

**Clinical trial results:****iNNOVATE Study: A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study of Ibrutinib or Placebo in Combination with Rituximab in Subjects with Waldenstrom's Macroglobulinemia****Summary**

EudraCT number	2013-005478-22
Trial protocol	IT DE ES GR GB
Global end of trial date	

Results information

Result version number	v1
This version publication date	24 February 2019
First version publication date	24 February 2019

Trial information**Trial identification**

Sponsor protocol code	PCYC-1127-CA
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02165397
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Pharmacyclics
Sponsor organisation address	995 East Arques Avenue, Sunnyvale, United States, 94085-4521
Public contact	Medical Monitor, Pharmacyclics, Incorporated Lori Styles 995 East Arques Avenue Sunnyvale CA 94085-4521 US, 001 4082153770, lstyles@pcyc.com
Scientific contact	Medical Monitor, Pharmacyclics, Incorporated Lori Styles 995 East Arques Avenue Sunnyvale CA 94085-4521 US, 001 4082153770, lstyles@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	Interim
Date of interim/final analysis	17 October 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	17 October 2017
Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the effect of the addition of ibrutinib to rituximab on progression-free survival (PFS) assessed by an independent review committee (IRC) in subjects with Waldenstrom`s Macroglobulinemia WM. Efficacy evaluations will be based on the modified Consensus Response Criteria from the Vth International Workshop for WM (NCCN 2014).

Protection of trial subjects:

This study was conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki and that are consistent with Good Clinical Practices and applicable regulatory requirements, with the exception of the issues discussed in Section 4.4 of the CSR. These issues/non-conformances did not have an impact on the overall conclusions of this study

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	07 July 2014
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy, Scientific research
Long term follow-up duration	3 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 18
Country: Number of subjects enrolled	United Kingdom: 2
Country: Number of subjects enrolled	France: 30
Country: Number of subjects enrolled	Germany: 6
Country: Number of subjects enrolled	Greece: 29
Country: Number of subjects enrolled	Italy: 25
Country: Number of subjects enrolled	United States: 26
Country: Number of subjects enrolled	Canada: 18
Country: Number of subjects enrolled	Australia: 27
Worldwide total number of subjects	181
EEA total number of subjects	110

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)	72
From 65 to 84 years	99
85 years and over	10

Subject disposition

Recruitment

Recruitment details:

Multi-center, randomized in 1:1 ibrutinib and rituximab or placebo and rituximab. Phase 3 study conducted at a total of 48 sites, 10 sites in the US, 30 sites in Europe, 4 sites in Canada and 4 sites in Australia

Pre-assignment

Screening details:

Eligible subjects were ≥ 18 years of age with untreated WM or previously treated WM. During the screening phase, the subjects' eligibility was to be determined. Eligible subjects must have had clinicopathological diagnosis of WM confirmed by central pathology review and in accordance with the consensus panel of the Second IWWM.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Blinding implementation details:

Double-blind study: subjects, investigators, and the Sponsor's study team members were blinded to treatment assignment. Data that could potentially unblind the treatment assignment (ie, study drug plasma concentrations) was to be handled with special care to ensure that the integrity of the blind was maintained and the potential for bias minimized.

This included making special provisions, such as segregating the data in question from view by the investigators and the team involved in the study.

Arms

Are arms mutually exclusive?	Yes
Arm title	Ibrutinib and Rituximab

Arm description:

subjects who received ibrutinib and rituximab in combination

Arm type	Experimental
Investigational medicinal product name	Rituximab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for solution for injection
Routes of administration	Intravenous drip use

Dosage and administration details:

Rituximab 375 mg/m² IV was administered per package insert instructions weekly for 4 consecutive weeks, followed by a second 4-week rituximab course after a 3-month interval (Day 1 of Weeks 1-4 and Weeks 17-20 (total of 8 infusions of rituximab).

Investigational medicinal product name	Ibrutinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Ibrutinib was administered daily at a dose of 420 mg (3 capsules of 140 mg) until progression, discontinuation due to toxicity or other reasons to discontinue treatment.

Arm title	Placebo and Rituximab
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Arm description:

Subjects receiving placebo and rituximab in combination.

Arm type	Placebo
Investigational medicinal product name	Rituximab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for solution for injection
Routes of administration	Intravenous drip use

Dosage and administration details:

Rituximab 375 mg/m² IV was administered per package insert instructions weekly for 4 consecutive weeks, followed by a second 4-week rituximab course after a 3-month interval (Day 1 of Weeks 1-4 and Weeks 17-20 (total of 8 infusions of rituximab)).

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Placebo was administered as capsules identical to ibrutinib until progression, discontinuation due to toxicity or other reasons for discontinuation of treatment.

Arm title	Open-label ritux refractory arm
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Arm description:

Subject in this arm were treated with ibrutinib 420 mg monotherapy in an open-labeled substudy independently of the 2 randomized main treatment arm (R+I and R+P)

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

Dosage and administration details:

Ibrutinib was administered daily at a dose of 420 mg (3 capsules of 140 mg) until disease progression, discontinuation due to toxicity or other reasons to discontinue treatment.

Number of subjects in period 1	Ibrutinib and Rituximab	Placebo and Rituximab	Open-label ritux refractory arm
Started	75	75	31
Completed	13	42	12
Not completed	62	33	19
Consent withdrawn by subject	6	7	2
treatment ongoing	56	26	17

Baseline characteristics

Reporting groups

Reporting group title	Ibrutinib and Rituximab
Reporting group description:	
subjects who received ibrutinib and rituximab in combination	
Reporting group title	Placebo and Rituximab
Reporting group description:	
Subjects receiving placebo and rituximab in combination.	
Reporting group title	Open-label ritux refractory arm
Reporting group description:	
Subject in this arm were treated with ibrutinib 420 mg monotherapy in an open-labeled substudy independently of the 2 randomized main treatment arm (R+I and R+P)	

Reporting group values	Ibrutinib and Rituximab	Placebo and Rituximab	Open-label ritux refractory arm
Number of subjects	75	75	31
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	28	30	14
From 65-84 years	42	43	14
85 years and over	5	2	3
Age continuous			
Mean age of subjects incl. standard deviation			
Units: years			
arithmetic mean	69.2	66.1	66.4
standard deviation	± 10.90	± 11.10	± 10.76
Gender categorical			
Units: Subjects			
Female	30	21	11
Male	45	54	20

Reporting group values	Total		
Number of subjects	181		
Age categorical			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	72		
From 65-84 years	99		
85 years and over	10		
Age continuous			
Mean age of subjects incl. standard deviation			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	62		
Male	119		

End points

End points reporting groups

Reporting group title	Ibrutinib and Rituximab
Reporting group description: subjects who received ibrutinib and rituximab in combination	
Reporting group title	Placebo and Rituximab
Reporting group description: Subjects receiving placebo and rituximab in combination.	
Reporting group title	Open-label ritux refractory arm
Reporting group description: Subject in this arm were treated with ibrutinib 420 mg monotherapy in an open-labeled substudy independently of the 2 randomized main treatment arm (R+I and R+P)	

Primary: Progression free survival (30 month landmark)

End point title	Progression free survival (30 month landmark)
End point description: KM point estimates of the PFS rate per IRC assessment at 30 months. PFS is defined as time from the date of randomization to the date of first IRC-confirmed disease progression (PD) or date of death due to any cause, whichever occurs first, regardless of the use of subsequent antineoplastic therapy prior to documented PD or death. As the median PFS was not reached in the Ibr+R and the open-label ritux refractory arm (20.3 months in the Pbo+R arm), PFS rates at 30 months are presented.	
End point type	Primary
End point timeframe: Results at a median time on study of 26.5 months for Ibr+R and Pbo+R and 34.4 months for the open-label ritux refractory arm.	

End point values	Ibrutinib and Rituximab	Placebo and Rituximab	Open-label ritux refractory arm	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	75	75	31	
Units: percentage				
number (confidence interval 95%)	81.6 (70.5 to 88.9)	27.5 (12.8 to 44.4)	57.5 (38.2 to 72.7)	

Statistical analyses

Statistical analysis title	Progression free survival (PFS)
Statistical analysis description: The treatment effect was tested with a stratified log rank test. The hazard ratio and its 95% confidence interval were based on a Cox regression model stratified by the randomization stratification factors.	
Comparison groups	Ibrutinib and Rituximab v Placebo and Rituximab

Number of subjects included in analysis	150
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.202
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.107
upper limit	0.38

Secondary: Response rate (CR, VGPR, PR)

End point title	Response rate (CR, VGPR, PR)
End point description:	
Response rate is defined as proportion of subjects achieving a best overall response of confirmed CR, VGPR, or PR per the IRC assessment.	
End point type	Secondary
End point timeframe:	
Response rate at a median time on study of 26.5 months for Ibr+R and Pbo+R and 34.4 months for the open-label ritux refractory arm	

End point values	Ibrutinib and Rituximab	Placebo and Rituximab	Open-label ritux refractory arm	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	75	75	31	
Units: percentage				
number (not applicable)	72	32	71	

Statistical analyses

Statistical analysis title	Response Rate
Statistical analysis description:	
Response rate was compared using Cochran-Mantel-Haenszel (CMH) chi-square test.	
Comparison groups	Ibrutinib and Rituximab v Placebo and Rituximab
Number of subjects included in analysis	150
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Rate ratio
Point estimate	2.299

Confidence interval	
level	95 %
sides	2-sided
lower limit	1.592
upper limit	3.319

Secondary: Time to next treatment (30 month landmark)

End point title	Time to next treatment (30 month landmark)
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End point description:

TTnT is defined as time from the date of randomization to the start date of any subsequent WM treatment. As the median TTnT was not reached in the Ibr+R and the open-label ritux refractory arm (18.1 months in the Pbo+R arm), TTnT rates at 30 months are presented.

End point type	Secondary
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End point timeframe:

Results at a median time on study of 26.5 months for Ibr+R and Pbo+R and 34.4 months for the open-label ritux refractory arm.

End point values	Ibrutinib and Rituximab	Placebo and Rituximab	Open-label ritux refractory arm	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	75	75	31	
Units: percentage				
number (confidence interval 95%)	91.5 (82.0 to 96.1)	41.4 (29.1 to 53.3)	82.9 (63.7 to 92.5)	

Statistical analyses

Statistical analysis title	Time to next treatment (TTnT)
Comparison groups	Ibrutinib and Rituximab v Placebo and Rituximab
Number of subjects included in analysis	150
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.096
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.04
upper limit	0.227

Secondary: Sustained improvement in hemoglobin

End point title	Sustained improvement in hemoglobin
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End point description:

Sustained hemoglobin improvement is defined as hemoglobin improvement that sustained continuously for ≥ 56 days without blood transfusion or growth factors which includes hemoglobin > 110 g/L with at least a 5 g/L improvement if baseline ≤ 110 g/L or increase ≥ 20 g/L over baseline.

End point type	Secondary
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End point timeframe:

Sustained improvement in hemoglobin at a median time on study of 26.5 months for Ibr+R and Pbo+R and 34.4 months for the open-label ritux refractory arm

End point values	Ibrutinib and Rituximab	Placebo and Rituximab	Open-label ritux refractory arm	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	75	75	31	
Units: percent				
number (not applicable)	73.3	41.3	71.0	

Statistical analyses

Statistical analysis title	Sustained improvement in hemoglobin
Comparison groups	Ibrutinib and Rituximab v Placebo and Rituximab
Number of subjects included in analysis	150
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Chi-squared
Parameter estimate	Rate ratio
Point estimate	1.774
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.311
upper limit	2.4

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose of study drug up to 30 days after the last dose of study drug

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	20.0
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Reporting groups

Reporting group title	ibrutinib and rituximab
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Reporting group description:

subjects who received ibrutinib and rituximab in combination

Reporting group title	Placebo and Rituximab
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Reporting group description:

subjects who received placebo and rituximab in combination

Reporting group title	Open-label ritux refractory arm
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Reporting group description:

Subject in this arm were treated with ibrutinib 420 mg monotherapy in an open-labeled substudy independently of the 2 randomized main treatment arm (R+I and R+P)

Serious adverse events	ibrutinib and rituximab	Placebo and Rituximab	Open-label ritux refractory arm
Total subjects affected by serious adverse events			
subjects affected / exposed	32 / 75 (42.67%)	25 / 75 (33.33%)	11 / 31 (35.48%)
number of deaths (all causes)	0	3	0
number of deaths resulting from adverse events	0	3	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	1 / 75 (1.33%)	0 / 75 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Benign pancreatic neoplasm			
subjects affected / exposed	0 / 75 (0.00%)	1 / 75 (1.33%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma			
subjects affected / exposed	0 / 75 (0.00%)	1 / 75 (1.33%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Diffuse large B-cell lymphoma subjects affected / exposed	0 / 75 (0.00%)	0 / 75 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal cell carcinoma subjects affected / exposed	0 / 75 (0.00%)	0 / 75 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Aortic stenosis subjects affected / exposed	1 / 75 (1.33%)	0 / 75 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertension subjects affected / exposed	1 / 75 (1.33%)	1 / 75 (1.33%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Circulatory collapse subjects affected / exposed	0 / 75 (0.00%)	1 / 75 (1.33%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension subjects affected / exposed	0 / 75 (0.00%)	1 / 75 (1.33%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Gait disturbance subjects affected / exposed	1 / 75 (1.33%)	0 / 75 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oedema peripheral subjects affected / exposed	1 / 75 (1.33%)	0 / 75 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Death			
subjects affected / exposed	0 / 75 (0.00%)	1 / 75 (1.33%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Fatigue			
subjects affected / exposed	0 / 75 (0.00%)	1 / 75 (1.33%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General physical health deterioration			
subjects affected / exposed	0 / 75 (0.00%)	1 / 75 (1.33%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Asthenia			
subjects affected / exposed	0 / 75 (0.00%)	0 / 75 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Prostatitis			
subjects affected / exposed	1 / 75 (1.33%)	0 / 75 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breast mass			
subjects affected / exposed	0 / 75 (0.00%)	1 / 75 (1.33%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Bronchopneumopathy			
subjects affected / exposed	1 / 75 (1.33%)	0 / 75 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			

subjects affected / exposed	1 / 75 (1.33%)	0 / 75 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epistaxis			
subjects affected / exposed	0 / 75 (0.00%)	1 / 75 (1.33%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	0 / 75 (0.00%)	1 / 75 (1.33%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Neutrophil count decreased			
subjects affected / exposed	0 / 75 (0.00%)	1 / 75 (1.33%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	2 / 75 (2.67%)	0 / 75 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower limb fracture			
subjects affected / exposed	1 / 75 (1.33%)	0 / 75 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pelvic fracture			
subjects affected / exposed	1 / 75 (1.33%)	0 / 75 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infusion related reaction			
subjects affected / exposed	0 / 75 (0.00%)	5 / 75 (6.67%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 8	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Spinal compression fracture			
subjects affected / exposed	0 / 75 (0.00%)	1 / 75 (1.33%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tendon injury			
subjects affected / exposed	0 / 75 (0.00%)	1 / 75 (1.33%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femur fracture			
subjects affected / exposed	0 / 75 (0.00%)	0 / 75 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Congenital, familial and genetic disorders			
Hypertrophic cardiomyopathy			
subjects affected / exposed	1 / 75 (1.33%)	0 / 75 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	5 / 75 (6.67%)	1 / 75 (1.33%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	5 / 5	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure congestive			
subjects affected / exposed	2 / 75 (2.67%)	0 / 75 (0.00%)	9 / 31 (29.03%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial ischaemia			
subjects affected / exposed	2 / 75 (2.67%)	0 / 75 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina unstable			
subjects affected / exposed	1 / 75 (1.33%)	0 / 75 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Cardiac failure			
subjects affected / exposed	1 / 75 (1.33%)	0 / 75 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac tamponade			
subjects affected / exposed	1 / 75 (1.33%)	0 / 75 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prinzmetal angina			
subjects affected / exposed	1 / 75 (1.33%)	0 / 75 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina pectoris			
subjects affected / exposed	0 / 75 (0.00%)	1 / 75 (1.33%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery disease			
subjects affected / exposed	0 / 75 (0.00%)	1 / 75 (1.33%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	0 / 75 (0.00%)	1 / 75 (1.33%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericarditis			
subjects affected / exposed	0 / 75 (0.00%)	1 / 75 (1.33%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Haemorrhage intracranial			
subjects affected / exposed	0 / 75 (0.00%)	1 / 75 (1.33%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Nervous system disorder			

subjects affected / exposed	0 / 75 (0.00%)	1 / 75 (1.33%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Syncope			
subjects affected / exposed	0 / 75 (0.00%)	0 / 75 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	0 / 75 (0.00%)	0 / 75 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 75 (2.67%)	0 / 75 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Leukopenia			
subjects affected / exposed	1 / 75 (1.33%)	0 / 75 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune thrombocytopenic purpura			
subjects affected / exposed	0 / 75 (0.00%)	1 / 75 (1.33%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	0 / 75 (0.00%)	0 / 75 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	0 / 75 (0.00%)	0 / 75 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			

Ulcerative keratitis			
subjects affected / exposed	1 / 75 (1.33%)	0 / 75 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	1 / 75 (1.33%)	1 / 75 (1.33%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Melaena			
subjects affected / exposed	1 / 75 (1.33%)	0 / 75 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain			
subjects affected / exposed	0 / 75 (0.00%)	1 / 75 (1.33%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	0 / 75 (0.00%)	1 / 75 (1.33%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 75 (0.00%)	1 / 75 (1.33%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain upper			
subjects affected / exposed	0 / 75 (0.00%)	0 / 75 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Faecalith			
subjects affected / exposed	0 / 75 (0.00%)	0 / 75 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus			

subjects affected / exposed	0 / 75 (0.00%)	0 / 75 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 75 (1.33%)	1 / 75 (1.33%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis acute			
subjects affected / exposed	1 / 75 (1.33%)	0 / 75 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Purpura			
subjects affected / exposed	1 / 75 (1.33%)	0 / 75 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 75 (1.33%)	0 / 75 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary retention			
subjects affected / exposed	1 / 75 (1.33%)	0 / 75 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysuria			
subjects affected / exposed	0 / 75 (0.00%)	1 / 75 (1.33%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematuria			
subjects affected / exposed	0 / 75 (0.00%)	1 / 75 (1.33%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 75 (2.67%)	0 / 75 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Joint swelling			
subjects affected / exposed	1 / 75 (1.33%)	0 / 75 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psoriatic arthropathy			
subjects affected / exposed	1 / 75 (1.33%)	0 / 75 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Soft tissue necrosis			
subjects affected / exposed	1 / 75 (1.33%)	0 / 75 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Synovial cyst			
subjects affected / exposed	1 / 75 (1.33%)	0 / 75 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fracture pain			
subjects affected / exposed	0 / 75 (0.00%)	1 / 75 (1.33%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tendonitis			
subjects affected / exposed	0 / 75 (0.00%)	1 / 75 (1.33%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia			
subjects affected / exposed	6 / 75 (8.00%)	2 / 75 (2.67%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	3 / 6	1 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Respiratory tract infection			
subjects affected / exposed	3 / 75 (4.00%)	0 / 75 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	1 / 3	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	2 / 75 (2.67%)	0 / 75 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arthritis bacterial			
subjects affected / exposed	1 / 75 (1.33%)	0 / 75 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atypical pneumonia			
subjects affected / exposed	1 / 75 (1.33%)	0 / 75 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	1 / 75 (1.33%)	0 / 75 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteomyelitis			
subjects affected / exposed	1 / 75 (1.33%)	0 / 75 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumocystis jirovecii infection			
subjects affected / exposed	1 / 75 (1.33%)	0 / 75 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia bacterial			
subjects affected / exposed	1 / 75 (1.33%)	0 / 75 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory syncytial virus infection			

subjects affected / exposed	1 / 75 (1.33%)	0 / 75 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	1 / 75 (1.33%)	0 / 75 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Streptococcal bacteraemia			
subjects affected / exposed	1 / 75 (1.33%)	0 / 75 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subcutaneous abscess			
subjects affected / exposed	1 / 75 (1.33%)	0 / 75 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection			
subjects affected / exposed	1 / 75 (1.33%)	0 / 75 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			
subjects affected / exposed	1 / 75 (1.33%)	0 / 75 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enterococcal sepsis			
subjects affected / exposed	0 / 75 (0.00%)	1 / 75 (1.33%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	0 / 75 (0.00%)	1 / 75 (1.33%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Staphylococcal sepsis			

subjects affected / exposed	0 / 75 (0.00%)	1 / 75 (1.33%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Escherichia sepsis			
subjects affected / exposed	0 / 75 (0.00%)	0 / 75 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Orchitis			
subjects affected / exposed	0 / 75 (0.00%)	0 / 75 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostatic abscess			
subjects affected / exposed	0 / 75 (0.00%)	0 / 75 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hyponatraemia			
subjects affected / exposed	1 / 75 (1.33%)	0 / 75 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dehydration			
subjects affected / exposed	0 / 75 (0.00%)	1 / 75 (1.33%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fluid overload			
subjects affected / exposed	0 / 75 (0.00%)	1 / 75 (1.33%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	ibrutinib and rituximab	Placebo and Rituximab	Open-label ritux refractory arm
Total subjects affected by non-serious adverse events			
subjects affected / exposed	75 / 75 (100.00%)	73 / 75 (97.33%)	30 / 31 (96.77%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour flare			
subjects affected / exposed	6 / 75 (8.00%)	35 / 75 (46.67%)	0 / 31 (0.00%)
occurrences (all)	7	50	0
Vascular disorders			
Hypertension			
subjects affected / exposed	13 / 75 (17.33%)	3 / 75 (4.00%)	7 / 31 (22.58%)
occurrences (all)	21	4	10
Hypotension			
subjects affected / exposed	1 / 75 (1.33%)	3 / 75 (4.00%)	2 / 31 (6.45%)
occurrences (all)	1	3	3
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	13 / 75 (17.33%)	9 / 75 (12.00%)	5 / 31 (16.13%)
occurrences (all)	17	12	8
Asthenia			
subjects affected / exposed	12 / 75 (16.00%)	19 / 75 (25.33%)	4 / 31 (12.90%)
occurrences (all)	13	26	5
Fatigue			
subjects affected / exposed	10 / 75 (13.33%)	20 / 75 (26.67%)	5 / 31 (16.13%)
occurrences (all)	20	27	7
Pyrexia			
subjects affected / exposed	10 / 75 (13.33%)	12 / 75 (16.00%)	7 / 31 (22.58%)
occurrences (all)	11	18	9
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	13 / 75 (17.33%)	8 / 75 (10.67%)	4 / 31 (12.90%)
occurrences (all)	19	9	4
Dyspnoea			
subjects affected / exposed	7 / 75 (9.33%)	10 / 75 (13.33%)	2 / 31 (6.45%)
occurrences (all)	8	13	4
Epistaxis			

subjects affected / exposed occurrences (all)	7 / 75 (9.33%) 8	5 / 75 (6.67%) 6	3 / 31 (9.68%) 3
Rhinorrhoea subjects affected / exposed occurrences (all)	4 / 75 (5.33%) 4	5 / 75 (6.67%) 5	1 / 31 (3.23%) 1
Productive cough subjects affected / exposed occurrences (all)	3 / 75 (4.00%) 3	4 / 75 (5.33%) 7	1 / 31 (3.23%) 1
Oropharyngeal pain subjects affected / exposed occurrences (all)	3 / 75 (4.00%) 3	2 / 75 (2.67%) 2	2 / 31 (6.45%) 2
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	8 / 75 (10.67%) 9	3 / 75 (4.00%) 3	2 / 31 (6.45%) 2
Depression subjects affected / exposed occurrences (all)	0 / 75 (0.00%) 0	0 / 75 (0.00%) 0	2 / 31 (6.45%) 2
Investigations Weight decreased subjects affected / exposed occurrences (all)	1 / 75 (1.33%) 1	3 / 75 (4.00%) 3	2 / 31 (6.45%) 2
Injury, poisoning and procedural complications Infusion related reaction subjects affected / exposed occurrences (all)	32 / 75 (42.67%) 60	43 / 75 (57.33%) 122	0 / 31 (0.00%) 0
Contusion subjects affected / exposed occurrences (all)	6 / 75 (8.00%) 7	1 / 75 (1.33%) 2	1 / 31 (3.23%) 1
Traumatic haematoma subjects affected / exposed occurrences (all)	4 / 75 (5.33%) 4	0 / 75 (0.00%) 0	0 / 31 (0.00%) 0
Fall subjects affected / exposed occurrences (all)	2 / 75 (2.67%) 2	3 / 75 (4.00%) 4	3 / 31 (9.68%) 4
Cardiac disorders			

Atrial fibrillation subjects affected / exposed occurrences (all)	10 / 75 (13.33%) 15	1 / 75 (1.33%) 1	0 / 31 (0.00%) 0
Nervous system disorders			
Headache subjects affected / exposed occurrences (all)	10 / 75 (13.33%) 14	17 / 75 (22.67%) 18	5 / 31 (16.13%) 6
Dizziness subjects affected / exposed occurrences (all)	8 / 75 (10.67%) 8	5 / 75 (6.67%) 5	3 / 31 (9.68%) 3
Dysgeusia subjects affected / exposed occurrences (all)	4 / 75 (5.33%) 4	1 / 75 (1.33%) 1	1 / 31 (3.23%) 1
Paraesthesia subjects affected / exposed occurrences (all)	4 / 75 (5.33%) 4	4 / 75 (5.33%) 4	2 / 31 (6.45%) 2
Peripheral sensory neuropathy subjects affected / exposed occurrences (all)	4 / 75 (5.33%) 5	4 / 75 (5.33%) 5	2 / 31 (6.45%) 2
Sciatica subjects affected / exposed occurrences (all)	4 / 75 (5.33%) 4	0 / 75 (0.00%) 0	3 / 31 (9.68%) 3
Blood and lymphatic system disorders			
Anaemia subjects affected / exposed occurrences (all)	13 / 75 (17.33%) 18	22 / 75 (29.33%) 40	4 / 31 (12.90%) 4
Neutropenia subjects affected / exposed occurrences (all)	10 / 75 (13.33%) 15	7 / 75 (9.33%) 7	9 / 31 (29.03%) 14
Increased tendency to bruise subjects affected / exposed occurrences (all)	7 / 75 (9.33%) 7	2 / 75 (2.67%) 2	7 / 31 (22.58%) 7
Thrombocytopenia subjects affected / exposed occurrences (all)	4 / 75 (5.33%) 5	8 / 75 (10.67%) 17	6 / 31 (19.35%) 12
Spontaneous haematoma			

subjects affected / exposed occurrences (all)	3 / 75 (4.00%) 6	0 / 75 (0.00%) 0	2 / 31 (6.45%) 2
Lymphadenopathy subjects affected / exposed occurrences (all)	1 / 75 (1.33%) 1	2 / 75 (2.67%) 2	2 / 31 (6.45%) 3
Ear and labyrinth disorders Tinnitus subjects affected / exposed occurrences (all)	0 / 75 (0.00%) 0	3 / 75 (4.00%) 3	4 / 31 (12.90%) 4
Eye disorders Visual acuity reduced subjects affected / exposed occurrences (all)	6 / 75 (8.00%) 7	3 / 75 (4.00%) 3	0 / 31 (0.00%) 0
Cataract subjects affected / exposed occurrences (all)	5 / 75 (6.67%) 5	1 / 75 (1.33%) 1	4 / 31 (12.90%) 4
Eye irritation subjects affected / exposed occurrences (all)	5 / 75 (6.67%) 5	1 / 75 (1.33%) 1	0 / 31 (0.00%) 0
Dry eye subjects affected / exposed occurrences (all)	4 / 75 (5.33%) 5	5 / 75 (6.67%) 7	2 / 31 (6.45%) 2
Lacrimation increased subjects affected / exposed occurrences (all)	4 / 75 (5.33%) 4	3 / 75 (4.00%) 4	1 / 31 (3.23%) 1
Photophobia subjects affected / exposed occurrences (all)	4 / 75 (5.33%) 4	2 / 75 (2.67%) 2	0 / 31 (0.00%) 0
Vision blurred subjects affected / exposed occurrences (all)	4 / 75 (5.33%) 5	2 / 75 (2.67%) 3	2 / 31 (6.45%) 2
Diplopia subjects affected / exposed occurrences (all)	2 / 75 (2.67%) 2	0 / 75 (0.00%) 0	2 / 31 (6.45%) 2
Gastrointestinal disorders			

Diarrhoea			
subjects affected / exposed	21 / 75 (28.00%)	11 / 75 (14.67%)	12 / 31 (38.71%)
occurrences (all)	26	13	20
Nausea			
subjects affected / exposed	16 / 75 (21.33%)	9 / 75 (12.00%)	7 / 31 (22.58%)
occurrences (all)	20	14	8
Dyspepsia			
subjects affected / exposed	12 / 75 (16.00%)	1 / 75 (1.33%)	2 / 31 (6.45%)
occurrences (all)	13	1	2
Constipation			
subjects affected / exposed	9 / 75 (12.00%)	8 / 75 (10.67%)	5 / 31 (16.13%)
occurrences (all)	11	11	10
Abdominal pain upper			
subjects affected / exposed	4 / 75 (5.33%)	2 / 75 (2.67%)	1 / 31 (3.23%)
occurrences (all)	9	2	1
Dry mouth			
subjects affected / exposed	4 / 75 (5.33%)	0 / 75 (0.00%)	0 / 31 (0.00%)
occurrences (all)	4	0	0
Vomiting			
subjects affected / exposed	2 / 75 (2.67%)	8 / 75 (10.67%)	1 / 31 (3.23%)
occurrences (all)	5	10	1
Abdominal pain			
subjects affected / exposed	3 / 75 (4.00%)	2 / 75 (2.67%)	3 / 31 (9.68%)
occurrences (all)	3	2	4
Gastrooesophageal reflux disease			
subjects affected / exposed	2 / 75 (2.67%)	1 / 75 (1.33%)	3 / 31 (9.68%)
occurrences (all)	2	1	3
Abdominal discomfort			
subjects affected / exposed	1 / 75 (1.33%)	0 / 75 (0.00%)	3 / 31 (9.68%)
occurrences (all)	1	0	4
Abdominal distension			
subjects affected / exposed	1 / 75 (1.33%)	2 / 75 (2.67%)	2 / 31 (6.45%)
occurrences (all)	1	2	2
Gingival bleeding			
subjects affected / exposed	1 / 75 (1.33%)	0 / 75 (0.00%)	2 / 31 (6.45%)
occurrences (all)	1	0	2

Skin and subcutaneous tissue disorders			
Ecchymosis			
subjects affected / exposed	8 / 75 (10.67%)	0 / 75 (0.00%)	0 / 31 (0.00%)
occurrences (all)	10	0	0
Petechiae			
subjects affected / exposed	7 / 75 (9.33%)	0 / 75 (0.00%)	3 / 31 (9.68%)
occurrences (all)	8	0	4
Pruritus			
subjects affected / exposed	4 / 75 (5.33%)	4 / 75 (5.33%)	2 / 31 (6.45%)
occurrences (all)	6	4	2
Rash erythematous			
subjects affected / exposed	4 / 75 (5.33%)	2 / 75 (2.67%)	2 / 31 (6.45%)
occurrences (all)	4	4	2
Rash maculo-papular			
subjects affected / exposed	3 / 75 (4.00%)	3 / 75 (4.00%)	2 / 31 (6.45%)
occurrences (all)	3	4	6
Dry skin			
subjects affected / exposed	2 / 75 (2.67%)	0 / 75 (0.00%)	4 / 31 (12.90%)
occurrences (all)	2	0	4
Actinic keratosis			
subjects affected / exposed	1 / 75 (1.33%)	1 / 75 (1.33%)	2 / 31 (6.45%)
occurrences (all)	1	3	4
Onychoclasia			
subjects affected / exposed	1 / 75 (1.33%)	0 / 75 (0.00%)	3 / 31 (9.68%)
occurrences (all)	1	0	3
Onycholysis			
subjects affected / exposed	0 / 75 (0.00%)	0 / 75 (0.00%)	2 / 31 (6.45%)
occurrences (all)	0	0	2
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	3 / 75 (4.00%)	0 / 75 (0.00%)	2 / 31 (6.45%)
occurrences (all)	3	0	2
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	17 / 75 (22.67%)	8 / 75 (10.67%)	5 / 31 (16.13%)
occurrences (all)	24	9	9

Muscle spasms			
subjects affected / exposed	13 / 75 (17.33%)	9 / 75 (12.00%)	5 / 31 (16.13%)
occurrences (all)	19	10	6
Pain in extremity			
subjects affected / exposed	9 / 75 (12.00%)	5 / 75 (6.67%)	4 / 31 (12.90%)
occurrences (all)	10	5	4
Back pain			
subjects affected / exposed	8 / 75 (10.67%)	6 / 75 (8.00%)	8 / 31 (25.81%)
occurrences (all)	11	6	12
Myalgia			
subjects affected / exposed	5 / 75 (6.67%)	3 / 75 (4.00%)	2 / 31 (6.45%)
occurrences (all)	8	8	2
Osteoarthritis			
subjects affected / exposed	5 / 75 (6.67%)	1 / 75 (1.33%)	0 / 31 (0.00%)
occurrences (all)	5	1	0
Musculoskeletal chest pain			
subjects affected / exposed	2 / 75 (2.67%)	0 / 75 (0.00%)	2 / 31 (6.45%)
occurrences (all)	2	0	2
Muscular weakness			
subjects affected / exposed	1 / 75 (1.33%)	1 / 75 (1.33%)	2 / 31 (6.45%)
occurrences (all)	2	1	2
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	10 / 75 (13.33%)	0 / 75 (0.00%)	3 / 31 (9.68%)
occurrences (all)	16	0	5
Bronchitis			
subjects affected / exposed	9 / 75 (12.00%)	5 / 75 (6.67%)	3 / 31 (9.68%)
occurrences (all)	11	8	4
Influenza			
subjects affected / exposed	9 / 75 (12.00%)	5 / 75 (6.67%)	2 / 31 (6.45%)
occurrences (all)	9	5	2
Viral upper respiratory tract infection			
subjects affected / exposed	8 / 75 (10.67%)	5 / 75 (6.67%)	2 / 31 (6.45%)
occurrences (all)	11	7	2
Upper respiratory tract infection			

subjects affected / exposed occurrences (all)	6 / 75 (8.00%) 9	3 / 75 (4.00%) 6	6 / 31 (19.35%) 15
Herpes zoster subjects affected / exposed occurrences (all)	5 / 75 (6.67%) 6	1 / 75 (1.33%) 1	2 / 31 (6.45%) 2
Oral herpes subjects affected / exposed occurrences (all)	4 / 75 (5.33%) 5	0 / 75 (0.00%) 0	0 / 31 (0.00%) 0
Pneumonia subjects affected / exposed occurrences (all)	4 / 75 (5.33%) 5	2 / 75 (2.67%) 2	2 / 31 (6.45%) 3
Rhinitis subjects affected / exposed occurrences (all)	4 / 75 (5.33%) 4	1 / 75 (1.33%) 3	1 / 31 (3.23%) 1
Respiratory tract infection subjects affected / exposed occurrences (all)	3 / 75 (4.00%) 4	2 / 75 (2.67%) 3	5 / 31 (16.13%) 7
Cellulitis subjects affected / exposed occurrences (all)	2 / 75 (2.67%) 2	1 / 75 (1.33%) 1	3 / 31 (9.68%) 3
Conjunctivitis subjects affected / exposed occurrences (all)	2 / 75 (2.67%) 2	3 / 75 (4.00%) 4	4 / 31 (12.90%) 5
Paronychia subjects affected / exposed occurrences (all)	1 / 75 (1.33%) 1	0 / 75 (0.00%) 0	2 / 31 (6.45%) 2
Sinusitis subjects affected / exposed occurrences (all)	1 / 75 (1.33%) 1	2 / 75 (2.67%) 3	2 / 31 (6.45%) 2
Metabolism and nutrition disorders			
Hypokalaemia subjects affected / exposed occurrences (all)	8 / 75 (10.67%) 11	1 / 75 (1.33%) 2	2 / 31 (6.45%) 2
Gout subjects affected / exposed occurrences (all)	4 / 75 (5.33%) 5	1 / 75 (1.33%) 1	1 / 31 (3.23%) 1

Hyperuricaemia			
subjects affected / exposed	4 / 75 (5.33%)	4 / 75 (5.33%)	2 / 31 (6.45%)
occurrences (all)	5	4	2
Decreased appetite			
subjects affected / exposed	1 / 75 (1.33%)	7 / 75 (9.33%)	3 / 31 (9.68%)
occurrences (all)	1	7	3

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 March 2014	Added open-label substudy treatment arm for subjects refractory to the last prior rituximab-containing therapy in alignment with the scientific advice received from the European Medicines Agency (subjects not suitable for Ibr+R or Pbo+R treatment in the randomized study may be enrolled into the substudy to received single-agent ibrutinib), with efficacy and safety to be descriptively summarized and analyzed separately from the randomized treatment arms. • Revised inclusion criteria to allow ECOG PS status of 2. • Changed a randomization factor from prior rituximab exposure (yes vs. no) to ECOG PS (0-1 vs. 2) to ensure treatment balance for subjects with ECOG PS of 2. • Changed FACT-An from a secondary to an exploratory objective.
09 February 2015	• Allowed inclusion of subjects with untreated WM. • Updated the number of prior systemic treatment regimens for stratification from 1-2 vs. ≥ 3 to 0 vs. 1-2 vs. ≥ 3 to maintain balance between the 2 randomized treatment arms with regard to the addition of previously untreated subjects. • Revised the O'Brien-Fleming boundary from 60% (~42 PFS events) to 70% (~50 PFS events) for the interim analysis for the randomized arms. • Added new or additional guidance or information on the use of anticoagulants, antiplatelets, prednisone or equivalent, P-glycoprotein substrates, dose modifications for subjects with hepatic impairment, and major hemorrhage.
09 October 2015	• Updated enrollment criteria to allow for the inclusion of subjects with abnormal coagulation results unrelated to coagulopathy or bleeding disorders due to interfering substances. • Clarified enrollment criteria abstinence language. • Updated enrollment criteria for next-line ibrutinib therapy to allow involvement of CNS by WM. • Added planned subgroup analyses to be conducted for the PFS primary efficacy endpoint. • Updated risk sections and CYP3A section to align with current version of IB.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported