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
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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 paramenter, 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
Arm title	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/m2, 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/m2 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	

Arm title	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/m2 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/m2, 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/m2 twice daily, Cycle 1-6, Day 1-5	

Number of subjects in period 1	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)	

Reporting group values	arm A	arm B	Total
Number of subjects	100	102	202
Age categorical 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 Units: Subjects			
Female	33	34	67
Male	67	68	135

End points

End points 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)	
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.
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

Statistical analysis title	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.

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)	67.5	68.8		

Statistical analyses

Statistical analysis title	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

End point values	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

Statistical analysis title	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:	
four weeks after end of induction therapy	

End point values	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

Statistical analysis title	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

End point values	arm A	arm B	ITT population	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	90[1]	96[2]	186[3]	
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

Statistical analysis title	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.

End point values	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

Statistical analysis title	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	

End point values	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

Statistical analysis title	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)

Serious adverse events	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	
Second primary malignancy			
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	
Squamous cell carcinoma			
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	
Vascular disorders			
Hypotension			
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	
General disorders and administration site conditions			
Chest pain			
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	
Chills			
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	
Death			
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	
General physical health deterioration			
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	
Sepsis			
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	
Urinary tract infection			
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	
Metabolism and nutrition disorders			
Tumour lysis syndrome			
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 %

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

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

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

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

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported