



Clinical trial results:

A Randomized, Multicenter, Open-label, Phase 3 Study of the Bruton's Tyrosine Kinase (BTK) Inhibitor Ibrutinib (PCI-32765) versus Ofatumumab in Patients with Relapsed or Refractory Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

Summary

EudraCT number	2012-000694-23
Trial protocol	GB IE PL ES IT AT BE
Global end of trial date	

Results information

Result version number	v1
This version publication date	14 October 2016
First version publication date	14 October 2016

Trial information

Trial identification

Sponsor protocol code	PCYC-1112-CA
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01578707
WHO universal trial number (UTN)	-
Other trial identifiers	provider NLM_DES study id: S0003GEU

Notes:

Sponsors

Sponsor organisation name	Pharmacyclics LLC
Sponsor organisation address	999 E Arques Ave, Sunnyvale, United States, 94085
Public contact	Devon Chung, Pharmacyclics LLC, 001 855-427-8846, pharmacyclics@medcomsol.com
Scientific contact	Dr. George Cole, Pharmacyclics LLC, 001 408-990-7340, gecole@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	06 November 2013
Is this the analysis of the primary completion data?	Yes
Primary completion date	06 November 2013
Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of the study was to evaluate whether treatment with ibrutinib as a monotherapy results in a clinically significant improvement in progression free survival (PFS) as compared to treatment with ofatumumab in patients with relapsed or refractory Chronic Lymphocytic Leukemia (CLL) or Small Lymphocytic Lymphoma (SLL)

Protection of trial subjects:

The study was conducted in accordance with the Declaration of Helsinki and ICH GCP.

Background therapy: -

Evidence for comparator:

NCCN and ESMO Guidelines Support the use of ofatumumab in the target patient population.

Actual start date of recruitment	22 June 2012
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy, Regulatory reason
Long term follow-up duration	5 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 29
Country: Number of subjects enrolled	United States: 192
Country: Number of subjects enrolled	Spain: 17
Country: Number of subjects enrolled	France: 27
Country: Number of subjects enrolled	United Kingdom: 73
Country: Number of subjects enrolled	Italy: 20
Country: Number of subjects enrolled	Poland: 8
Country: Number of subjects enrolled	Ireland: 9
Country: Number of subjects enrolled	Austria: 16
Worldwide total number of subjects	391
EEA total number of subjects	170

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)	152
From 65 to 84 years	235
85 years and over	4

Subject disposition

Recruitment

Recruitment details:

A total of 391 subjects were enrolled in the study from sites located in the US, Europe, and Australia. The first subject consented 22 June 2012, the data base lock for the present analysis was 06 November 2013.

Pre-assignment

Screening details:

Patients with previously treated CLL were screened for potential participation by the investigators based on the eligibility criteria. Patients who met the criteria were asked whether they were willing to participate in the study. A total of 391 subjects were randomized.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Ofatumumab (Arm A)

Arm description:

An anti-CD20 monoclonal antibody. The ofatumumab (IV) dosage and schedule was 12 doses administered over 24 weeks or until disease Progression or unacceptable toxicity.

Week 1: 300 mg Initial dose

Week 2 through 8: 2,000 mg (once weekly)

Week 12, 16, 20, and 24: 2,000 mg (every 4 weeks)

Arm type	Active comparator
Investigational medicinal product name	ofatumumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

The ofatumumab (IV) dosage and schedule is 12 doses administered over 24 weeks or until disease progression, unacceptable toxicity.

Week 1: 300 mg initial dose

Week 2 through 8: 2,000 mg (once weekly)

Week 12, 16, 20 and 24: 2,000 mg (every 4 weeks)

Arm title	ibrutinib (Arm B)
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Arm description:

Ibrutinib 420 mg daily

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

Dosage and administration details:

ibrutinib 420 mg (3 x 140-mg capsules) was administered orally once daily until disease progression or unacceptable toxicity

Number of subjects in period 1	Ofatumumab (Arm A)	ibrutinib (Arm B)
Started	196	195
Completed	188	193
Not completed	8	2
Consent withdrawn by subject	8	2

Baseline characteristics

Reporting groups

Reporting group title	Ofatumumab (Arm A)
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Reporting group description:

An anti-CD20 monoclonal antibody. The ofatumumab (IV) dosage and schedule was 12 doses administered over 24 weeks or until disease Progression or unacceptable toxicity.

Week 1: 300 mg Initial dose

Week 2 through 8: 2,000 mg (once weekly)

Week 12, 16, 20, and 24: 2,000 mg (every 4 weeks)

Reporting group title	ibrutinib (Arm B)
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Reporting group description:

Ibrutinib 420 mg daily

Reporting group values	Ofatumumab (Arm A)	ibrutinib (Arm B)	Total
Number of subjects	196	195	391
Age Categorical Units: Subjects			
<=18 years	0	0	0
Between 18 and 65 years	75	77	152
>=65 years	121	118	239
Age Continuous Units: years			
arithmetic mean	66.8	66.1	
standard deviation	± 8.88	± 10.15	-
Gender, Male/Female Units: Subjects			
Female	59	66	125
Male	137	129	266

End points

End points reporting groups

Reporting group title	Ofatumumab (Arm A)
Reporting group description: An anti-CD20 monoclonal antibody. The ofatumumab (IV) dosage and schedule was 12 doses administered over 24 weeks or until disease Progression or unacceptable toxicity. Week 1: 300 mg Initial dose Week 2 through 8: 2,000 mg (once weekly) Week 12, 16, 20, and 24: 2,000 mg (every 4 weeks)	
Reporting group title	ibrutinib (Arm B)
Reporting group description: Ibrutinib 420 mg daily	

Primary: PFS (Progression Free Survival)

End point title	PFS (Progression Free Survival)
End point description: The primary objective of this study was to evaluate the efficacy of ibrutinib compared to ofatumumab based on progression-free survival (PFS) assessed by the Independent Review Committee (IRC) per International Workshop on Chronic Lymphocytic Leukemia Criteria (IWCLL; Hallek et al, 2008) in subjects with relapsed or refractory CLL/SLL.	
End point type	Primary
End point timeframe: Analysis was conducted after observing 146 PFS Events. Median follow-up time in the study was 9.4 month. As the median PFS was not reached in the ibrutinib arm (8.1 months in the ofatumumab arm), PFS rates at 12 months are presented.	

End point values	Ofatumumab (Arm A)	ibrutinib (Arm B)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	196	195		
Units: percentage				
number (not applicable)	5.9	65.7		

Statistical analyses

Statistical analysis title	PFS (Progression free survival)
Comparison groups	Ofatumumab (Arm A) v ibrutinib (Arm B)
Number of subjects included in analysis	391
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Kaplan-Meier estimates
Parameter estimate	Hazard ratio (HR)
Point estimate	0.215

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.146
upper limit	0.317

Secondary: OS (Overall Survival)

End point title	OS (Overall Survival)
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End point description:

End point type	Secondary
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End point timeframe:

Analysis was conducted after observing 146 PFS Events. Median follow-up time in the study was 9.4 month. As the median OS was not reached in either arm, OS rates at 12 months are presented.

End point values	Ofatumumab (Arm A)	ibrutinib (Arm B)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	196	195		
Units: percentage				
number (not applicable)	81.3	90.2		

Statistical analyses

Statistical analysis title	OS (Overall Survival)
Comparison groups	ibrutinib (Arm B) v Ofatumumab (Arm A)
Number of subjects included in analysis	391
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.049
Method	Kaplan-Meier Estimates
Parameter estimate	Hazard ratio (HR)
Point estimate	0.434
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.238
upper limit	0.789

Secondary: ORR (Overall Response Rate)

End point title	ORR (Overall Response Rate)
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End point description:

ORR was defined as the Proportion of subjects who achieved complete Response (CR), complete Response with incomplete marrow recovery (CRi), nodule partial Response (nPR), partial response (PR), or partial response with lymphocytosis (PRL) per IRC assessment.

End point type	Secondary
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End point timeframe:

Analysis was conducted after observing 146 PFS events. Median follow-up time in the study was 9.4 months.

End point values	Ofatumumab (Arm A)	ibrutinib (Arm B)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	196	195		
Units: percentage				
number (not applicable)	4.1	42.6		

Statistical analyses

Statistical analysis title	ORR (Overall response rate)
Comparison groups	Ofatumumab (Arm A) v ibrutinib (Arm B)
Number of subjects included in analysis	391
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Fisher exact

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From June 2012 through Nov 2013

Adverse event reporting additional description:

Note: Safety has not been updated from the primary analysis, as only efficacy updates were requested on the present study and as the times of exposures were comparable in both arms at that time point.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	16.1
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Reporting groups

Reporting group title	ibrutinib (Arm B)
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Reporting group description:

A Bruton Tyrosine Kinase Inhibitor

ibrutinib: ibrutinib 420 mg (3 x 140-mg capsules) will be administered orally once daily until disease progression or unacceptable toxicity

Reporting group title	Ofatumumab (Arm A)
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Reporting group description:

An anti-CD20 monoclonal antibody

ofatumumab: The ofatumumab (IV) dosage and schedule is 12 doses administered over 24 weeks or until disease progression, unacceptable toxicity.

Week 1: 300 mg initial dose

Week 2 through 8: 2,000 mg (once weekly)

Week 12, 16, 20 and 24: 2,000 mg (every 4 weeks)

Serious adverse events	ibrutinib (Arm B)	Ofatumumab (Arm A)	
Total subjects affected by serious adverse events			
subjects affected / exposed	81 / 195 (41.54%)	58 / 191 (30.37%)	
number of deaths (all causes)	12	16	
number of deaths resulting from adverse events	1	2	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Leukaemia			
subjects affected / exposed	1 / 195 (0.51%)	0 / 191 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Chronic lymphocytic leukaemia			
subjects affected / exposed	3 / 195 (1.54%)	3 / 191 (1.57%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 2	0 / 2	

Gastrointestinal carcinoma			
subjects affected / exposed	1 / 195 (0.51%)	0 / 191 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Lung adenocarcinoma metastatic			
subjects affected / exposed	1 / 195 (0.51%)	0 / 191 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma of lung			
subjects affected / exposed	1 / 195 (0.51%)	0 / 191 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma			
subjects affected / exposed	0 / 195 (0.00%)	1 / 191 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Sarcoma			
subjects affected / exposed	1 / 195 (0.51%)	0 / 191 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastatic squamous cell carcinoma			
subjects affected / exposed	0 / 195 (0.00%)	1 / 191 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Richter's syndrome			
subjects affected / exposed	1 / 195 (0.51%)	0 / 191 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Tumour flare			
subjects affected / exposed	1 / 195 (0.51%)	0 / 191 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour pain			

subjects affected / exposed	0 / 195 (0.00%)	1 / 191 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 195 (0.00%)	1 / 191 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aneurysm			
subjects affected / exposed	1 / 195 (0.51%)	0 / 191 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Cyst			
subjects affected / exposed	1 / 195 (0.51%)	0 / 191 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	1 / 195 (0.51%)	0 / 191 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	1 / 195 (0.51%)	0 / 191 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza like illness			
subjects affected / exposed	1 / 195 (0.51%)	0 / 191 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	2 / 195 (1.03%)	0 / 191 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Injection site discharge alternative assessment type: Non-systematic subjects affected / exposed	1 / 195 (0.51%)	0 / 191 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia alternative assessment type: Non-systematic subjects affected / exposed	6 / 195 (3.08%)	4 / 191 (2.09%)	
occurrences causally related to treatment / all	5 / 10	2 / 5	
deaths causally related to treatment / all	0 / 0	0 / 1	
Immune system disorders Anaphylactic shock subjects affected / exposed	0 / 195 (0.00%)	1 / 191 (0.52%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Social circumstances Pregnancy of partner subjects affected / exposed	1 / 195 (0.51%)	0 / 191 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders Dyspnoea subjects affected / exposed	2 / 195 (1.03%)	1 / 191 (0.52%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopneumopathy subjects affected / exposed	1 / 195 (0.51%)	0 / 191 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis subjects affected / exposed	0 / 195 (0.00%)	1 / 191 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			

subjects affected / exposed	0 / 195 (0.00%)	1 / 191 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 195 (0.51%)	1 / 191 (0.52%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	1 / 195 (0.51%)	1 / 191 (0.52%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	0 / 195 (0.00%)	1 / 191 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary mass			
subjects affected / exposed	0 / 195 (0.00%)	1 / 191 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract inflammation			
subjects affected / exposed	0 / 195 (0.00%)	1 / 191 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Confusional state			
subjects affected / exposed	0 / 195 (0.00%)	1 / 191 (0.52%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Major depression			
subjects affected / exposed	0 / 195 (0.00%)	1 / 191 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychotic disorder			

subjects affected / exposed	1 / 195 (0.51%)	0 / 191 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mania			
subjects affected / exposed	1 / 195 (0.51%)	0 / 191 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Immunoglobulins decreased			
subjects affected / exposed	1 / 195 (0.51%)	0 / 191 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Muscle strain			
subjects affected / exposed	0 / 195 (0.00%)	1 / 191 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haemorrhage			
subjects affected / exposed	1 / 195 (0.51%)	0 / 191 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infusion related reaction			
subjects affected / exposed	0 / 195 (0.00%)	2 / 191 (1.05%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal compression fracture			
subjects affected / exposed	1 / 195 (0.51%)	1 / 191 (0.52%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple fractures			
subjects affected / exposed	1 / 195 (0.51%)	1 / 191 (0.52%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Subdural haematoma			
subjects affected / exposed	1 / 195 (0.51%)	0 / 191 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 195 (0.00%)	1 / 191 (0.52%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	6 / 195 (3.08%)	1 / 191 (0.52%)	
occurrences causally related to treatment / all	1 / 9	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial tachycardia			
subjects affected / exposed	1 / 195 (0.51%)	0 / 191 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			
subjects affected / exposed	1 / 195 (0.51%)	0 / 191 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block			
subjects affected / exposed	1 / 195 (0.51%)	0 / 191 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	1 / 195 (0.51%)	0 / 191 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac failure			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 195 (0.51%)	1 / 191 (0.52%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	

Cardiac failure congestive subjects affected / exposed	2 / 195 (1.03%)	0 / 191 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus tachycardia subjects affected / exposed	0 / 195 (0.00%)	1 / 191 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia subjects affected / exposed	0 / 195 (0.00%)	1 / 191 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction alternative assessment type: Non- systematic subjects affected / exposed	1 / 195 (0.51%)	1 / 191 (0.52%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders Febrile neutropenia subjects affected / exposed	3 / 195 (1.54%)	4 / 191 (2.09%)	
occurrences causally related to treatment / all	3 / 4	4 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Autoimmune haemolytic anaemia subjects affected / exposed	0 / 195 (0.00%)	1 / 191 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia subjects affected / exposed	2 / 195 (1.03%)	4 / 191 (2.09%)	
occurrences causally related to treatment / all	2 / 2	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia subjects affected / exposed	2 / 195 (1.03%)	3 / 191 (1.57%)	
occurrences causally related to treatment / all	2 / 2	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	

Methaemoglobinaemia			
subjects affected / exposed	0 / 195 (0.00%)	1 / 191 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphadenopathy			
subjects affected / exposed	1 / 195 (0.51%)	0 / 191 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemolytic anaemia			
subjects affected / exposed	0 / 195 (0.00%)	1 / 191 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Hearing impaired			
subjects affected / exposed	1 / 195 (0.51%)	0 / 191 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Colitis			
subjects affected / exposed	1 / 195 (0.51%)	0 / 191 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	0 / 195 (0.00%)	1 / 191 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	3 / 195 (1.54%)	1 / 191 (0.52%)	
occurrences causally related to treatment / all	2 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
alternative assessment type: Non-systematic			

subjects affected / exposed	2 / 195 (1.03%)	1 / 191 (0.52%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestinal obstruction			
subjects affected / exposed	1 / 195 (0.51%)	0 / 191 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malabsorption			
subjects affected / exposed	0 / 195 (0.00%)	1 / 191 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	2 / 195 (1.03%)	0 / 191 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal spasm			
subjects affected / exposed	1 / 195 (0.51%)	0 / 191 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	1 / 195 (0.51%)	0 / 191 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			
subjects affected / exposed	1 / 195 (0.51%)	0 / 191 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Poor dental condition			
subjects affected / exposed	1 / 195 (0.51%)	0 / 191 (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	0 / 195 (0.00%)	1 / 191 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Umbilical hernia			
subjects affected / exposed	1 / 195 (0.51%)	0 / 191 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 195 (0.51%)	0 / 191 (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			
Angioedema			
subjects affected / exposed	1 / 195 (0.51%)	0 / 191 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal failure acute			
subjects affected / exposed	1 / 195 (0.51%)	2 / 191 (1.05%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Renal impairment			
subjects affected / exposed	0 / 195 (0.00%)	1 / 191 (0.52%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	0 / 195 (0.00%)	1 / 191 (0.52%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			

subjects affected / exposed	1 / 195 (0.51%)	0 / 191 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	1 / 195 (0.51%)	0 / 191 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis			
subjects affected / exposed	1 / 195 (0.51%)	0 / 191 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone pain			
subjects affected / exposed	1 / 195 (0.51%)	1 / 191 (0.52%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myalgia			
subjects affected / exposed	1 / 195 (0.51%)	0 / 191 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pathological fracture			
subjects affected / exposed	1 / 195 (0.51%)	0 / 191 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abscess limb			
subjects affected / exposed	0 / 195 (0.00%)	1 / 191 (0.52%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal infection			
subjects affected / exposed	0 / 195 (0.00%)	1 / 191 (0.52%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspergillus infection			

subjects affected / exposed	2 / 195 (1.03%)	0 / 191 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	1 / 195 (0.51%)	2 / 191 (1.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteroides bacteraemia			
subjects affected / exposed	1 / 195 (0.51%)	0 / 191 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 195 (0.00%)	2 / 191 (1.05%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Breast cellulitis			
subjects affected / exposed	0 / 195 (0.00%)	1 / 191 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopulmonary aspergillosis			
subjects affected / exposed	2 / 195 (1.03%)	0 / 191 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopneumonia			
subjects affected / exposed	1 / 195 (0.51%)	1 / 191 (0.52%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Bronchitis bacterial			
subjects affected / exposed	1 / 195 (0.51%)	0 / 191 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Campylobacter gastroenteritis			

subjects affected / exposed	1 / 195 (0.51%)	0 / 191 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	3 / 195 (1.54%)	1 / 191 (0.52%)	
occurrences causally related to treatment / all	2 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterococcal infection			
subjects affected / exposed	1 / 195 (0.51%)	0 / 191 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis infectious			
subjects affected / exposed	1 / 195 (0.51%)	0 / 191 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia urinary tract infection			
subjects affected / exposed	1 / 195 (0.51%)	0 / 191 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis viral			
subjects affected / exposed	1 / 195 (0.51%)	0 / 191 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Folliculitis			
subjects affected / exposed	0 / 195 (0.00%)	1 / 191 (0.52%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile infection			
subjects affected / exposed	1 / 195 (0.51%)	1 / 191 (0.52%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal infection			

subjects affected / exposed	1 / 195 (0.51%)	0 / 191 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes simplex			
subjects affected / exposed	0 / 195 (0.00%)	1 / 191 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemophilus sepsis			
subjects affected / exposed	1 / 195 (0.51%)	0 / 191 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemophilus bacteraemia			
subjects affected / exposed	1 / 195 (0.51%)	0 / 191 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes virus infection			
subjects affected / exposed	1 / 195 (0.51%)	0 / 191 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	0 / 195 (0.00%)	1 / 191 (0.52%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	1 / 195 (0.51%)	1 / 191 (0.52%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Impetigo			
subjects affected / exposed	1 / 195 (0.51%)	0 / 191 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infectious pleural effusion			

subjects affected / exposed	0 / 195 (0.00%)	1 / 191 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	0 / 195 (0.00%)	1 / 191 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Lung infection			
subjects affected / exposed	5 / 195 (2.56%)	0 / 191 (0.00%)	
occurrences causally related to treatment / all	3 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	4 / 195 (2.05%)	2 / 191 (1.05%)	
occurrences causally related to treatment / all	2 / 4	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lobar pneumonia			
subjects affected / exposed	0 / 195 (0.00%)	1 / 191 (0.52%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral discitis			
subjects affected / exposed	1 / 195 (0.51%)	0 / 191 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymph gland infection			
subjects affected / exposed	1 / 195 (0.51%)	0 / 191 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumococcal sepsis			
subjects affected / exposed	1 / 195 (0.51%)	0 / 191 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parainfluenzae virus infection			

subjects affected / exposed	1 / 195 (0.51%)	0 / 191 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nocardiosis			
subjects affected / exposed	0 / 195 (0.00%)	1 / 191 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Neutropenic sepsis			
subjects affected / exposed	2 / 195 (1.03%)	2 / 191 (1.05%)	
occurrences causally related to treatment / all	1 / 2	2 / 2	
deaths causally related to treatment / all	0 / 1	1 / 1	
Pneumocystis jirovecii infection			
subjects affected / exposed	1 / 195 (0.51%)	0 / 191 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumocystis jirovecii pneumonia			
subjects affected / exposed	0 / 195 (0.00%)	1 / 191 (0.52%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	17 / 195 (8.72%)	12 / 191 (6.28%)	
occurrences causally related to treatment / all	8 / 20	6 / 13	
deaths causally related to treatment / all	1 / 3	0 / 2	
Pneumonia bacterial			
subjects affected / exposed	1 / 195 (0.51%)	1 / 191 (0.52%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia mycoplasmal			
subjects affected / exposed	0 / 195 (0.00%)	1 / 191 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia pseudomonas aeruginosa			

subjects affected / exposed	0 / 195 (0.00%)	3 / 191 (1.57%)	
occurrences causally related to treatment / all	0 / 0	2 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	0 / 195 (0.00%)	1 / 191 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory tract infection			
subjects affected / exposed	0 / 195 (0.00%)	2 / 191 (1.05%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis syndrome			
subjects affected / exposed	0 / 195 (0.00%)	1 / 191 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Rhinovirus infection			
subjects affected / exposed	1 / 195 (0.51%)	0 / 191 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	2 / 195 (1.03%)	2 / 191 (1.05%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 2	0 / 0	
Tonsillitis fungal			
subjects affected / exposed	1 / 195 (0.51%)	0 / 191 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinusitis			
subjects affected / exposed	1 / 195 (0.51%)	0 / 191 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			

subjects affected / exposed	1 / 195 (0.51%)	4 / 191 (2.09%)	
occurrences causally related to treatment / all	0 / 1	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
Stenotrophomonas infection			
subjects affected / exposed	0 / 195 (0.00%)	2 / 191 (1.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal skin infection			
subjects affected / exposed	1 / 195 (0.51%)	0 / 191 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 195 (0.00%)	1 / 191 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral pharyngitis			
subjects affected / exposed	1 / 195 (0.51%)	0 / 191 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	1 / 195 (0.51%)	0 / 191 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	4 / 195 (2.05%)	0 / 191 (0.00%)	
occurrences causally related to treatment / all	0 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urethritis			
subjects affected / exposed	1 / 195 (0.51%)	0 / 191 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hypokalaemia			

subjects affected / exposed	1 / 195 (0.51%)	0 / 191 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour lysis syndrome			
subjects affected / exposed	0 / 195 (0.00%)	1 / 191 (0.52%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	2 / 195 (1.03%)	0 / 191 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	ibrutinib (Arm B)	Ofatumumab (Arm A)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	194 / 195 (99.49%)	187 / 191 (97.91%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	10 / 195 (5.13%)	0 / 191 (0.00%)	
occurrences (all)	12	0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	13 / 195 (6.67%)	0 / 191 (0.00%)	
occurrences (all)	17	0	
Fatigue			
subjects affected / exposed	54 / 195 (27.69%)	57 / 191 (29.84%)	
occurrences (all)	77	78	
Pyrexia			
subjects affected / exposed	42 / 195 (21.54%)	26 / 191 (13.61%)	
occurrences (all)	58	37	
Oedema peripheral			
subjects affected / exposed	22 / 195 (11.28%)	15 / 191 (7.85%)	
occurrences (all)	27	17	
Respiratory, thoracic and mediastinal			

disorders			
Dyspnoea			
subjects affected / exposed	22 / 195 (11.28%)	20 / 191 (10.47%)	
occurrences (all)	25	22	
Cough			
subjects affected / exposed	38 / 195 (19.49%)	44 / 191 (23.04%)	
occurrences (all)	52	53	
Epistaxis			
subjects affected / exposed	17 / 195 (8.72%)	0 / 191 (0.00%)	
occurrences (all)	17	0	
Oropharyngeal pain			
subjects affected / exposed	13 / 195 (6.67%)	0 / 191 (0.00%)	
occurrences (all)	14	0	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	0 / 195 (0.00%)	17 / 191 (8.90%)	
occurrences (all)	0	17	
Investigations			
Weight decreased			
subjects affected / exposed	11 / 195 (5.64%)	12 / 191 (6.28%)	
occurrences (all)	12	12	
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	0 / 195 (0.00%)	51 / 191 (26.70%)	
occurrences (all)	0	74	
Contusion			
subjects affected / exposed	21 / 195 (10.77%)	0 / 191 (0.00%)	
occurrences (all)	29	0	
Nervous system disorders			
Headache			
subjects affected / exposed	27 / 195 (13.85%)	11 / 191 (5.76%)	
occurrences (all)	35	11	
Dizziness			
subjects affected / exposed	22 / 195 (11.28%)	10 / 191 (5.24%)	
occurrences (all)	25	11	
Paraesthesia			

subjects affected / exposed occurrences (all)	0 / 195 (0.00%) 0	10 / 191 (5.24%) 12	
Peripheral sensory neuropathy subjects affected / exposed occurrences (all)	0 / 195 (0.00%) 0	24 / 191 (12.57%) 29	
Blood and lymphatic system disorders			
Anaemia subjects affected / exposed occurrences (all)	43 / 195 (22.05%) 88	31 / 191 (16.23%) 59	
Increased tendency to bruise subjects affected / exposed occurrences (all)	17 / 195 (8.72%) 21	0 / 191 (0.00%) 0	
Neutropenia subjects affected / exposed occurrences (all)	42 / 195 (21.54%) 95	26 / 191 (13.61%) 59	
Thrombocytopenia subjects affected / exposed occurrences (all)	33 / 195 (16.92%) 55	22 / 191 (11.52%) 30	
Eye disorders			
Lacrimation increased subjects affected / exposed occurrences (all)	10 / 195 (5.13%) 11	0 / 191 (0.00%) 0	
Dry eye subjects affected / exposed occurrences (all)	14 / 195 (7.18%) 15	10 / 191 (5.24%) 10	
Vision blurred subjects affected / exposed occurrences (all)	19 / 195 (9.74%) 20	0 / 191 (0.00%) 0	
Gastrointestinal disorders			
Dry mouth subjects affected / exposed occurrences (all)	16 / 195 (8.21%) 20	0 / 191 (0.00%) 0	
Dyspepsia subjects affected / exposed occurrences (all)	15 / 195 (7.69%) 20	0 / 191 (0.00%) 0	
Constipation			

subjects affected / exposed	30 / 195 (15.38%)	18 / 191 (9.42%)	
occurrences (all)	33	19	
Diarrhoea			
subjects affected / exposed	92 / 195 (47.18%)	34 / 191 (17.80%)	
occurrences (all)	142	41	
Abdominal pain			
subjects affected / exposed	15 / 195 (7.69%)	18 / 191 (9.42%)	
occurrences (all)	17	20	
Vomiting			
subjects affected / exposed	28 / 195 (14.36%)	11 / 191 (5.76%)	
occurrences (all)	36	14	
Nausea			
subjects affected / exposed	51 / 195 (26.15%)	35 / 191 (18.32%)	
occurrences (all)	72	50	
Stomatitis			
subjects affected / exposed	20 / 195 (10.26%)	0 / 191 (0.00%)	
occurrences (all)	23	0	
Skin and subcutaneous tissue disorders			
Rash maculo-papular			
subjects affected / exposed	13 / 195 (6.67%)	0 / 191 (0.00%)	
occurrences (all)	19	0	
Pruritus			
subjects affected / exposed	0 / 195 (0.00%)	18 / 191 (9.42%)	
occurrences (all)	0	20	
Rash			
subjects affected / exposed	15 / 195 (7.69%)	0 / 191 (0.00%)	
occurrences (all)	24	0	
Rash erythematous			
subjects affected / exposed	13 / 195 (6.67%)	10 / 191 (5.24%)	
occurrences (all)	14	14	
Petechiae			
subjects affected / exposed	27 / 195 (13.85%)	0 / 191 (0.00%)	
occurrences (all)	33	0	
Urticaria			
subjects affected / exposed	0 / 195 (0.00%)	12 / 191 (6.28%)	
occurrences (all)	0	15	

Night sweats subjects affected / exposed occurrences (all)	10 / 195 (5.13%) 11	24 / 191 (12.57%) 27	
Musculoskeletal and connective tissue disorders			
Back pain subjects affected / exposed occurrences (all)	21 / 195 (10.77%) 22	12 / 191 (6.28%) 15	
Arthralgia subjects affected / exposed occurrences (all)	34 / 195 (17.44%) 58	13 / 191 (6.81%) 16	
Pain in extremity subjects affected / exposed occurrences (all)	20 / 195 (10.26%) 24	0 / 191 (0.00%) 0	
Myalgia subjects affected / exposed occurrences (all)	18 / 195 (9.23%) 23	0 / 191 (0.00%) 0	
Muscle spasms subjects affected / exposed occurrences (all)	25 / 195 (12.82%) 33	16 / 191 (8.38%) 18	
Infections and infestations			
Sinusitis subjects affected / exposed occurrences (all)	21 / 195 (10.77%) 26	12 / 191 (6.28%) 14	
Upper respiratory tract infection subjects affected / exposed occurrences (all)	30 / 195 (15.38%) 36	16 / 191 (8.38%) 18	
Urinary tract infection subjects affected / exposed occurrences (all)	17 / 195 (8.72%) 18	10 / 191 (5.24%) 11	
Metabolism and nutrition disorders			
Hyperglycaemia subjects affected / exposed occurrences (all)	11 / 195 (5.64%) 17	0 / 191 (0.00%) 0	
Hyperuricaemia subjects affected / exposed occurrences (all)	10 / 195 (5.13%) 12	0 / 191 (0.00%) 0	

Decreased appetite			
subjects affected / exposed	13 / 195 (6.67%)	14 / 191 (7.33%)	
occurrences (all)	16	14	
Hypokalaemia			
subjects affected / exposed	12 / 195 (6.15%)	0 / 191 (0.00%)	
occurrences (all)	17	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 September 2012	Updated the following information: • Secondary and exploratory objectives/endpoints including corresponding changes to statistical analysis section • Updated response criteria inclusive of the June 2012 clarification to IWCLL 2008 criteria for assessing response with BCR-inhibiting agents, including guidance to assess the clinical improvement in other disease parameters upon observation of lymphocytosis • Guidelines for concomitant use of CYP inhibiting/inducing drugs, QT prolonging medications, and antiplatelet agents and anticoagulants • Revised Inclusion criteria #5 to include subjects age ≥ 70 years who have received ≥ 2 prior lines of systemic therapy • Clarified that 2 separate randomization schemes were to be generated (one for each geographic region [US versus non-US])
13 December 2012	• Provided instructions on administration of ibrutinib in case of planned or unplanned surgery • Allowed allogeneic stem cell transplant within 6 months prior to randomization with no active graft vs. host disease. • Clarified that pre-treatment FISH should be performed on marrow sample for subjects without lymphocytosis (eg, SLL) • Included provisional language for supplying ibrutinib to control arm subjects • Allowed screening computed tomography (CT) scan from up to 6 weeks prior to randomization
08 August 2013	• Allowed subjects treated with ofatumumab and with documented IRC-confirmed progression to receive therapy with ibrutinib at investigator's discretion • Updated guideline for concomitant use local site or hormonal therapy for non-B cell malignancies and growth factors • Added collection for other malignancies that develop at anytime during study follow-up
24 September 2013	• Changed the overall two-sided significance level for PFS from 0.01 to 0.05 following review with global regulatory authorities.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/24881631>