                       | arm A v arm B                          |
| Number of subjects included in analysis | 202                                    |
| Analysis specification                  | Post-hoc                               |
| Analysis type                           | superiority                            |
| P-value                                 | = 0.83                                 |
| Method                                  | Fine and gray test                     |

## Secondary: Response rate (RR) and overall response rate (ORR) after therapy

|   |  |
|---|--|
| End point title   | Response rate (RR) and overall response rate (ORR) after therapy |
| End point description:  |  |
| End point type  | Secondary  |
| End point timeframe:<br>four weeks after end of induction therapy |  |

| <b>End point values</b>     | arm A           | arm B           | ITT population       |  |
|-----------------------------|-----------------|-----------------|----------------------|--|
| Subject group type          | Reporting group | Reporting group | Subject analysis set |  |
| Number of subjects analysed | 90              | 94              | 184                  |  |
| Units: %                    |                 |                 |                      |  |
| number (not applicable)     |                 |                 |                      |  |
| Complete remission/response | 1.1             | 2.1             | 1.6                  |  |
| Very good partial response  | 8.9             | 15.8            | 12.4                 |  |
| Partial remission           | 56.7            | 60.0            | 58.5                 |  |
| Minor response              | 21.1            | 15.8            | 18.4                 |  |
| Stable disease              | 8.9             | 4.2             | 6.5                  |  |
| Progressive disease         | 3.3             | 2.1             | 2.7                  |  |
| ORR (CR, VGPR, PR, MR)      | 87.7            | 93.7            | 90.8                 |  |

## Statistical analyses

|   |               |
|---|---------------|
| <b>Statistical analysis title</b>       | response rate |
| Comparison groups                       | arm A v arm B |
| Number of subjects included in analysis | 184           |
| Analysis specification                  | Pre-specified |
| Analysis type                           | superiority   |
| P-value                                 | = 0.35        |
| Method                                  | Fisher exact  |

**Secondary: Best response**

|   |               |
|---|---------------|
| End point title                                   | Best response |
| End point description:                            |               |
| End point type                                    | Secondary     |
| End point timeframe:                              |               |
| from end of induction therapy to end of follow-up |               |

| <b>End point values</b>     | arm A             | arm B             | ITT population       |  |
|-----------------------------|-------------------|-------------------|----------------------|--|
| Subject group type          | Reporting group   | Reporting group   | Subject analysis set |  |
| Number of subjects analysed | 90 <sup>[1]</sup> | 96 <sup>[2]</sup> | 186 <sup>[3]</sup>   |  |
| Units: %                    |                   |                   |                      |  |
| number (not applicable)     |                   |                   |                      |  |
| Complete remission/response | 1.1               | 5.2               | 3.2                  |  |
| Very good partial response  | 21.1              | 30.2              | 25.8                 |  |
| Partial remission           | 62.3              | 53.1              | 57.5                 |  |
| Minor response              | 11.1              | 7.3               | 9.2                  |  |
| Stable disease              | 2.2               | 3.1               | 2.7                  |  |
| Progressive disease         | 2.2               | 1.1               | 1.6                  |  |

Notes:

[1] - 10 not assessable

[2] - 6 not assessable

[3] - 16 not assessable

**Statistical analyses**

|   |               |
|---|---------------|
| <b>Statistical analysis title</b>       | best response |
| Comparison groups                       | arm A v arm B |
| Number of subjects included in analysis | 186           |
| Analysis specification                  | Pre-specified |
| Analysis type                           | superiority   |
| P-value                                 | = 0.32        |
| Method                                  | Fisher exact  |

**Secondary: Time to treatment failure (TTF)**

|   |                                 |
|---|---------------------------------|
| End point title   | Time to treatment failure (TTF) |
| End point description:  |                                 |
| End point type  | Secondary                       |
| End point timeframe:  |                                 |
| Time of randomization to discontinuation of therapy for any reason including death from any cause, progression, toxicity or add-on of new anti-cancer therapy. Patients alive without treatment failure are censored at the latest tumor assessment date. |                                 |

| <b>End point values</b>     | arm A           | arm B           |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 100             | 102             |  |  |
| Units: months               |                 |                 |  |  |
| number (not applicable)     | 40.5            | 51.5            |  |  |

### Statistical analyses

|   |                                 |
|---|---------------------------------|
| <b>Statistical analysis title</b>       | Time to treatment failure (TTF) |
| Comparison groups                       | arm A v arm B                   |
| Number of subjects included in analysis | 202                             |
| Analysis specification                  | Pre-specified                   |
| Analysis type                           | superiority                     |
| P-value                                 | = 0.3                           |
| Method                                  | Logrank                         |

### Secondary: Cumulative incidence of best response

|                                |                                       |
|--------------------------------|---------------------------------------|
| End point title                | Cumulative incidence of best response |
| End point description:         |                                       |
| End point type                 | Secondary                             |
| End point timeframe:           |                                       |
| 12-months cumulative incidence |                                       |

| <b>End point values</b>          | arm A           | arm B           |  |  |
|----------------------------------|-----------------|-----------------|--|--|
| Subject group type               | Reporting group | Reporting group |  |  |
| Number of subjects analysed      | 100             | 102             |  |  |
| Units: %                         |                 |                 |  |  |
| number (confidence interval 95%) | 67 (58 to 76)   | 74 (65 to 83)   |  |  |

### Statistical analyses

|   |                                       |
|---|---------------------------------------|
| <b>Statistical analysis title</b>       | Cumulative incidence of best response |
| Comparison groups                       | arm A v arm B                         |
| Number of subjects included in analysis | 202                                   |
| Analysis specification                  | Pre-specified                         |
| Analysis type                           | superiority                           |
| P-value                                 | = 0.21                                |
| Method                                  | Fine and gray test                    |



## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

All adverse events will be recorded from the time the subject receives study treatment to 28 days after the last dose of treatment.

Adverse event reporting additional description:

All subjects will be monitored for AEs during the study. Assessments may include monitoring of any or all of the following parameters: the subject's clinical symptoms, laboratory, pathological, radiological or surgical findings, physical examination findings, or other appropriate tests and procedures.

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 27.0 |
|--------------------|------|

### Reporting groups

|                       |       |
|-----------------------|-------|
| Reporting group title | ARM A |
|-----------------------|-------|

Reporting group description:

Induction standard arm - reference therapy (Dexamethasone, Rituximab, Cyclophosphamide)

|                       |       |
|-----------------------|-------|
| Reporting group title | ARM B |
|-----------------------|-------|

Reporting group description:

Induction experimental arm - (Bortezomib, Dexamethasone, Rituximab, Cyclophosphamide)

| <b>Serious adverse events</b>                                       | ARM A            | ARM B            |  |
|---|------------------|------------------|--|
| Total subjects affected by serious adverse events                   |                  |                  |  |
| subjects affected / exposed   | 27 / 96 (28.13%) | 14 / 99 (14.14%) |  |
| number of deaths (all causes)                                       | 9                | 17               |  |
| number of deaths resulting from adverse events                      |                  |                  |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                  |                  |  |
| Basal cell carcinoma  |                  |                  |  |
| subjects affected / exposed   | 1 / 96 (1.04%)   | 1 / 99 (1.01%)   |  |
| occurrences causally related to treatment / all                     | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all                          | 0 / 0            | 0 / 0            |  |
| Myelodysplastic syndrome  |                  |                  |  |
| subjects affected / exposed   | 1 / 96 (1.04%)   | 0 / 99 (0.00%)   |  |
| occurrences causally related to treatment / all                     | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all                          | 0 / 0            | 0 / 0            |  |
| Pancreatic carcinoma  |                  |                  |  |

|   |                |                |  |
|---|----------------|----------------|--|
| subjects affected / exposed                                 | 0 / 96 (0.00%) | 1 / 99 (1.01%) |  |
| occurrences causally related to treatment / all             | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all                  | 0 / 0          | 1 / 1          |  |
| <b>Second primary malignancy</b>                            |                |                |  |
| subjects affected / exposed                                 | 1 / 96 (1.04%) | 0 / 99 (0.00%) |  |
| occurrences causally related to treatment / all             | 1 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all                  | 0 / 0          | 0 / 0          |  |
| <b>Squamous cell carcinoma</b>                              |                |                |  |
| subjects affected / exposed                                 | 0 / 96 (0.00%) | 1 / 99 (1.01%) |  |
| occurrences causally related to treatment / all             | 0 / 0          | 1 / 1          |  |
| deaths causally related to treatment / all                  | 0 / 0          | 0 / 0          |  |
| <b>Vascular disorders</b>                                   |                |                |  |
| <b>Hypotension</b>  |                |                |  |
| subjects affected / exposed                                 | 1 / 96 (1.04%) | 0 / 99 (0.00%) |  |
| occurrences causally related to treatment / all             | 1 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all                  | 0 / 0          | 0 / 0          |  |
| <b>General disorders and administration site conditions</b> |                |                |  |
| <b>Chest pain</b>   |                |                |  |
| subjects affected / exposed                                 | 1 / 96 (1.04%) | 0 / 99 (0.00%) |  |
| occurrences causally related to treatment / all             | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all                  | 0 / 0          | 0 / 0          |  |
| <b>Chills</b>   |                |                |  |
| subjects affected / exposed                                 | 0 / 96 (0.00%) | 1 / 99 (1.01%) |  |
| occurrences causally related to treatment / all             | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all                  | 0 / 0          | 0 / 0          |  |
| <b>Death</b>  |                |                |  |
| subjects affected / exposed                                 | 0 / 96 (0.00%) | 1 / 99 (1.01%) |  |
| occurrences causally related to treatment / all             | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all                  | 0 / 0          | 0 / 0          |  |
| <b>General physical health deterioration</b>                |                |                |  |
| subjects affected / exposed                                 | 0 / 96 (0.00%) | 2 / 99 (2.02%) |  |
| occurrences causally related to treatment / all             | 0 / 0          | 1 / 2          |  |
| deaths causally related to treatment / all                  | 0 / 0          | 0 / 0          |  |

|   |                |                |  |
|---|----------------|----------------|--|
| Pyrexia   |                |                |  |
| subjects affected / exposed                     | 4 / 96 (4.17%) | 1 / 99 (1.01%) |  |
| occurrences causally related to treatment / all | 3 / 4          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Sudden death                                    |                |                |  |
| subjects affected / exposed                     | 1 / 96 (1.04%) | 0 / 99 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Immune system disorders                         |                |                |  |
| Hypersensitivity                                |                |                |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 99 (1.01%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Reproductive system and breast disorders        |                |                |  |
| Benign prostatic hyperplasia                    |                |                |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 99 (1.01%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Respiratory, thoracic and mediastinal disorders |                |                |  |
| Acute pulmonary oedema                          |                |                |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 99 (1.01%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Asthmatic crisis                                |                |                |  |
| subjects affected / exposed                     | 1 / 96 (1.04%) | 0 / 99 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Bronchospasm                                    |                |                |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 99 (1.01%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Cough   |                |                |  |

|   |                |                |  |
|---|----------------|----------------|--|
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 99 (1.01%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 2          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Dyspnoea  |                |                |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 2 / 99 (2.02%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 3          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Lung disorder                                   |                |                |  |
| subjects affected / exposed                     | 1 / 96 (1.04%) | 1 / 99 (1.01%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 1 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Pleural effusion                                |                |                |  |
| subjects affected / exposed                     | 2 / 96 (2.08%) | 0 / 99 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 1          | 0 / 0          |  |
| Respiratory tract inflammation                  |                |                |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 99 (1.01%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Injury, poisoning and procedural complications  |                |                |  |
| Ankle fracture                                  |                |                |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 99 (1.01%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Shoulder fracture                               |                |                |  |
| subjects affected / exposed                     | 1 / 96 (1.04%) | 0 / 99 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Spinal fracture                                 |                |                |  |
| subjects affected / exposed                     | 1 / 96 (1.04%) | 0 / 99 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Cardiac disorders                               |                |                |  |

|   |                |                |  |
|---|----------------|----------------|--|
| Arrhythmia                                      |                |                |  |
| subjects affected / exposed                     | 1 / 96 (1.04%) | 0 / 99 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Atrial flutter                                  |                |                |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 99 (1.01%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Cardiac failure                                 |                |                |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 99 (1.01%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 1          |  |
| Coronary artery stenosis                        |                |                |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 99 (1.01%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Nervous system disorders                        |                |                |  |
| Brain hypoxia                                   |                |                |  |
| subjects affected / exposed                     | 1 / 96 (1.04%) | 0 / 99 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 1 / 1          | 0 / 0          |  |
| Peripheral sensory neuropathy                   |                |                |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 99 (1.01%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Syncope   |                |                |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 99 (1.01%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Blood and lymphatic system disorders            |                |                |  |
| Febrile neutropenia                             |                |                |  |
| subjects affected / exposed                     | 2 / 96 (2.08%) | 0 / 99 (0.00%) |  |
| occurrences causally related to treatment / all | 2 / 2          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |

|   |                |                |  |
|---|----------------|----------------|--|
| Hyperviscosity syndrome                         |                |                |  |
| subjects affected / exposed                     | 1 / 96 (1.04%) | 0 / 99 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Neutropenia                                     |                |                |  |
| subjects affected / exposed                     | 1 / 96 (1.04%) | 0 / 99 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Pancytopenia                                    |                |                |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 99 (1.01%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Eye disorders                                   |                |                |  |
| Diplopia  |                |                |  |
| subjects affected / exposed                     | 1 / 96 (1.04%) | 0 / 99 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Gastrointestinal disorders                      |                |                |  |
| Abdominal pain                                  |                |                |  |
| subjects affected / exposed                     | 2 / 96 (2.08%) | 0 / 99 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Dysphagia                                       |                |                |  |
| subjects affected / exposed                     | 1 / 96 (1.04%) | 0 / 99 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Gastrointestinal haemorrhage                    |                |                |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 99 (1.01%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Nausea  |                |                |  |
| subjects affected / exposed                     | 1 / 96 (1.04%) | 0 / 99 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |

|   |                |                |  |
|---|----------------|----------------|--|
| Vomiting  |                |                |  |
| subjects affected / exposed                     | 1 / 96 (1.04%) | 0 / 99 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Hepatobiliary disorders                         |                |                |  |
| Cholangitis                                     |                |                |  |
| subjects affected / exposed                     | 1 / 96 (1.04%) | 0 / 99 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Skin and subcutaneous tissue disorders          |                |                |  |
| Erythema  |                |                |  |
| subjects affected / exposed                     | 1 / 96 (1.04%) | 0 / 99 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Musculoskeletal and connective tissue disorders |                |                |  |
| Arthritis                                       |                |                |  |
| subjects affected / exposed                     | 1 / 96 (1.04%) | 0 / 99 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Infections and infestations                     |                |                |  |
| Bronchitis                                      |                |                |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 99 (1.01%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Influenza                                       |                |                |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 2 / 99 (2.02%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 2          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Pneumococcal sepsis                             |                |                |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 99 (1.01%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Pneumonia                                       |                |                |  |

|   |                |                |  |
|---|----------------|----------------|--|
| subjects affected / exposed                     | 1 / 96 (1.04%) | 1 / 99 (1.01%) |  |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| <b>Sepsis</b>                                   |                |                |  |
| subjects affected / exposed                     | 1 / 96 (1.04%) | 0 / 99 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| <b>Urinary tract infection</b>                  |                |                |  |
| subjects affected / exposed                     | 0 / 96 (0.00%) | 1 / 99 (1.01%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| <b>Metabolism and nutrition disorders</b>       |                |                |  |
| <b>Tumour lysis syndrome</b>                    |                |                |  |
| subjects affected / exposed                     | 1 / 96 (1.04%) | 0 / 99 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 1 / 1          | 0 / 0          |  |

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

| <b>Non-serious adverse events</b>                            | ARM A            | ARM B            |  |
|--|------------------|------------------|--|
| <b>Total subjects affected by non-serious adverse events</b> |                  |                  |  |
| subjects affected / exposed                                  | 91 / 96 (94.79%) | 97 / 99 (97.98%) |  |
| <b>Injury, poisoning and procedural complications</b>        |                  |                  |  |
| <b>Infusion related reaction</b>                             |                  |                  |  |
| subjects affected / exposed                                  | 5 / 96 (5.21%)   | 4 / 99 (4.04%)   |  |
| occurrences (all)  | 7                | 5                |  |
| <b>Nervous system disorders</b>                              |                  |                  |  |
| <b>Peripheral sensory neuropathy</b>                         |                  |                  |  |
| subjects affected / exposed                                  | 5 / 96 (5.21%)   | 21 / 99 (21.21%) |  |
| occurrences (all)  | 10               | 31               |  |
| <b>Headache</b>  |                  |                  |  |
| subjects affected / exposed                                  | 4 / 96 (4.17%)   | 5 / 99 (5.05%)   |  |
| occurrences (all)  | 6                | 6                |  |
| <b>Paraesthesia</b>  |                  |                  |  |

|   |                        |                        |  |
|---|------------------------|------------------------|--|
| subjects affected / exposed<br>occurrences (all)                          | 5 / 96 (5.21%)<br>5    | 4 / 99 (4.04%)<br>5    |  |
| Dizziness<br>subjects affected / exposed<br>occurrences (all)             | 1 / 96 (1.04%)<br>1    | 7 / 99 (7.07%)<br>7    |  |
| Neuropathy peripheral<br>subjects affected / exposed<br>occurrences (all) | 4 / 96 (4.17%)<br>4    | 5 / 99 (5.05%)<br>6    |  |
| <b>Blood and lymphatic system disorders</b>                               |                        |                        |  |
| Anaemia<br>subjects affected / exposed<br>occurrences (all)               | 23 / 96 (23.96%)<br>36 | 21 / 99 (21.21%)<br>41 |  |
| Neutropenia<br>subjects affected / exposed<br>occurrences (all)           | 28 / 96 (29.17%)<br>80 | 34 / 99 (34.34%)<br>99 |  |
| Thrombocytopenia<br>subjects affected / exposed<br>occurrences (all)      | 9 / 96 (9.38%)<br>22   | 18 / 99 (18.18%)<br>39 |  |
| Leukopenia<br>subjects affected / exposed<br>occurrences (all)            | 6 / 96 (6.25%)<br>22   | 9 / 99 (9.09%)<br>19   |  |
| <b>General disorders and administration<br/>site conditions</b>           |                        |                        |  |
| Fatigue<br>subjects affected / exposed<br>occurrences (all)               | 21 / 96 (21.88%)<br>29 | 20 / 99 (20.20%)<br>34 |  |
| Pyrexia<br>subjects affected / exposed<br>occurrences (all)               | 18 / 96 (18.75%)<br>21 | 16 / 99 (16.16%)<br>21 |  |
| Chills<br>subjects affected / exposed<br>occurrences (all)                | 7 / 96 (7.29%)<br>7    | 5 / 99 (5.05%)<br>5    |  |
| <b>Gastrointestinal disorders</b>   |                        |                        |  |
| Nausea<br>subjects affected / exposed<br>occurrences (all)                | 39 / 96 (40.63%)<br>66 | 43 / 99 (43.43%)<br>74 |  |
| Diarrhea  |                        |                        |  |

|   |                        |                        |  |
|---|------------------------|------------------------|--|
| subjects affected / exposed<br>occurrences (all)  | 8 / 96 (8.33%)<br>8    | 17 / 99 (17.17%)<br>32 |  |
| Constipation<br>subjects affected / exposed<br>occurrences (all)  | 10 / 96 (10.42%)<br>13 | 21 / 99 (21.21%)<br>24 |  |
| Vomiting<br>subjects affected / exposed<br>occurrences (all)  | 13 / 96 (13.54%)<br>13 | 23 / 99 (23.23%)<br>28 |  |
| Abdominal pain<br>subjects affected / exposed<br>occurrences (all)  | 7 / 96 (7.29%)<br>9    | 6 / 99 (6.06%)<br>7    |  |
| Respiratory, thoracic and mediastinal disorders<br>Cough<br>subjects affected / exposed<br>occurrences (all)      | 5 / 96 (5.21%)<br>6    | 4 / 99 (4.04%)<br>5    |  |
| Dyspnoea<br>subjects affected / exposed<br>occurrences (all)  | 6 / 96 (6.25%)<br>6    | 6 / 99 (6.06%)<br>7    |  |
| Epistaxis<br>subjects affected / exposed<br>occurrences (all)   | 5 / 96 (5.21%)<br>5    | 2 / 99 (2.02%)<br>2    |  |
| Psychiatric disorders<br>Insomnia<br>subjects affected / exposed<br>occurrences (all)                             | 6 / 96 (6.25%)<br>7    | 1 / 99 (1.01%)<br>1    |  |
| Musculoskeletal and connective tissue disorders<br>Arthralgia<br>subjects affected / exposed<br>occurrences (all) | 7 / 96 (7.29%)<br>8    | 1 / 99 (1.01%)<br>1    |  |
| Back pain<br>subjects affected / exposed<br>occurrences (all)   | 7 / 96 (7.29%)<br>7    | 3 / 99 (3.03%)<br>4    |  |
| Bone pain<br>subjects affected / exposed<br>occurrences (all)   | 6 / 96 (6.25%)<br>9    | 6 / 99 (6.06%)<br>7    |  |
| Infections and infestations   |                        |                        |  |

|                                    |                |                |  |
|------------------------------------|----------------|----------------|--|
| Bronchitis                         |                |                |  |
| subjects affected / exposed        | 2 / 96 (2.08%) | 9 / 99 (9.09%) |  |
| occurrences (all)                  | 4              | 9              |  |
| Rash pustular                      |                |                |  |
| subjects affected / exposed        | 1 / 96 (1.04%) | 5 / 99 (5.05%) |  |
| occurrences (all)                  | 1              | 5              |  |
| Upper respiratory tract infection  |                |                |  |
| subjects affected / exposed        | 1 / 96 (1.04%) | 5 / 99 (5.05%) |  |
| occurrences (all)                  | 1              | 7              |  |
| Urinary tract infection            |                |                |  |
| subjects affected / exposed        | 2 / 96 (2.08%) | 9 / 99 (9.09%) |  |
| occurrences (all)                  | 2              | 10             |  |
| Metabolism and nutrition disorders |                |                |  |
| Decreased appetite                 |                |                |  |
| subjects affected / exposed        | 2 / 96 (2.08%) | 5 / 99 (5.05%) |  |
| occurrences (all)                  | 3              | 6              |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date              | Amendment   |
|-------------------|---|
| 21 September 2018 | The study was conducted as planned in the protocol until 21-SEP-2018 when the recruitment was terminated early. 202 patients (instead of 384) were recruited over a period of 4 years and 8 months before the study prematurely stopped recruitment. Planned duration of recruitment was approximately 3.3 years. The early recruitment termination was due to the fact that the treatment landscape had changed tremendously through ibrutinib availability. |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported