



Clinical trial results:

A Randomized, Multicenter, Open-label, Phase 3 Study of the Bruton's Tyrosine Kinase Inhibitor Ibrutinib versus Chlorambucil in Patients 65 Years or Older with Treatment-naïve Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma (RESONATE™-2)

Summary

EudraCT number	2012-003967-23
Trial protocol	BE IE CZ DE ES GB IT
Global end of trial date	04 May 2015

Results information

Result version number	v1 (current)
This version publication date	14 October 2016
First version publication date	14 October 2016

Trial information

Trial identification

Sponsor protocol code	PCYC-1115-CA
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01722487
WHO universal trial number (UTN)	-
Other trial identifiers	provider NLM_DES study id: S0003U0X

Notes:

Sponsors

Sponsor organisation name	Pharmacyclics LLC
Sponsor organisation address	999 E Arques Ave, Sunnyvale, United States, 94085
Public contact	Deepali Suri, Pharmacyclics LLC, 001 855-427-8846, medinfo@pcyc.com
Scientific contact	Dr. Lori Styles, Medical Monitor, Pharmacyclics LLC, 001 408-215-3770, 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	Final
Date of interim/final analysis	28 May 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	04 May 2015
Global end of trial reached?	Yes
Global end of trial date	04 May 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to evaluate the efficacy of ibrutinib compared with chlorambucil based on the independent review committee (IRC) assessment of PFS in subjects 65 years of age or older with treatment-naïve CLL or SLL.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator:

Chlorambucil alone or in combination is often used in this patient population.

Actual start date of recruitment	21 March 2013
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	5 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 60
Country: Number of subjects enrolled	United Kingdom: 30
Country: Number of subjects enrolled	Italy: 27
Country: Number of subjects enrolled	Poland: 20
Country: Number of subjects enrolled	Ukraine: 13
Country: Number of subjects enrolled	Belgium: 12
Country: Number of subjects enrolled	Spain: 12
Country: Number of subjects enrolled	Czech Republic: 10
Country: Number of subjects enrolled	Ireland: 5
Country: Number of subjects enrolled	Russian Federation: 1
Country: Number of subjects enrolled	Australia: 18
Country: Number of subjects enrolled	Israel: 16
Country: Number of subjects enrolled	New Zealand: 13
Country: Number of subjects enrolled	China: 11
Country: Number of subjects enrolled	Canada: 11
Country: Number of subjects enrolled	Turkey: 10
Worldwide total number of subjects	269
EEA total number of subjects	116

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)	0
From 65 to 84 years	258
85 years and over	11

Subject disposition

Recruitment

Recruitment details:

This study was conducted in 88 sites: 16 in the US, 36 in the EEA, and 36 sites in 8 additional countries incl. Canada, China, and Australia. The first subject consented on 21 March 2013 and the data cutoff for the last visit of the last subject was on 04 May 2015.

Pre-assignment

Screening details:

Patients with previously untreated 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 269 subjects were randomized and evaluated in this study.

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	Ibrutinib

Arm description:

Ibrutinib 420 mg daily

Arm type	Experimental
Investigational medicinal product name	Ibrutinib
Investigational medicinal product code	PCI-32765
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Ibrutinib was supplied as hard gelatin 140-mg capsules for oral (PO) administration. Ibrutinib 420 mg (3 x 140-mg capsules) was administered orally once daily. The first dose was delivered in the clinic on Day 1, after which subsequent dosing was typically on an outpatient basis. Ibrutinib was dispensed to patients in bottles at each visit.

Arm title	Chlorambucil
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Arm description:

Chlorambucil 0.5 mg/kg (to maximum 0.8 mg/kg) days 1 and 15 of 28-day cycle up to 12 cycles

Arm type	Active comparator
Investigational medicinal product name	Chlorambucil
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Chlorambucil was supplied as 2-mg tablets for PO administration. Chlorambucil was administered orally on Days 1 and 15 of each 28-day cycle. The starting dosage (Cycle 1) was 0.5 mg/kg. If well tolerated, the Chlorambucil dose could be increased starting at Cycle 2, with increments of 0.1 mg/kg on Day 1 of each cycle to a maximum of 0.8 mg/kg.

Number of subjects in period 1	Ibrutinib	Chlorambucil
Started	136	133
Completed	134	126
Not completed	2	7
Consent withdrawn by subject	2	7

Baseline characteristics

Reporting groups

Reporting group title	Ibrutinib
Reporting group description: Ibrutinib 420 mg daily	
Reporting group title	Chlorambucil
Reporting group description: Chlorambucil 0.5 mg/kg (to maximum 0.8 mg/kg) days 1 and 15 of 28-day cycle up to 12 cycles	

Reporting group values	Ibrutinib	Chlorambucil	Total
Number of subjects	136	133	269
Age Categorical Units: Subjects			
<=18 years	0	0	0
Between 18 and 65 years	0	0	0
>=65 years	136	133	269
Age Continuous Units: years			
arithmetic mean	73.1	73.4	
standard deviation	± 5.67	± 5.95	-
Gender, Male/Female Units: Subjects			
Female	48	52	100
Male	88	81	169

End points

End points reporting groups

Reporting group title	Ibrutinib
Reporting group description:	
Ibrutinib 420 mg daily	
Reporting group title	Chlorambucil
Reporting group description:	
Chlorambucil 0.5 mg/kg (to maximum 0.8 mg/kg) days 1 and 15 of 28-day cycle up to 12 cycles	

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 with Chlorambucil based on the independent review committee (IRC) assessment of PFS. Progressive disease according to 2008 IWCLL guidelines was defined as:	
• Group A - o Lymphadenopathy, increase $\geq 50\%$ - o Hepatomegaly, increase $\geq 50\%$ - o Splenomegaly, increase $\geq 50\%$ - o Blood lymphocytes, increase $\geq 50\%$ over baseline • Group B - o Platelets counts, decrease of $\geq 50\%$ from baseline secondary to CLL - o Hemoglobin, decrease of > 2 g/dL from baseline secondary to CLL	
End point type	Primary
End point timeframe:	
Analysis was conducted when 15 months had elapsed after the last subject was randomized. The median follow-up time is 18 month. Median PFS has not been reached in the ibrutinib group, therefore, PFS rates at 18 months are presented.	

End point values	Ibrutinib	Chlorambucil		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	136	133		
Units: percentage				
number (confidence interval 95%)	89.9 (83.2 to 94)	51.5 (41.9 to 60.3)		

Statistical analyses

Statistical analysis title	PFS (Progression free survival)
Comparison groups	Ibrutinib v Chlorambucil

Number of subjects included in analysis	269
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.09
upper limit	0.28

Secondary: ORR (Overall Response Rate)

End point title	ORR (Overall Response Rate)
End point description:	
ORR is defined as the proportion of subjects who achieved complete response (CR), complete response with incomplete marrow recovery (CRi), nodule partial response (nPR) or PR per IRC assessment. Response criteria are as outlined in the International Workshop on CLL (iwCLL) 2008 criteria with the 2012 iwCLL modification stating that treatment-related lymphocytosis in the setting of improvement in other parameters was not considered as PD and the 2013 iwCLL clarification of criteria for a partial response to therapy.	
End point type	Secondary
End point timeframe:	
Analysis was conducted when 15 months had elapsed after the last subject was randomized with the cutoff date of 4 May 2015. The median follow-up time is 18 month.	

End point values	Ibrutinib	Chlorambucil		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	136	133		
Units: percentage of participants				
number (not applicable)	82.4	35.3		

Statistical analyses

Statistical analysis title	ORR (Overall Response Rate)
Comparison groups	Ibrutinib v Chlorambucil
Number of subjects included in analysis	269
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Cochran-Mantel-Haenszel

Secondary: Overall survival

End point title	Overall survival
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End point description:

End point type	Secondary
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End point timeframe:

Analysis was conducted when 15 months had elapsed after the last subject was randomized. The median follow-up time is 18 month. Median OS has not been reached in the ibrutinib group, therefore, OS rates at 18 months are presented.

End point values	Ibrutinib	Chlorambucil		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	136	133		
Units: percentage				
number (confidence interval 95%)	97.8 (93.3 to 99.3)	87.2 (79.9 to 92)		

Statistical analyses

Statistical analysis title	OS (overall survival)
Comparison groups	Chlorambucil v Ibrutinib
Number of subjects included in analysis	269
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.05
upper limit	0.56

Secondary: Proportion of Sustained Hemoglobin Improvement

End point title	Proportion of Sustained Hemoglobin Improvement
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End point description:

The proportion of subjects who achieved Hemoglobin >11 g/dL or increase ≥ 2 g/dL over baseline and persisted continuously for ≥ 56 days (8 weeks) without blood transfusion or growth factors.

End point type	Secondary
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End point timeframe:

Analysis was conducted when 15 months had elapsed after the last subject was randomized with the cutoff date of 4 May 2015. The median follow-up time is 18 month.

End point values	Ibrutinib	Chlorambucil		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	136	133		
Units: Percentage				
number (not applicable)	45.6	20.3		

Statistical analyses

Statistical analysis title	Proportion of Sustained Hemoglobin Improvement
Comparison groups	Ibrutinib v Chlorambucil
Number of subjects included in analysis	269
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Chi-squared

Secondary: Proportion of Sustained Hemoglobin Improvement in Subjects With Baseline Anemia

End point title	Proportion of Sustained Hemoglobin Improvement in Subjects With Baseline Anemia
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End point description:

In randomized subjects with baseline hemoglobin ≤ 11 g/dL, the proportion of subjects who achieved Hemoglobin >11 g/dL or increase ≥ 2 g/dL over baseline persisted continuously for ≥ 56 days (8 weeks) without blood transfusion or growth factors.

End point type	Secondary
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End point timeframe:

Analysis was conducted when 15 months had elapsed after the last subject was randomized with the cutoff date of 4 May 2015. The median follow-up time is 18 month.

End point values	Ibrutinib	Chlorambucil		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	51	55		
Units: percentage				
number (not applicable)	84.3	45.5		

Statistical analyses

Statistical analysis title	Sustained HGB improvement in baseline anemia
Comparison groups	Ibrutinib v Chlorambucil
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Chi-squared

Secondary: Proportion of Sustained Platelet Improvement

End point title	Proportion of Sustained Platelet Improvement
End point description: The proportion of subjects who achieved platelet $>100 \times 10^9/L$ or increase $\geq 50\%$ over baseline and persisted continuously for ≥ 56 days (8 weeks) without blood transfusion or growth factors.	
End point type	Secondary
End point timeframe: Analysis was conducted when 15 months had elapsed after the last subject was randomized with the cutoff date of 4 May 2015. The median follow-up time is 18 month.	

End point values	Ibrutinib	Chlorambucil		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	136	133		
Units: percentage				
number (not applicable)	27.2	11.3		

Statistical analyses

Statistical analysis title	Proportion of sustained platelet improvement
Comparison groups	Ibrutinib v Chlorambucil
Number of subjects included in analysis	269
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0009
Method	Chi-squared

Secondary: Proportion of Sustained Platelet Improvement in Subjects With Baseline Thrombocytopenia

End point title	Proportion of Sustained Platelet Improvement in Subjects With Baseline Thrombocytopenia
End point description: In randomized subjects with baseline platelet $\leq 100 \times 10^9/L$, the proportion of subjects who achieved platelet $>100 \times 10^9/L$ or increase $\geq 50\%$ over baseline persisted continuously for ≥ 56 days (8 weeks) without blood transfusion or growth factors.	

End point type	Secondary
End point timeframe:	
Analysis was conducted when 15 months had elapsed after the last subject was randomized with cutoff date of 4 May 2015. The median follow-up time is 18 month.	

End point values	Ibrutinib	Chlorambucil		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	28		
Units: percentage				
number (not applicable)	77.1	42.9		

Statistical analyses

Statistical analysis title	Sustained PLT Impr. in baseline thrombocytopenia
Comparison groups	Ibrutinib v Chlorambucil
Number of subjects included in analysis	63
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0054
Method	Chi-squared

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose of study drug to within 30 days of last dose or starting new anti-cancer therapy, whichever occurs earlier.

Adverse event reporting additional description:

269 subjects were randomized on the study of which 2 subjects withdrew without treatment and were not included in the number of participants at risk. Investigators assess the occurrence of AEs and SAEs at all patient evaluation time points during the study.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	17.1
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Reporting groups

Reporting group title	Chlorambucil
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Reporting group description:

Chlorambucil 0.5 mg/kg (to maximum 0.8 mg/kg) days 1 and 15 of 28-day cycle up to 12 cycles

Reporting group title	Ibrutinib
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Reporting group description:

Ibrutinib 420 mg daily.

Serious adverse events	Chlorambucil	Ibrutinib	
Total subjects affected by serious adverse events			
subjects affected / exposed	33 / 132 (25.00%)	55 / 135 (40.74%)	
number of deaths (all causes)	4	3	
number of deaths resulting from adverse events	1	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Squamous cell carcinoma			
subjects affected / exposed	1 / 132 (0.76%)	2 / 135 (1.48%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic lymphocytic leukaemia			
subjects affected / exposed	1 / 132 (0.76%)	0 / 135 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Basosquamous carcinoma of skin			
subjects affected / exposed	0 / 132 (0.00%)	1 / 135 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Adenocarcinoma			
subjects affected / exposed	0 / 132 (0.00%)	1 / 135 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon adenoma			
subjects affected / exposed	0 / 132 (0.00%)	1 / 135 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Basal cell carcinoma			
subjects affected / exposed	0 / 132 (0.00%)	5 / 135 (3.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-small cell lung cancer			
subjects affected / exposed	0 / 132 (0.00%)	1 / 135 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung adenocarcinoma			
subjects affected / exposed	0 / 132 (0.00%)	1 / 135 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma of skin			
subjects affected / exposed	0 / 132 (0.00%)	1 / 135 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer			
subjects affected / exposed	0 / 132 (0.00%)	2 / 135 (1.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Aortic stenosis			
subjects affected / exposed	1 / 132 (0.76%)	0 / 135 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral artery aneurysm			

subjects affected / exposed	1 / 132 (0.76%)	0 / 135 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	0 / 132 (0.00%)	2 / 135 (1.48%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chills			
subjects affected / exposed	1 / 132 (0.76%)	0 / 135 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	1 / 132 (0.76%)	1 / 135 (0.74%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	1 / 132 (0.76%)	0 / 135 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	5 / 132 (3.79%)	1 / 135 (0.74%)	
occurrences causally related to treatment / all	3 / 5	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	0 / 132 (0.00%)	2 / 135 (1.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Immune system disorders			
Immunodeficiency			
subjects affected / exposed	0 / 132 (0.00%)	1 / 135 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	1 / 132 (0.76%)	0 / 135 (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			
Lung infiltration			
subjects affected / exposed	1 / 132 (0.76%)	0 / 135 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	2 / 132 (1.52%)	2 / 135 (1.48%)	
occurrences causally related to treatment / all	0 / 4	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory failure			
subjects affected / exposed	0 / 132 (0.00%)	1 / 135 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cough			
subjects affected / exposed	0 / 132 (0.00%)	1 / 135 (0.74%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	0 / 132 (0.00%)	1 / 135 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercapnia			
subjects affected / exposed	0 / 132 (0.00%)	1 / 135 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumomediastinum			

subjects affected / exposed	0 / 132 (0.00%)	1 / 135 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wheezing			
subjects affected / exposed	0 / 132 (0.00%)	1 / 135 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Somatoform disorder cardiovascular			
subjects affected / exposed	1 / 132 (0.76%)	0 / 135 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Confusional state			
subjects affected / exposed	0 / 132 (0.00%)	1 / 135 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Fibrin D dimer increased			
subjects affected / exposed	1 / 132 (0.76%)	0 / 135 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic enzyme increased			
subjects affected / exposed	1 / 132 (0.76%)	0 / 135 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Heart rate irregular			
subjects affected / exposed	0 / 132 (0.00%)	1 / 135 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Upper limb fracture			
subjects affected / exposed	1 / 132 (0.76%)	0 / 135 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Femur fracture			
subjects affected / exposed	1 / 132 (0.76%)	0 / 135 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Overdose			
subjects affected / exposed	1 / 132 (0.76%)	0 / 135 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Limb traumatic amputation			
subjects affected / exposed	0 / 132 (0.00%)	1 / 135 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	0 / 132 (0.00%)	1 / 135 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar vertebral fracture			
subjects affected / exposed	0 / 132 (0.00%)	1 / 135 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laceration			
subjects affected / exposed	0 / 132 (0.00%)	1 / 135 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscle strain			
subjects affected / exposed	0 / 132 (0.00%)	1 / 135 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haematoma			
subjects affected / exposed	0 / 132 (0.00%)	1 / 135 (0.74%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radius fracture			

subjects affected / exposed	0 / 132 (0.00%)	1 / 135 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Traumatic haematoma			
subjects affected / exposed	0 / 132 (0.00%)	1 / 135 (0.74%)	
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	0 / 132 (0.00%)	1 / 135 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative wound complication			
subjects affected / exposed	0 / 132 (0.00%)	1 / 135 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxicity to various agents			
subjects affected / exposed	0 / 132 (0.00%)	1 / 135 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ulna fracture			
subjects affected / exposed	0 / 132 (0.00%)	1 / 135 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 132 (0.76%)	2 / 135 (1.48%)	
occurrences causally related to treatment / all	1 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic valve disease mixed			
subjects affected / exposed	1 / 132 (0.76%)	0 / 135 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			

subjects affected / exposed	1 / 132 (0.76%)	0 / 135 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial ischaemia			
subjects affected / exposed	1 / 132 (0.76%)	0 / 135 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	1 / 132 (0.76%)	1 / 135 (0.74%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic valve disease			
subjects affected / exposed	0 / 132 (0.00%)	1 / 135 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	0 / 132 (0.00%)	1 / 135 (0.74%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease			
subjects affected / exposed	0 / 132 (0.00%)	1 / 135 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	0 / 132 (0.00%)	2 / 135 (1.48%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Presyncope			
subjects affected / exposed	1 / 132 (0.76%)	0 / 135 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post herpetic neuralgia			

subjects affected / exposed	1 / 132 (0.76%)	0 / 135 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	1 / 132 (0.76%)	0 / 135 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Cognitive disorder			
subjects affected / exposed	1 / 132 (0.76%)	0 / 135 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy			
subjects affected / exposed	1 / 132 (0.76%)	0 / 135 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	2 / 132 (1.52%)	0 / 135 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	1 / 132 (0.76%)	1 / 135 (0.74%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cauda equina syndrome			
subjects affected / exposed	0 / 132 (0.00%)	1 / 135 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haemorrhage			
subjects affected / exposed	0 / 132 (0.00%)	1 / 135 (0.74%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			

subjects affected / exposed	0 / 132 (0.00%)	1 / 135 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subarachnoid haemorrhage			
subjects affected / exposed	0 / 132 (0.00%)	1 / 135 (0.74%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Autoimmune haemolytic anaemia			
subjects affected / exposed	1 / 132 (0.76%)	0 / 135 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	2 / 132 (1.52%)	2 / 135 (1.48%)	
occurrences causally related to treatment / all	1 / 2	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemolytic anaemia			
subjects affected / exposed	1 / 132 (0.76%)	0 / 135 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			
subjects affected / exposed	2 / 132 (1.52%)	2 / 135 (1.48%)	
occurrences causally related to treatment / all	1 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	2 / 132 (1.52%)	1 / 135 (0.74%)	
occurrences causally related to treatment / all	1 / 2	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphadenopathy			
subjects affected / exposed	1 / 132 (0.76%)	0 / 135 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			

Vitreous haemorrhage			
subjects affected / exposed	0 / 132 (0.00%)	1 / 135 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal vein occlusion			
subjects affected / exposed	0 / 132 (0.00%)	1 / 135 (0.74%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal vascular occlusion			
subjects affected / exposed	0 / 132 (0.00%)	1 / 135 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyphaema			
subjects affected / exposed	0 / 132 (0.00%)	1 / 135 (0.74%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blindness unilateral			
subjects affected / exposed	0 / 132 (0.00%)	2 / 135 (1.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 132 (0.76%)	0 / 135 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	0 / 132 (0.00%)	1 / 135 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	0 / 132 (0.00%)	1 / 135 (0.74%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			

subjects affected / exposed	0 / 132 (0.00%)	1 / 135 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatitis toxic			
subjects affected / exposed	1 / 132 (0.76%)	0 / 135 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Cholecystitis			
subjects affected / exposed	1 / 132 (0.76%)	0 / 135 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bile duct stone			
subjects affected / exposed	0 / 132 (0.00%)	1 / 135 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangitis			
subjects affected / exposed	0 / 132 (0.00%)	1 / 135 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Rash macular			
subjects affected / exposed	0 / 132 (0.00%)	1 / 135 (0.74%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dermatitis allergic			
subjects affected / exposed	0 / 132 (0.00%)	1 / 135 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash maculo-papular			
subjects affected / exposed	0 / 132 (0.00%)	1 / 135 (0.74%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subcutaneous emphysema			

subjects affected / exposed	0 / 132 (0.00%)	1 / 135 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal haemorrhage			
subjects affected / exposed	1 / 132 (0.76%)	0 / 135 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	1 / 132 (0.76%)	0 / 135 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure chronic			
subjects affected / exposed	0 / 132 (0.00%)	1 / 135 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydronephrosis			
subjects affected / exposed	0 / 132 (0.00%)	1 / 135 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure acute			
subjects affected / exposed	0 / 132 (0.00%)	1 / 135 (0.74%)	
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 / 132 (0.00%)	1 / 135 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Calculus ureteric			
subjects affected / exposed	0 / 132 (0.00%)	1 / 135 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal impairment			

subjects affected / exposed	0 / 132 (0.00%)	1 / 135 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 132 (0.00%)	1 / 135 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Acute hepatitis B			
subjects affected / exposed	1 / 132 (0.76%)	0 / 135 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Neutropenic sepsis			
subjects affected / exposed	1 / 132 (0.76%)	1 / 135 (0.74%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	2 / 132 (1.52%)	5 / 135 (3.70%)	
occurrences causally related to treatment / all	1 / 2	2 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	1 / 132 (0.76%)	2 / 135 (1.48%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia bacterial			
subjects affected / exposed	1 / 132 (0.76%)	1 / 135 (0.74%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 132 (0.76%)	1 / 135 (0.74%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pneumonia fungal			
subjects affected / exposed	1 / 132 (0.76%)	0 / 135 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess limb			
subjects affected / exposed	0 / 132 (0.00%)	1 / 135 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis bacterial			
subjects affected / exposed	0 / 132 (0.00%)	1 / 135 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal abscess			
subjects affected / exposed	0 / 132 (0.00%)	1 / 135 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	0 / 132 (0.00%)	1 / 135 (0.74%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopneumonia			
subjects affected / exposed	0 / 132 (0.00%)	2 / 135 (1.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile infection			
subjects affected / exposed	0 / 132 (0.00%)	1 / 135 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia infection			
subjects affected / exposed	0 / 132 (0.00%)	1 / 135 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia bacteraemia			

subjects affected / exposed	0 / 132 (0.00%)	1 / 135 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis viral			
subjects affected / exposed	0 / 132 (0.00%)	1 / 135 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia sepsis			
subjects affected / exposed	0 / 132 (0.00%)	2 / 135 (1.48%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Klebsiella infection			
subjects affected / exposed	0 / 132 (0.00%)	1 / 135 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Lung infection pseudomonal			
subjects affected / exposed	0 / 132 (0.00%)	1 / 135 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lobar pneumonia			
subjects affected / exposed	0 / 132 (0.00%)	1 / 135 (0.74%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	0 / 132 (0.00%)	2 / 135 (1.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia legionella			
subjects affected / exposed	0 / 132 (0.00%)	1 / 135 (0.74%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia viral			

subjects affected / exposed	0 / 132 (0.00%)	1 / 135 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			
subjects affected / exposed	0 / 132 (0.00%)	1 / 135 (0.74%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subcutaneous abscess			
subjects affected / exposed	0 / 132 (0.00%)	1 / 135 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	0 / 132 (0.00%)	1 / 135 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 132 (0.76%)	1 / 135 (0.74%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	0 / 132 (0.00%)	3 / 135 (2.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Chlorambucil	Ibrutinib	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	123 / 132 (93.18%)	133 / 135 (98.52%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	0 / 132 (0.00%)	7 / 135 (5.19%)	
occurrences (all)	0	9	

Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 132 (0.00%)	18 / 135 (13.33%)	
occurrences (all)	0	34	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	17 / 132 (12.88%)	22 / 135 (16.30%)	
occurrences (all)	26	24	
Fatigue			
subjects affected / exposed	50 / 132 (37.88%)	41 / 135 (30.37%)	
occurrences (all)	85	57	
Oedema peripheral			
subjects affected / exposed	12 / 132 (9.09%)	25 / 135 (18.52%)	
occurrences (all)	12	38	
Asthenia			
subjects affected / exposed	0 / 132 (0.00%)	10 / 135 (7.41%)	
occurrences (all)	0	10	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	20 / 132 (15.15%)	30 / 135 (22.22%)	
occurrences (all)	24	45	
Dyspnoea			
subjects affected / exposed	13 / 132 (9.85%)	14 / 135 (10.37%)	
occurrences (all)	16	23	
Oropharyngeal pain			
subjects affected / exposed	0 / 132 (0.00%)	8 / 135 (5.93%)	
occurrences (all)	0	11	
Epistaxis			
subjects affected / exposed	0 / 132 (0.00%)	8 / 135 (5.93%)	
occurrences (all)	0	10	
Pleural effusion			
subjects affected / exposed	0 / 132 (0.00%)	9 / 135 (6.67%)	
occurrences (all)	0	15	
Psychiatric disorders			
Insomnia			

subjects affected / exposed occurrences (all)	9 / 132 (6.82%) 11	11 / 135 (8.15%) 12	
Anxiety subjects affected / exposed occurrences (all)	0 / 132 (0.00%) 0	7 / 135 (5.19%) 8	
Investigations Weight decreased subjects affected / exposed occurrences (all)	16 / 132 (12.12%) 16	14 / 135 (10.37%) 15	
Platelet count decreased subjects affected / exposed occurrences (all)	0 / 132 (0.00%) 0	7 / 135 (5.19%) 45	
Injury, poisoning and procedural complications Contusion subjects affected / exposed occurrences (all)	0 / 132 (0.00%) 0	11 / 135 (8.15%) 21	
Cardiac disorders Atrial fibrillation subjects affected / exposed occurrences (all)	0 / 132 (0.00%) 0	7 / 135 (5.19%) 8	
Nervous system disorders Headache subjects affected / exposed occurrences (all)	13 / 132 (9.85%) 23	16 / 135 (11.85%) 27	
Dizziness subjects affected / exposed occurrences (all)	16 / 132 (12.12%) 22	15 / 135 (11.11%) 18	
Blood and lymphatic system disorders Neutropenia subjects affected / exposed occurrences (all)	29 / 132 (21.97%) 51	20 / 135 (14.81%) 33	
Anaemia subjects affected / exposed occurrences (all)	27 / 132 (20.45%) 56	24 / 135 (17.78%) 52	
Thrombocytopenia			

subjects affected / exposed occurrences (all)	17 / 132 (12.88%) 29	11 / 135 (8.15%) 29	
Increased tendency to bruise subjects affected / exposed occurrences (all)	0 / 132 (0.00%) 0	8 / 135 (5.93%) 9	
Eye disorders			
Lacrimation increased subjects affected / exposed occurrences (all)	8 / 132 (6.06%) 10	18 / 135 (13.33%) 35	
Vision blurred subjects affected / exposed occurrences (all)	10 / 132 (7.58%) 10	18 / 135 (13.33%) 21	
Dry eye subjects affected / exposed occurrences (all)	0 / 132 (0.00%) 0	23 / 135 (17.04%) 30	
Eye pain subjects affected / exposed occurrences (all)	0 / 132 (0.00%) 0	8 / 135 (5.93%) 8	
Visual acuity reduced subjects affected / exposed occurrences (all)	0 / 132 (0.00%) 0	15 / 135 (11.11%) 19	
Vitreous floaters subjects affected / exposed occurrences (all)	0 / 132 (0.00%) 0	8 / 135 (5.93%) 10	
Cataract subjects affected / exposed occurrences (all)	0 / 132 (0.00%) 0	7 / 135 (5.19%) 7	
Gastrointestinal disorders			
Abdominal pain subjects affected / exposed occurrences (all)	14 / 132 (10.61%) 14	17 / 135 (12.59%) 22	
Diarrhoea subjects affected / exposed occurrences (all)	22 / 132 (16.67%) 33	57 / 135 (42.22%) 99	
Nausea			

subjects affected / exposed	52 / 132 (39.39%)	30 / 135 (22.22%)	
occurrences (all)	74	40	
Constipation			
subjects affected / exposed	21 / 132 (15.91%)	20 / 135 (14.81%)	
occurrences (all)	21	24	
Vomiting			
subjects affected / exposed	27 / 132 (20.45%)	18 / 135 (13.33%)	
occurrences (all)	41	19	
Dyspepsia			
subjects affected / exposed	0 / 132 (0.00%)	15 / 135 (11.11%)	
occurrences (all)	0	19	
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 132 (0.00%)	9 / 135 (6.67%)	
occurrences (all)	0	9	
Stomatitis			
subjects affected / exposed	0 / 132 (0.00%)	11 / 135 (8.15%)	
occurrences (all)	0	16	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	7 / 132 (5.30%)	8 / 135 (5.93%)	
occurrences (all)	16	9	
Night sweats			
subjects affected / exposed	10 / 132 (7.58%)	9 / 135 (6.67%)	
occurrences (all)	12	9	
Rash erythematous			
subjects affected / exposed	0 / 132 (0.00%)	13 / 135 (9.63%)	
occurrences (all)	0	21	
Dry skin			
subjects affected / exposed	0 / 132 (0.00%)	7 / 135 (5.19%)	
occurrences (all)	0	7	
Rash maculo-papular			
subjects affected / exposed	0 / 132 (0.00%)	8 / 135 (5.93%)	
occurrences (all)	0	16	
Renal and urinary disorders			
Haematuria			

subjects affected / exposed occurrences (all)	0 / 132 (0.00%) 0	8 / 135 (5.93%) 9	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	9 / 132 (6.82%)	16 / 135 (11.85%)	
occurrences (all)	9	19	
Pain in extremity			
subjects affected / exposed	7 / 132 (5.30%)	13 / 135 (9.63%)	
occurrences (all)	7	13	
Arthralgia			
subjects affected / exposed	9 / 132 (6.82%)	22 / 135 (16.30%)	
occurrences (all)	15	33	
Muscle spasms			
subjects affected / exposed	7 / 132 (5.30%)	15 / 135 (11.11%)	
occurrences (all)	8	18	
Musculoskeletal pain			
subjects affected / exposed	0 / 132 (0.00%)	11 / 135 (8.15%)	
occurrences (all)	0	11	
Myalgia			
subjects affected / exposed	0 / 132 (0.00%)	8 / 135 (5.93%)	
occurrences (all)	0	11	
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	23 / 132 (17.42%)	22 / 135 (16.30%)	
occurrences (all)	29	29	
Urinary tract infection			
subjects affected / exposed	10 / 132 (7.58%)	13 / 135 (9.63%)	
occurrences (all)	15	23	
Herpes zoster			
subjects affected / exposed	7 / 132 (5.30%)	0 / 135 (0.00%)	
occurrences (all)	8	0	
Conjunctivitis			
subjects affected / exposed	0 / 132 (0.00%)	11 / 135 (8.15%)	
occurrences (all)	0	20	
Skin infection			

subjects affected / exposed	0 / 132 (0.00%)	7 / 135 (5.19%)	
occurrences (all)	0	7	
Cellulitis			
subjects affected / exposed	0 / 132 (0.00%)	8 / 135 (5.93%)	
occurrences (all)	0	8	
Sinusitis			
subjects affected / exposed	0 / 132 (0.00%)	7 / 135 (5.19%)	
occurrences (all)	0	8	
Nasopharyngitis			
subjects affected / exposed	0 / 132 (0.00%)	10 / 135 (7.41%)	
occurrences (all)	0	13	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	19 / 132 (14.39%)	13 / 135 (9.63%)	
occurrences (all)	26	16	
Hypokalaemia			
subjects affected / exposed	0 / 132 (0.00%)	8 / 135 (5.93%)	
occurrences (all)	0	9	
Hyponatraemia			
subjects affected / exposed	0 / 132 (0.00%)	7 / 135 (5.19%)	
occurrences (all)	0	11	
Hyperuricaemia			
subjects affected / exposed	0 / 132 (0.00%)	8 / 135 (5.93%)	
occurrences (all)	0	9	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 January 2013	- Removed the 12-month time limit after last chlorambucil dose to receive second-line ibrutinib in Study 1116 - Updated guidance on missed dose, treatment-related lymphocytosis, use of anti-coagulant, anti-platelet and QT-prolonging agents - Added guidance on perioperative management of ibrutinib - Required that SAEs that occur >30 days after the last dose of study drug, if deemed ibrutinib-related, be reported to the Sponsor - Added that other malignancies were to be reported throughout the study - Updated the Summary of Safety section to align with the IB and the FDA approved product label
05 March 2014	- Updated the guidance for the management of ibrutinib with concomitant CYP3A inhibitors or inducers - Required screening FISH analysis results to be available prior to randomization
17 February 2015	- Clarified that in the event that a bone marrow sample for MRD assessment could not be obtained, a peripheral blood sample should be submitted - Clarified criteria for hematological improvement - Specified that PFS will not be censored at the start of new anti-cancer therapy - Clarified criteria defining PR and PRL based on updated response criteria (Hallek et al, 2013; Cheson et al, 2012; Hallek et al, 2012) - Updated safety information and concomitant medication administration sections to align with the IB and the FDA-approved product label - Revised assessment of EFS and revised the schedule for subjects confirmed as MRD negative in the marrow to be followed by peripheral blood MRD analyses, from every 3 months to every 4 months to be consistent with the 4-month visit schedule

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/26639149>