Clinical trial results:
A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Efficacy and Safety of Idelalisib (GS-1101) in Combination with Rituximab for Previously Treated Chronic Lymphocytic Leukemia

Summary

EudraCT number	2011-005180-24
Trial protocol	GB DE
Global end of trial date	20 April 2014

Results information

Result version number	v1 (current)
This version publication date	22 March 2016
First version publication date	06 August 2015

Trial information

Trial identification

Sponsor protocol code	GS-US-312-0116

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01539512
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Gilead Sciences
Sponsor organisation address	333 Lakeside Drive, Foster City, CA, United States, 94404
Public contact	Clinical Trial Mailbox, Gilead Sciences International Ltd, ClinicalTrialDisclosures@gilead.com
Scientific contact	Clinical Trial Mailbox, Gilead Sciences International Ltd, ClinicalTrialDisclosures@gilead.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	20 April 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	20 April 2014
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

This Phase 3, randomized, double-blind, placebo-controlled study is to evaluate the effect of idelalisib in combination with rituximab on the onset, magnitude, and duration of tumor control in participants previously treated for chronic lymphocytic leukemia (CLL). Eligible patients will be randomized with a 1:1 ratio into 1 of the 2 treatment arms to receive either idelalisib plus rituximab or placebo plus rituximab. Participants who are tolerating primary study therapy but experience definitive CLL progression are eligible to receive active idelalisib therapy in the extension study, GS-US-312-0117.

Protection of trial subjects:

The protocol and consent/assent forms were submitted by each investigator to a duly constituted Independent Ethics Committee (IEC) or Institutional Review Board (IRB) for review and approval before study initiation. All revisions to the consent/assent forms (if applicable) after initial IEC/IRB approval were submitted by the investigator to the IEC/IRB for review and approval before implementation in accordance with regulatory requirements.

This study was conducted in accordance with recognized international scientific and ethical standards, including but not limited to the International Conference on Harmonization guideline for Good Clinical Practice (ICH GCP) and the original principles embodied in the Declaration of Helsinki.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	03 April 2012
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
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	France: 6
Country: Number of subjects enrolled	Germany: 12
Country: Number of subjects enrolled	Italy: 7
Country: Number of subjects enrolled	United States: 163
Country: Number of subjects enrolled	United Kingdom: 32
Worldwide total number of subjects	220
EEA total number of subjects	57

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)	48
From 65 to 84 years	165
85 years and over	7

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled at a total of 53 study sites in the United States and Europe. The first participant was screened on 03 April 2012. The last study visit occurred on 20 April 2014.

Pre-assignment

Screening details:

Participants were evaluated at a screening visit, and eligible participants were randomized at a 1:1 ratio into 1 of 2 treatment groups.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Idelalisib + rituximab

Arm description:

Participants were randomized to receive idelalisib plus rituximab for the duration of the study.

Arm type	Active comparator
Investigational medicinal product name	Idelalisib
Investigational medicinal product code	
Other name	Zydelig®, GS-1101
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Idelalisib 150 mg tablet administered orally twice daily

Investigational medicinal product name	Rituximab
Investigational medicinal product code	
Other name	Rituxan®, MabThera®
Pharmaceutical forms	Concentrate for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Rituximab administered as 8 intravenous doses through Week 20: Day 1: 375 mg/m^2, and 500 mg/m^2 thereafter

Arm title	Placebo + rituximab

Arm description:

Participants were randomized to receive placebo to match idelalisib plus rituximab for the duration of the study.

Arm type	Placebo
Investigational medicinal product name	Placebo to match idelalisib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo to match idelalisib administered orally twice daily

Investigational medicinal product name	Rituximab
Investigational medicinal product code	
Other name	Rituxan®, MabThera®
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Rituximab administered as 8 intravenous doses through Week 20: Day 1: 375 mg/m^2, and 500 mg/m^2 thereafter

Number of subjects in period 1	Idelalisib + rituximab	Placebo + rituximab
Started	110	110
Completed	87	97
Not completed	23	13
Adverse event, serious fatal	-	4
Physician decision	1	1
Consent withdrawn by subject	12	5
Adverse event, non-fatal	9	3
Richter's Transformation	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Idelalisib + rituximab
Reporting group description:	
Participants were randomized to receive idelalisib plus rituximab for the duration of the study.	
Reporting group title	Placebo + rituximab
Reporting group description:	
Participants were randomized to receive placebo to match idelalisib plus rituximab for the duration of the study.	

Reporting group values	Idelalisib + rituximab	Placebo + rituximab	Total
Number of subjects	110	110	220
Age, Customized Units: participants			
< 65 years	21	27	48
≥ 65 years	89	83	172
Age Continuous Units: years			
arithmetic mean	71	70	
standard deviation	± 7.7	± 8.1	-
Gender, Male/Female Units: participants			
Female	34	42	76
Male	76	68	144
Ethnicity Units: Subjects			
Hispanic or Latino	3	2	5
Not Hispanic or Latino	101	102	203
Not Permitted	6	6	12
Race Units: Subjects			
White	100	98	198
Black or African American	3	3	6
Other	2	2	4
Not Permitted	5	7	12
Karnofsky Performance Status			
Classifies patients according to their functional impairment. Scores range from 0-100; the lower the score, the worse the survival for most serious illnesses.			
Units: Subjects			
40	1	1	2
50	3	4	7
60	6	5	11
70	20	13	33
80	42	46	88
90	23	28	51
100	15	13	28
Rai Stage at Screening			
Rai staging categorizes the disease progression of chronic lymphocytic leukemia (CLL), with			

classifications of low- (Stage 0), intermediate- (Stage 1 and 2), and high-risk (Stages 3 and 4) categories. Rai Stage 0: high number of lymphocytes in the blood (lymphocytosis) only. Rai Stage 1: lymphocytosis with enlarged lymphoid tissues (lymphadenopathy). Rai Stage 2: lymphocytosis with enlarged liver (hepatomegaly) or spleen (splenomegaly). Rai Stage 3: lymphocytosis with low red blood cell count (anemia). Rai Stage 4: lymphocytosis with low number of blood platelets (thrombocytopenia).			
Units: Subjects			
Rai Stage 0	0	1	1
Rai Stage 1	18	19	37
Rai Stage 2	16	10	26
Rai Stage 3	22	18	40
Rai Stage 4	48	54	102
Missing	6	8	14
Binet Stage at Screening			
Binet staging classifies CLL according to the number of lymphoid tissues involved, as well as the presence of anemia or thrombocytopenia. Stage A: fewer than three areas of enlarged lymphoid tissue; enlarged lymph nodes of the neck, underarms, and groin, as well as the spleen, are each considered "one group" whether unilateral (one-sided) or bilateral (on both sides). Binet Stage B: more than three areas of enlarged lymphoid tissue. Binet Stage C: anemia plus thrombocytopenia.			
Units: Subjects			
Binet Stage A	7	4	11
Binet Stage B	29	32	61
Binet Stage C	63	60	123
Missing	11	14	25
Time Since Diagnosis			
Units: months			
arithmetic mean	108.3	106.4	
standard deviation	± 62.28	± 52.73	-

End points

End points reporting groups

Reporting group title	Idelalisib + rituximab
Reporting group description:	
Participants were randomized to receive idelalisib plus rituximab for the duration of the study.	
Reporting group title	Placebo + rituximab
Reporting group description:	
Participants were randomized to receive placebo to match idelalisib plus rituximab for the duration of the study.	

Primary: Progression-Free Survival

End point title	Progression-Free Survival
End point description:	
Progression-free survival was defined as the interval from randomization to the earlier of the first documentation of definitive disease progression or death from any cause. Definitive disease progression was CLL progression based on standard criteria (other than lymphocytosis alone) as defined by the 2008 update of the International Workshop on CLL guidelines, ie, appearance of any new lesion; increase by ≥ 50% in the sum of the products of the perpendicular diameters of measured lymph nodes (SPD); new or ≥ 50% enlargement of liver or spleen; transformation to a more aggressive histology (eg, Richter's or prolymphocytic transformation); reduction in the number of blood cells (cytopenia) attributable to CLL. 99999 = Upper limit of the 95% CI not reached due to insufficient number of events.	
End point type	Primary
End point timeframe:	
Up to 21 months	

End point values	Idelalisib + rituximab	Placebo + rituximab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	110	110		
Units: months				
median (confidence interval 95%)	19.4 (12.3 to 99999)	6.5 (4 to 7.3)		

Statistical analyses

Statistical analysis title	Difference in median months
Comparison groups	Idelalisib + rituximab v Placebo + rituximab
Number of subjects included in analysis	220
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [1]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.15

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.09
upper limit	0.24

Notes:

[1] - P-value is from stratified log-rank test, adjusted for randomization stratification factors.

Secondary: Overall Response Rate

End point title	Overall Response Rate

End point description:

Overall response rate was defined as the percentage of participants who achieved a best overall response of complete response or partial response.
Complete response was defined as no lymphadenopathy, hepatomegaly, splenomegaly; normal complete blood count; confirmed by bone marrow aspirate & biopsy.

Partial response was defined as >1 of the following criteria: a 50% decrease in peripheral blood lymphocytes, lymphadenopathy, liver size, spleen size; plus ≥ 1 of the following: ≥ 1500/µL absolute neutrophil count, > 100000/µL platelets, > 11.0 g/dL hemoglobin or 50% improvement for either of these parameters without transfusions or growth factors.

End point type	Secondary

End point timeframe:

Up to 21 months

End point values	Idelalisib + rituximab	Placebo + rituximab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	110	110		
Units: percentage of participants				
number (confidence interval 95%)	83.6 (75.4 to 90)	15.5 (9.3 to 23.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Lymph Node Response Rate

End point title	Lymph Node Response Rate

End point description:

Lymph node response rate was defined as the percentage of participants who achieved a ≥ 50% decrease from baseline in the SPD of index lymph nodes.

End point type	Secondary

End point timeframe:

Up to 21 months

End point values	Idelalisib + rituximab	Placebo + rituximab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	110	110		
Units: percentage of participants				
number (confidence interval 95%)	96.2 (90.6 to 99)	6.7 (2.7 to 13.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival

End point title	Overall Survival

End point description:

Overall survival was defined as the interval from randomization to death from any cause.

999 = Lower limit of the 95% CI not reached due to insufficient number of events.
9999 = Median not reached due to insufficient number of events.
99999 = Upper limit of the 95% CI not reached due to insufficient number of events.

End point type	Secondary

End point timeframe:

Up to 21 months

End point values	Idelalisib + rituximab	Placebo + rituximab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	110	110		
Units: months				
median (confidence interval 95%)	9999 (999 to 99999)	20.8 (14.8 to 99999)		

Statistical analyses

Statistical analysis title	Difference in median months
Comparison groups	Idelalisib + rituximab v Placebo + rituximab
Number of subjects included in analysis	220
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	0.34
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.19
upper limit	0.6

Secondary: Complete Response Rate

End point title	Complete Response Rate

End point description:

Complete response rate was defined as the percentage of participants who achieved a complete response.

End point type	Secondary

End point timeframe:

Up to 21 months

End point values	Idelalisib + rituximab	Placebo + rituximab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	110	110		
Units: percentage of participants				
number (not applicable)	0	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Up to 21 months plus 30 days	
Adverse event reporting additional description:	
Safety Analysis Set: randomized participants who received at least 1 dose of study drug, with treatment assignments designated according to the actual treatment received.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups	
Reporting group title	Idelalisib + rituximab
Reporting group description:	
Idelalisib 150 mg tablet administered orally twice daily plus rituximab (8 intravenous doses through Week 20: Day 1: 375 mg/m^2, and 500 mg/m^2 thereafter)	
Reporting group title	Placebo + rituximab
Reporting group description:	
Placebo to match idelalisib administered orally twice daily plus rituximab (8 intravenous doses through Week 20: Day 1: 375 mg/m^2, and 500 mg/m^2 thereafter)	

Serious adverse events	Idelalisib + rituximab	Placebo + rituximab	
Total subjects affected by serious adverse events			
subjects affected / exposed	65 / 110 (59.09%)	43 / 108 (39.81%)	
number of deaths (all causes)	10	15	
number of deaths resulting from adverse events	2	1	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Squamous cell carcinoma			
subjects affected / exposed	1 / 110 (0.91%)	0 / 108 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngeal squamous cell carcinoma			
subjects affected / exposed	0 / 110 (0.00%)	1 / 108 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchial carcinoma			
subjects affected / exposed	1 / 110 (0.91%)	0 / 108 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Vascular disorders			
Embolism			
subjects affected / exposed	0 / 110 (0.00%)	1 / 108 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	2 / 110 (1.82%)	0 / 108 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	2 / 110 (1.82%)	1 / 108 (0.93%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 110 (0.91%)	0 / 108 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chills			
subjects affected / exposed	0 / 110 (0.00%)	1 / 108 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthenia			
subjects affected / exposed	2 / 110 (1.82%)	3 / 108 (2.78%)	
occurrences causally related to treatment / all	1 / 2	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device dislocation			
subjects affected / exposed	1 / 110 (0.91%)	0 / 108 (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	0 / 110 (0.00%)	1 / 108 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

General physical health deterioration			
subjects affected / exposed	0 / 110 (0.00%)	1 / 108 (0.93%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Oedema peripheral			
subjects affected / exposed	0 / 110 (0.00%)	2 / 108 (1.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	1 / 110 (0.91%)	1 / 108 (0.93%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multi-organ failure			
subjects affected / exposed	0 / 110 (0.00%)	1 / 108 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pyrexia			
subjects affected / exposed	10 / 110 (9.09%)	3 / 108 (2.78%)	
occurrences causally related to treatment / all	2 / 11	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	2 / 110 (1.82%)	3 / 108 (2.78%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cough			
subjects affected / exposed	0 / 110 (0.00%)	1 / 108 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 110 (0.91%)	1 / 108 (0.93%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	

Acute respiratory failure			
subjects affected / exposed	1 / 110 (0.91%)	1 / 108 (0.93%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 1	
Haemoptysis			
subjects affected / exposed	1 / 110 (0.91%)	0 / 108 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	2 / 110 (1.82%)	1 / 108 (0.93%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	2 / 110 (1.82%)	1 / 108 (0.93%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	4 / 110 (3.64%)	1 / 108 (0.93%)	
occurrences causally related to treatment / all	3 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	1 / 110 (0.91%)	0 / 108 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary mass			
subjects affected / exposed	1 / 110 (0.91%)	0 / 108 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			
subjects affected / exposed	0 / 110 (0.00%)	2 / 108 (1.85%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Psychiatric disorders			

Agitation			
subjects affected / exposed	1 / 110 (0.91%)	0 / 108 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anxiety			
subjects affected / exposed	1 / 110 (0.91%)	0 / 108 (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	1 / 110 (0.91%)	0 / 108 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental status changes			
subjects affected / exposed	0 / 110 (0.00%)	1 / 108 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood creatinine increased			
subjects affected / exposed	0 / 110 (0.00%)	2 / 108 (1.85%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
International normalised ratio increased			
subjects affected / exposed	0 / 110 (0.00%)	1 / 108 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutrophil count decreased			
subjects affected / exposed	1 / 110 (0.91%)	0 / 108 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transaminases increased			
subjects affected / exposed	1 / 110 (0.91%)	0 / 108 (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			
Femur fracture			
subjects affected / exposed	0 / 110 (0.00%)	1 / 108 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	0 / 110 (0.00%)	1 / 108 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infusion related reaction			
subjects affected / exposed	1 / 110 (0.91%)	2 / 108 (1.85%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 110 (0.91%)	0 / 108 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	0 / 110 (0.00%)	1 / 108 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac failure congestive			
subjects affected / exposed	1 / 110 (0.91%)	0 / 108 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left ventricular failure			
subjects affected / exposed	0 / 110 (0.00%)	1 / 108 (0.93%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Myocardial infarction			
subjects affected / exposed	0 / 110 (0.00%)	1 / 108 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Right ventricular failure			
subjects affected / exposed	1 / 110 (0.91%)	0 / 108 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Amnesia			
subjects affected / exposed	1 / 110 (0.91%)	0 / 108 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Iiird nerve disorder			
subjects affected / exposed	0 / 110 (0.00%)	1 / 108 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	0 / 110 (0.00%)	1 / 108 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Convulsion			
subjects affected / exposed	1 / 110 (0.91%)	0 / 108 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	1 / 110 (0.91%)	0 / 108 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lethargy			
subjects affected / exposed	1 / 110 (0.91%)	0 / 108 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	2 / 110 (1.82%)	0 / 108 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			

subjects affected / exposed	0 / 110 (0.00%)	1 / 108 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Presyncope			
subjects affected / exposed	0 / 110 (0.00%)	1 / 108 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post herpetic neuralgia			
subjects affected / exposed	1 / 110 (0.91%)	0 / 108 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	5 / 110 (4.55%)	6 / 108 (5.56%)	
occurrences causally related to treatment / all	1 / 5	1 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			
subjects affected / exposed	1 / 110 (0.91%)	1 / 108 (0.93%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemolytic anaemia			
subjects affected / exposed	1 / 110 (0.91%)	0 / 108 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	3 / 110 (2.73%)	0 / 108 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Splenic infarction			
subjects affected / exposed	0 / 110 (0.00%)	1 / 108 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			

subjects affected / exposed	0 / 110 (0.00%)	1 / 108 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	1 / 110 (0.91%)	1 / 108 (0.93%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Eye pain			
subjects affected / exposed	1 / 110 (0.91%)	0 / 108 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 110 (0.91%)	1 / 108 (0.93%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	1 / 110 (0.91%)	0 / 108 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric mucosa erythema			
subjects affected / exposed	1 / 110 (0.91%)	0 / 108 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	8 / 110 (7.27%)	0 / 108 (0.00%)	
occurrences causally related to treatment / all	6 / 9	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	1 / 110 (0.91%)	1 / 108 (0.93%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			

subjects affected / exposed	4 / 110 (3.64%)	0 / 108 (0.00%)	
occurrences causally related to treatment / all	4 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	1 / 110 (0.91%)	0 / 108 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oral pain			
subjects affected / exposed	1 / 110 (0.91%)	0 / 108 (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 / 110 (0.91%)	0 / 108 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dermatitis exfoliative			
subjects affected / exposed	1 / 110 (0.91%)	0 / 108 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin disorder			
subjects affected / exposed	1 / 110 (0.91%)	0 / 108 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash macular			
subjects affected / exposed	0 / 110 (0.00%)	1 / 108 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash			
subjects affected / exposed	0 / 110 (0.00%)	1 / 108 (0.93%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urticaria			

subjects affected / exposed	1 / 110 (0.91%)	0 / 108 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Pollakiuria			
subjects affected / exposed	0 / 110 (0.00%)	1 / 108 (0.93%)	
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	1 / 110 (0.91%)	0 / 108 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Inappropriate antidiuretic hormone secretion			
subjects affected / exposed	1 / 110 (0.91%)	0 / 108 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 110 (0.91%)	0 / 108 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint effusion			
subjects affected / exposed	0 / 110 (0.00%)	1 / 108 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myalgia			
subjects affected / exposed	0 / 110 (0.00%)	1 / 108 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in jaw			

subjects affected / exposed	1 / 110 (0.91%)	0 / 108 (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	0 / 110 (0.00%)	1 / 108 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhabdomyolysis			
subjects affected / exposed	1 / 110 (0.91%)	0 / 108 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abscess limb			
subjects affected / exposed	0 / 110 (0.00%)	1 / 108 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Alpha haemolytic streptococcal infection			
subjects affected / exposed	1 / 110 (0.91%)	0 / 108 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			
subjects affected / exposed	0 / 110 (0.00%)	1 / 108 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Bronchitis			
subjects affected / exposed	1 / 110 (0.91%)	1 / 108 (0.93%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopulmonary aspergillosis			
subjects affected / exposed	1 / 110 (0.91%)	0 / 108 (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	1 / 110 (0.91%)	4 / 108 (3.70%)	
occurrences causally related to treatment / all	0 / 1	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	1 / 110 (0.91%)	0 / 108 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epididymitis			
subjects affected / exposed	1 / 110 (0.91%)	0 / 108 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fungal oesophagitis			
subjects affected / exposed	0 / 110 (0.00%)	1 / 108 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes simplex			
subjects affected / exposed	0 / 110 (0.00%)	1 / 108 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 110 (0.91%)	1 / 108 (0.93%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster disseminated			
subjects affected / exposed	1 / 110 (0.91%)	0 / 108 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	3 / 110 (2.73%)	1 / 108 (0.93%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Listeriosis			

subjects affected / exposed	0 / 110 (0.00%)	1 / 108 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	1 / 110 (0.91%)	0 / 108 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	3 / 110 (2.73%)	1 / 108 (0.93%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucosal infection			
subjects affected / exposed	0 / 110 (0.00%)	1 / 108 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic sepsis			
subjects affected / exposed	2 / 110 (1.82%)	0 / 108 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oral herpes			
subjects affected / exposed	1 / 110 (0.91%)	0 / 108 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumocystis jirovecii pneumonia			
subjects affected / exposed	4 / 110 (3.64%)	1 / 108 (0.93%)	
occurrences causally related to treatment / all	2 / 4	0 / 1	
deaths causally related to treatment / all	1 / 1	0 / 0	
Pneumonia			
subjects affected / exposed	13 / 110 (11.82%)	10 / 108 (9.26%)	
occurrences causally related to treatment / all	4 / 15	1 / 11	
deaths causally related to treatment / all	0 / 0	0 / 2	
Pneumonia fungal			

subjects affected / exposed	2 / 110 (1.82%)	0 / 108 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Pneumonia legionella			
subjects affected / exposed	0 / 110 (0.00%)	1 / 108 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia pseudomonal			
subjects affected / exposed	1 / 110 (0.91%)	0 / 108 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	0 / 110 (0.00%)	1 / 108 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	7 / 110 (6.36%)	3 / 108 (2.78%)	
occurrences causally related to treatment / all	1 / 7	1 / 3	
deaths causally related to treatment / all	0 / 1	0 / 2	
Sepsis syndrome			
subjects affected / exposed	2 / 110 (1.82%)	0 / 108 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	0 / 110 (0.00%)	2 / 108 (1.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Soft tissue infection			
subjects affected / exposed	0 / 110 (0.00%)	1 / 108 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stenotrophomonas infection			

subjects affected / exposed	1 / 110 (0.91%)	0 / 108 (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 / 110 (0.91%)	0 / 108 (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	1 / 110 (0.91%)	1 / 108 (0.93%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	1 / 110 (0.91%)	2 / 108 (1.85%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	3 / 110 (2.73%)	0 / 108 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia			
subjects affected / exposed	2 / 110 (1.82%)	2 / 108 (1.85%)	
occurrences causally related to treatment / all	1 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	0 / 110 (0.00%)	1 / 108 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour lysis syndrome			
subjects affected / exposed	1 / 110 (0.91%)	1 / 108 (0.93%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypomagnesaemia			

subjects affected / exposed	1 / 110 (0.91%)	0 / 108 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	1 / 110 (0.91%)	0 / 108 (0.00%)	
occurrences causally related to treatment / all	1 / 1	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	Idelalisib + rituximab	Placebo + rituximab	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	103 / 110 (93.64%)	102 / 108 (94.44%)	
Vascular disorders			
Hypotension			
subjects affected / exposed	4 / 110 (3.64%)	7 / 108 (6.48%)	
occurrences (all)	4	7	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	8 / 110 (7.27%)	8 / 108 (7.41%)	
occurrences (all)	8	9	
Chills			
subjects affected / exposed	27 / 110 (24.55%)	16 / 108 (14.81%)	
occurrences (all)	33	20	
Fatigue			
subjects affected / exposed	34 / 110 (30.91%)	35 / 108 (32.41%)	
occurrences (all)	38	39	
Oedema peripheral			
subjects affected / exposed	12 / 110 (10.91%)	10 / 108 (9.26%)	
occurrences (all)	14	11	
Pyrexia			
subjects affected / exposed	40 / 110 (36.36%)	18 / 108 (16.67%)	
occurrences (all)	59	22	
Pain			

subjects affected / exposed	8 / 110 (7.27%)	1 / 108 (0.93%)	
occurrences (all)	8	1	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	27 / 110 (24.55%)	34 / 108 (31.48%)	
occurrences (all)	28	35	
Dyspnoea			
subjects affected / exposed	17 / 110 (15.45%)	22 / 108 (20.37%)	
occurrences (all)	21	26	
Nasal congestion			
subjects affected / exposed	6 / 110 (5.45%)	4 / 108 (3.70%)	
occurrences (all)	6	4	
Oropharyngeal pain			
subjects affected / exposed	6 / 110 (5.45%)	6 / 108 (5.56%)	
occurrences (all)	7	6	
Productive cough			
subjects affected / exposed	6 / 110 (5.45%)	4 / 108 (3.70%)	
occurrences (all)	7	4	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	3 / 110 (2.73%)	7 / 108 (6.48%)	
occurrences (all)	3	7	
Insomnia			
subjects affected / exposed	10 / 110 (9.09%)	7 / 108 (6.48%)	
occurrences (all)	10	7	
Investigations			
Weight decreased			
subjects affected / exposed	11 / 110 (10.00%)	9 / 108 (8.33%)	
occurrences (all)	12	9	
Aspartate aminotransferase increased			
subjects affected / exposed	8 / 110 (7.27%)	0 / 108 (0.00%)	
occurrences (all)	13	0	
Alanine aminotransferase increased			
subjects affected / exposed	8 / 110 (7.27%)	0 / 108 (0.00%)	
occurrences (all)	11	0	
Injury, poisoning and procedural			

complications			
Infusion related reaction			
subjects affected / exposed	21 / 110 (19.09%)	33 / 108 (30.56%)	
occurrences (all)	32	63	
Nervous system disorders			
Headache			
subjects affected / exposed	11 / 110 (10.00%)	9 / 108 (8.33%)	
occurrences (all)	12	11	
Dizziness			
subjects affected / exposed	7 / 110 (6.36%)	9 / 108 (8.33%)	
occurrences (all)	9	10	
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	8 / 110 (7.27%)	4 / 108 (3.70%)	
occurrences (all)	11	4	
Neutropenia			
subjects affected / exposed	28 / 110 (25.45%)	21 / 108 (19.44%)	
occurrences (all)	53	25	
Anaemia			
subjects affected / exposed	13 / 110 (11.82%)	11 / 108 (10.19%)	
occurrences (all)	14	13	
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	2 / 110 (1.82%)	6 / 108 (5.56%)	
occurrences (all)	2	6	
Abdominal pain			
subjects affected / exposed	9 / 110 (8.18%)	11 / 108 (10.19%)	
occurrences (all)	10	11	
Abdominal pain upper			
subjects affected / exposed	8 / 110 (7.27%)	3 / 108 (2.78%)	
occurrences (all)	9	3	
Colitis			
subjects affected / exposed	6 / 110 (5.45%)	1 / 108 (0.93%)	
occurrences (all)	6	1	
Constipation			
subjects affected / exposed	16 / 110 (14.55%)	15 / 108 (13.89%)	
occurrences (all)	17	15	

Diarrhoea			
subjects affected / exposed	31 / 110 (28.18%)	19 / 108 (17.59%)	
occurrences (all)	59	24	
Gastrooesophageal reflux disease			
subjects affected / exposed	11 / 110 (10.00%)	0 / 108 (0.00%)	
occurrences (all)	11	0	
Stomatitis			
subjects affected / exposed	7 / 110 (6.36%)	1 / 108 (0.93%)	
occurrences (all)	7	1	
Nausea			
subjects affected / exposed	30 / 110 (27.27%)	25 / 108 (23.15%)	
occurrences (all)	35	32	
Vomiting			
subjects affected / exposed	16 / 110 (14.55%)	9 / 108 (8.33%)	
occurrences (all)	17	9	
Skin and subcutaneous tissue disorders			
Night sweats			
subjects affected / exposed	12 / 110 (10.91%)	13 / 108 (12.04%)	
occurrences (all)	13	13	
Pruritus			
subjects affected / exposed	6 / 110 (5.45%)	5 / 108 (4.63%)	
occurrences (all)	6	6	
Skin lesion			
subjects affected / exposed	3 / 110 (2.73%)	7 / 108 (6.48%)	
occurrences (all)	3	8	
Rash			
subjects affected / exposed	16 / 110 (14.55%)	4 / 108 (3.70%)	
occurrences (all)	19	9	
Musculoskeletal and connective tissue disorders			
Muscle spasms			
subjects affected / exposed	8 / 110 (7.27%)	7 / 108 (6.48%)	
occurrences (all)	9	8	
Back pain			
subjects affected / exposed	6 / 110 (5.45%)	4 / 108 (3.70%)	
occurrences (all)	6	4	
Arthralgia			

subjects affected / exposed	9 / 110 (8.18%)	4 / 108 (3.70%)	
occurrences (all)	18	4	
Infections and infestations			
Bronchitis			
subjects affected / exposed	7 / 110 (6.36%)	4 / 108 (3.70%)	
occurrences (all)	9	4	
Sinusitis			
subjects affected / exposed	9 / 110 (8.18%)	6 / 108 (5.56%)	
occurrences (all)	11	7	
Pneumonia			
subjects affected / exposed	4 / 110 (3.64%)	6 / 108 (5.56%)	
occurrences (all)	4	7	
Cellulitis			
subjects affected / exposed	7 / 110 (6.36%)	2 / 108 (1.85%)	
occurrences (all)	7	2	
Upper respiratory tract infection			
subjects affected / exposed	9 / 110 (8.18%)	13 / 108 (12.04%)	
occurrences (all)	12	13	
Urinary tract infection			
subjects affected / exposed	8 / 110 (7.27%)	4 / 108 (3.70%)	
occurrences (all)	9	4	
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	8 / 110 (7.27%)	6 / 108 (5.56%)	
occurrences (all)	10	6	
Decreased appetite			
subjects affected / exposed	18 / 110 (16.36%)	12 / 108 (11.11%)	
occurrences (all)	18	12	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 January 2012	Increased number of study centers from 50 to 70; clarified the definition of CLL that warranted treatment; extended the screening period to 6 weeks in subjects for whom there was a delay in the analysis of stratification variables.
19 December 2012	Updated information regarding secondary and tertiary endpoints; clarified that the independent review committee (IRC) findings would be considered primary for analyses of PFS and other disease control endpoints.
21 June 2013	Increased planned sample size from 160 to 200 subjects in order to maintain the planned study duration.
10 September 2013	Updated figure of study scheme to add open-label extension to Study GS-US-312-0117 should the primary study be stopped early due to overwhelming efficacy.
16 December 2013	Added monitoring guidelines for subjects who are Hepatitis B core antibody positive at screening based on new recommendations and rituximab FDA black box warning ie, subjects who were HBc antibody positive at screening were monitored for hepatitis B virus (HBV) reactivation (manifested as detectable HBV DNA by quantitative PCR). Participants were tested monthly for the duration of rituximab therapy and every 3 months thereafter for 1 year from the end of therapy.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Following a recommendation by an independent Data Monitoring Committee (DMC), the study was stopped early due to highly statistically significant results in the experimental arm for the primary efficacy endpoint of progression-free survival.

Notes: