



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 Indolent Non-Hodgkin Lymphomas

Summary

EudraCT number	2012-004013-13
Trial protocol	DE GB SE ES HU CZ IT PT
Global end of trial date	18 May 2016

Results information

Result version number	v2 (current)
This version publication date	18 May 2019
First version publication date	15 April 2017
Version creation reason	<ul style="list-style-type: none">• Correction of full data set Adding text to "Limitations and Caveats" section

Trial information

Trial identification

Sponsor protocol code	GS-US-313-0124
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01732913
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 Trials Mailbox, Gilead Sciences International Ltd, ClinicalTrialDisclosures@gilead.com
Scientific contact	Clinical Trials 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	18 May 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	18 May 2016
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to evaluate the effect of the addition of idelalisib to rituximab on progression-free survival (PFS) in adults with previously treated indolent non-Hodgkin lymphoma (iNHL).

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	16 January 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 12
Country: Number of subjects enrolled	Portugal: 4
Country: Number of subjects enrolled	Romania: 1
Country: Number of subjects enrolled	Spain: 6
Country: Number of subjects enrolled	Sweden: 8
Country: Number of subjects enrolled	United Kingdom: 4
Country: Number of subjects enrolled	Czech Republic: 2
Country: Number of subjects enrolled	France: 42
Country: Number of subjects enrolled	Germany: 2
Country: Number of subjects enrolled	Hungary: 30
Country: Number of subjects enrolled	Italy: 11
Country: Number of subjects enrolled	Russian Federation: 9
Country: Number of subjects enrolled	Singapore: 9
Country: Number of subjects enrolled	United States: 99
Country: Number of subjects enrolled	Japan: 32

Country: Number of subjects enrolled	Taiwan: 2
Country: Number of subjects enrolled	Australia: 13
Country: Number of subjects enrolled	Israel: 3
Country: Number of subjects enrolled	Korea, Republic of: 6
Worldwide total number of subjects	295
EEA total number of subjects	122

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)	129
From 65 to 84 years	156
85 years and over	10

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled at study sites in the North America, Europe, and Asia Pacific. The first participant was screened on 16 January 2013. The last study visit occurred on 18 May 2016.

Pre-assignment

Screening details:

385 participants were screened.

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	Subject, Investigator, Carer

Arms

Are arms mutually exclusive?	Yes
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Arm title	Idelalisib + Rituximab
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Arm description:

Idelalisib (Zydelig®) 150 mg tablet orally twice daily + rituximab 375 mg/m² intravenously starting on Day 1 for a total of 8 infusions

Arm type	Experimental
Investigational medicinal product name	Idelalisib
Investigational medicinal product code	
Other name	Zydelig®, GS-1101, CAL-101
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

150 mg administered 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:

Single use vials administered at a dose of 375 mg/m² starting on Day 1 for a total of 8 infusions.

Arm title	Placebo + Rituximab
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Arm description:

Placebo tablet orally twice daily + rituximab 375 mg/m² intravenously starting on Day 1 for a total of 8 infusions

Arm type	Experimental
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Administered 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:

Single use vials administered at a dose of 375 mg/m² starting on Day 1 for a total of 8 infusions.

Number of subjects in period 1	Idelalisib + Rituximab	Placebo + Rituximab
Started	198	97
Completed	42	28
Not completed	156	69
Physician decision	14	7
Initiation of Other Anti-Cancer Therapy	3	2
Other Reason	7	1
Withdrawal by Subject	27	4
Study Terminated by Sponsor	105	55

Baseline characteristics

Reporting groups

Reporting group title	Idelalisib + Rituximab
Reporting group description: Idelalisib (Zydelig®) 150 mg tablet orally twice daily + rituximab 375 mg/m ² intravenously starting on Day 1 for a total of 8 infusions	
Reporting group title	Placebo + Rituximab
Reporting group description: Placebo tablet orally twice daily + rituximab 375 mg/m ² intravenously starting on Day 1 for a total of 8 infusions	

Reporting group values	Idelalisib + Rituximab	Placebo + Rituximab	Total
Number of subjects	198	97	295
Age categorical			
Units: Subjects			

Age continuous			
Units: years			
arithmetic mean	64	67	
standard deviation	± 11.4	± 11.4	-
Gender categorical			
Units: Subjects			
Female	99	48	147
Male	99	49	148
Race			
Units: Subjects			
Asian	35	17	52
Black or African American	5	4	9
White	123	54	177
Other	3	3	6
Not Permitted	32	19	51
Ethnicity			
Units: Subjects			
Hispanic or Latino	12	3	15
Not Hispanic or Latino	150	75	225
Unknown or Not Reported	36	19	55

End points

End points reporting groups

Reporting group title	Idelalisib + Rituximab
Reporting group description:	
Idelalisib (Zydelig®) 150 mg tablet orally twice daily + rituximab 375 mg/m ² intravenously starting on Day 1 for a total of 8 infusions	
Reporting group title	Placebo + Rituximab
Reporting group description:	
Placebo tablet orally twice daily + rituximab 375 mg/m ² intravenously starting on Day 1 for a total of 8 infusions	

Primary: Progression Free Survival

End point title	Progression Free Survival ^[1]
End point description:	
Progression-free survival (PFS) is defined as the interval from randomization to the earlier of the first documentation of definitive iNHL disease progression or death from any cause. PFS was to be assessed by an independent review committee (IRC). Due to the early termination of the study, efficacy data were not available for all participants, and therefore the prespecified analyses were not conducted.	
End point type	Primary
End point timeframe:	
Not applicable	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Due to the early termination of the study, efficacy data were not available for all participants, and therefore the prespecified analyses were not conducted.

End point values	Idelalisib + Rituximab	Placebo + Rituximab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0 ^[2]	0 ^[3]		
Units: Not applicable				

Notes:

[2] - Analysis was not performed due to early study termination.

[3] - Analysis was not performed due to early study termination.

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Response Rate

End point title	Overall Response Rate
End point description:	
Overall Response Rate (ORR) is defined as the proportion of participants who achieve a complete response or partial response (or very good partial response or minor response for participants with Waldenström's). ORR was to be assessed by an IRC. Due to the early termination of the study, efficacy data were not available for all participants, and therefore the prespecified analyses were not conducted.	
End point type	Secondary
End point timeframe:	
Not applicable	

End point values	Idelalisib + Rituximab	Placebo + Rituximab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0 ^[4]	0 ^[5]		
Units: Not applicable				

Notes:

[4] - Analysis was not performed due to early study termination.

[5] - Analysis was not performed due to early study termination.

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 is defined as the proportion of participants who achieve $\geq 50\%$ decrease from baseline in the sum of the products of the greatest perpendicular diameters of index lesions. Lymph node response rate was to be assessed by an IRC. Due to the early termination of the study, efficacy data were not available for all participants, and therefore the prespecified analyses were not conducted.	
End point type	Secondary
End point timeframe:	
Not applicable	

End point values	Idelalisib + Rituximab	Placebo + Rituximab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0 ^[6]	0 ^[7]		
Units: Not applicable				

Notes:

[6] - Analysis was not performed due to early study termination.

[7] - Analysis was not performed due to early study termination.

Statistical analyses

No statistical analyses for this end point

Secondary: Complete Response Rate

End point title	Complete Response Rate
End point description:	
Complete response rate is defined as the proportion of participants who achieve a complete response. Complete response rate was to be assessed by an IRC. Due to the early termination of the study, efficacy data were not available for all participants, and therefore the prespecified analyses were not conducted.	
End point type	Secondary
End point timeframe:	
Not applicable	

End point values	Idelalisib + Rituximab	Placebo + Rituximab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0 ^[8]	0 ^[9]		
Units: Not applicable				

Notes:

[8] - Analysis was not performed due to early study termination.

[9] - Analysis was not performed due to early study termination.

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival

End point title	Overall Survival
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End point description:

Overall survival is defined as the interval from randomization to death from any cause. Due to the early termination of the study, efficacy data were not mature for all participants, and therefore the prespecified analyses were not conducted.

End point type	Secondary
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End point timeframe:

Not applicable

End point values	Idelalisib + Rituximab	Placebo + Rituximab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0 ^[10]	0 ^[11]		
Units: Not applicable				

Notes:

[10] - Analysis was not performed due to early study termination.

[11] - Analysis was not performed due to early study termination.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 27 months plus 30 days

Adverse event reporting additional description:

Safety Analysis Set included all participants who took at least 1 dose of study drug.

NOTE: Serious adverse events and deaths causally related to "treatment" refers to events deemed related to idelalisib/placebo/rituximab treatment per investigator assessment.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	19.0
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Reporting groups

Reporting group title	Idelalisib + rituximab
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Reporting group description:

Idelalisib 150 mg tablet orally twice daily + rituximab 375 mg/m² intravenously starting on Day 1 for a total of 8 infusions

Reporting group title	Placebo + rituximab
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Reporting group description:

Placebo tablet orally twice daily + rituximab 375 mg/m² intravenously starting on Day 1 for a total of 8 infusions

Serious adverse events	Idelalisib + rituximab	Placebo + rituximab	
Total subjects affected by serious adverse events			
subjects affected / exposed	103 / 198 (52.02%)	11 / 95 (11.58%)	
number of deaths (all causes)	11	2	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer recurrent			
subjects affected / exposed	0 / 198 (0.00%)	1 / 95 (1.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Glioblastoma			
subjects affected / exposed	1 / 198 (0.51%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			

subjects affected / exposed	2 / 198 (1.01%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	1 / 198 (0.51%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Fatigue			
subjects affected / exposed	1 / 198 (0.51%)	1 / 95 (1.05%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gait disturbance			
subjects affected / exposed	1 / 198 (0.51%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema			
subjects affected / exposed	1 / 198 (0.51%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	9 / 198 (4.55%)	1 / 95 (1.05%)	
occurrences causally related to treatment / all	2 / 9	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 198 (0.51%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Bronchitis chronic			
subjects affected / exposed	1 / 198 (0.51%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Chronic obstructive pulmonary disease			
subjects affected / exposed	2 / 198 (1.01%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cough			
subjects affected / exposed	1 / 198 (0.51%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	3 / 198 (1.52%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Dyspnoea exertional			
subjects affected / exposed	1 / 198 (0.51%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	2 / 198 (1.01%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial lung disease			
subjects affected / exposed	1 / 198 (0.51%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung disorder			
subjects affected / exposed	2 / 198 (1.01%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	8 / 198 (4.04%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	7 / 8	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			

subjects affected / exposed	3 / 198 (1.52%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory failure			
subjects affected / exposed	1 / 198 (0.51%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 198 (0.51%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Major depression			
subjects affected / exposed	1 / 198 (0.51%)	0 / 95 (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	2 / 198 (1.01%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicidal ideation			
subjects affected / exposed	1 / 198 (0.51%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	11 / 198 (5.56%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	11 / 11	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	10 / 198 (5.05%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	10 / 10	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 198 (0.00%)	1 / 95 (1.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood creatinine increased			
subjects affected / exposed	1 / 198 (0.51%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood lactate dehydrogenase increased			
subjects affected / exposed	1 / 198 (0.51%)	0 / 95 (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 / 198 (0.51%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Clavicle fracture			
subjects affected / exposed	1 / 198 (0.51%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	1 / 198 (0.51%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infusion related reaction			
subjects affected / exposed	1 / 198 (0.51%)	2 / 95 (2.11%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laceration			
subjects affected / exposed	1 / 198 (0.51%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Rib fracture			
subjects affected / exposed	1 / 198 (0.51%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal compression fracture			
subjects affected / exposed	1 / 198 (0.51%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haematoma			
subjects affected / exposed	1 / 198 (0.51%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haemorrhage			
subjects affected / exposed	1 / 198 (0.51%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper limb fracture			
subjects affected / exposed	0 / 198 (0.00%)	1 / 95 (1.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	1 / 198 (0.51%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	1 / 198 (0.51%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			
subjects affected / exposed	0 / 198 (0.00%)	1 / 95 (1.05%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			

subjects affected / exposed	1 / 198 (0.51%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	1 / 198 (0.51%)	2 / 95 (2.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericarditis			
subjects affected / exposed	1 / 198 (0.51%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia			
subjects affected / exposed	1 / 198 (0.51%)	0 / 95 (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			
Cerebrovascular accident			
subjects affected / exposed	2 / 198 (1.01%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	2 / 198 (1.01%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	3 / 198 (1.52%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	3 / 198 (1.52%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			

Anaemia			
subjects affected / exposed	1 / 198 (0.51%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	7 / 198 (3.54%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	5 / 7	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Leukopenia			
subjects affected / exposed	1 / 198 (0.51%)	0 / 95 (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 / 198 (1.52%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	3 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	1 / 198 (0.51%)	1 / 95 (1.05%)	
occurrences causally related to treatment / all	0 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 198 (0.51%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	8 / 198 (4.04%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	8 / 9	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis ulcerative			
subjects affected / exposed	1 / 198 (0.51%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			

subjects affected / exposed	1 / 198 (0.51%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	18 / 198 (9.09%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	21 / 23	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteritis			
subjects affected / exposed	1 / 198 (0.51%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis			
subjects affected / exposed	1 / 198 (0.51%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incarcerated inguinal hernia			
subjects affected / exposed	1 / 198 (0.51%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	0 / 198 (0.00%)	1 / 95 (1.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	1 / 198 (0.51%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	1 / 198 (0.51%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Salivary gland disorder			

subjects affected / exposed	0 / 198 (0.00%)	1 / 95 (1.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			
subjects affected / exposed	1 / 198 (0.51%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	3 / 198 (1.52%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Salivary gland enlargement			
subjects affected / exposed	0 / 198 (0.00%)	1 / 95 (1.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	1 / 198 (0.51%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug-induced liver injury			
subjects affected / exposed	3 / 198 (1.52%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	5 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic failure			
subjects affected / exposed	1 / 198 (0.51%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Hepatic function abnormal			
subjects affected / exposed	2 / 198 (1.01%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaundice			

subjects affected / exposed	2 / 198 (1.01%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Psoriasis			
subjects affected / exposed	2 / 198 (1.01%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash			
subjects affected / exposed	4 / 198 (2.02%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	3 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	5 / 198 (2.53%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	1 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
subjects affected / exposed	1 / 198 (0.51%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	1 / 198 (0.51%)	0 / 95 (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 / 198 (0.51%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bronchitis			

subjects affected / exposed	1 / 198 (0.51%)	0 / 95 (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 / 198 (0.51%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	1 / 198 (0.51%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus infection			
subjects affected / exposed	2 / 198 (1.01%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eczema herpeticum			
subjects affected / exposed	1 / 198 (0.51%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fungaemia			
subjects affected / exposed	1 / 198 (0.51%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 198 (0.51%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster meningomyelitis			
subjects affected / exposed	1 / 198 (0.51%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			

subjects affected / exposed	1 / 198 (0.51%)	1 / 95 (1.05%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infective exacerbation of chronic obstructive airways disease			
subjects affected / exposed	1 / 198 (0.51%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	0 / 198 (0.00%)	1 / 95 (1.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metapneumovirus infection			
subjects affected / exposed	0 / 198 (0.00%)	1 / 95 (1.05%)	
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	1 / 198 (0.51%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Otitis externa			
subjects affected / exposed	1 / 198 (0.51%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumocystis jirovecii pneumonia			
subjects affected / exposed	1 / 198 (0.51%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	19 / 198 (9.60%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	10 / 22	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Sepsis			

subjects affected / exposed	5 / 198 (2.53%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	2 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	1 / 198 (0.51%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin bacterial infection			
subjects affected / exposed	1 / 198 (0.51%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal bacteraemia			
subjects affected / exposed	1 / 198 (0.51%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	2 / 198 (1.01%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	4 / 198 (2.02%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Cachexia			
subjects affected / exposed	1 / 198 (0.51%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Dehydration			
subjects affected / exposed	4 / 198 (2.02%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	3 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia			

subjects affected / exposed	1 / 198 (0.51%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	1 / 198 (0.51%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	1 / 198 (0.51%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	2 / 198 (1.01%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	2 / 198 (1.01%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Idelalisib + rituximab	Placebo + rituximab	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	189 / 198 (95.45%)	83 / 95 (87.37%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	12 / 198 (6.06%)	2 / 95 (2.11%)	
occurrences (all)	14	2	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	15 / 198 (7.58%)	9 / 95 (9.47%)	
occurrences (all)	17	11	
Chills			

subjects affected / exposed	11 / 198 (5.56%)	4 / 95 (4.21%)	
occurrences (all)	16	4	
Fatigue			
subjects affected / exposed	41 / 198 (20.71%)	20 / 95 (21.05%)	
occurrences (all)	47	21	
Oedema peripheral			
subjects affected / exposed	14 / 198 (7.07%)	5 / 95 (5.26%)	
occurrences (all)	15	5	
Pyrexia			
subjects affected / exposed	50 / 198 (25.25%)	11 / 95 (11.58%)	
occurrences (all)	67	12	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	28 / 198 (14.14%)	14 / 95 (14.74%)	
occurrences (all)	29	16	
Dyspnoea			
subjects affected / exposed	12 / 198 (6.06%)	2 / 95 (2.11%)	
occurrences (all)	13	2	
Oropharyngeal pain			
subjects affected / exposed	12 / 198 (6.06%)	3 / 95 (3.16%)	
occurrences (all)	15	3	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	10 / 198 (5.05%)	3 / 95 (3.16%)	
occurrences (all)	10	3	
Insomnia			
subjects affected / exposed	21 / 198 (10.61%)	11 / 95 (11.58%)	
occurrences (all)	25	12	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	65 / 198 (32.83%)	0 / 95 (0.00%)	
occurrences (all)	90	0	
Aspartate aminotransferase increased			
subjects affected / exposed	56 / 198 (28.28%)	0 / 95 (0.00%)	
occurrences (all)	72	0	
Gamma-glutamyltransferase			

increased			
subjects affected / exposed	11 / 198 (5.56%)	1 / 95 (1.05%)	
occurrences (all)	11	1	
Transaminases increased			
subjects affected / exposed	12 / 198 (6.06%)	1 / 95 (1.05%)	
occurrences (all)	17	1	
Weight decreased			
subjects affected / exposed	20 / 198 (10.10%)	1 / 95 (1.05%)	
occurrences (all)	20	2	
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	36 / 198 (18.18%)	20 / 95 (21.05%)	
occurrences (all)	42	27	
Nervous system disorders			
Dizziness			
subjects affected / exposed	12 / 198 (6.06%)	6 / 95 (6.32%)	
occurrences (all)	15	6	
Headache			
subjects affected / exposed	30 / 198 (15.15%)	12 / 95 (12.63%)	
occurrences (all)	42	15	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	12 / 198 (6.06%)	6 / 95 (6.32%)	
occurrences (all)	14	12	
Neutropenia			
subjects affected / exposed	25 / 198 (12.63%)	5 / 95 (5.26%)	
occurrences (all)	49	7	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	20 / 198 (10.10%)	4 / 95 (4.21%)	
occurrences (all)	24	5	
Constipation			
subjects affected / exposed	28 / 198 (14.14%)	13 / 95 (13.68%)	
occurrences (all)	30	14	
Diarrhoea			

subjects affected / exposed	88 / 198 (44.44%)	18 / 95 (18.95%)	
occurrences (all)	133	26	
Gastroesophageal reflux disease			
subjects affected / exposed	10 / 198 (5.05%)	3 / 95 (3.16%)	
occurrences (all)	10	3	
Nausea			
subjects affected / exposed	50 / 198 (25.25%)	12 / 95 (12.63%)	
occurrences (all)	65	14	
Vomiting			
subjects affected / exposed	29 / 198 (14.65%)	7 / 95 (7.37%)	
occurrences (all)	33	10	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	25 / 198 (12.63%)	4 / 95 (4.21%)	
occurrences (all)	29	4	
Rash			
subjects affected / exposed	38 / 198 (19.19%)	12 / 95 (12.63%)	
occurrences (all)	42	16	
Rash maculo-papular			
subjects affected / exposed	16 / 198 (8.08%)	2 / 95 (2.11%)	
occurrences (all)	19	3	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	9 / 198 (4.55%)	6 / 95 (6.32%)	
occurrences (all)	12	6	
Back pain			
subjects affected / exposed	9 / 198 (4.55%)	6 / 95 (6.32%)	
occurrences (all)	10	7	
Pain in extremity			
subjects affected / exposed	16 / 198 (8.08%)	3 / 95 (3.16%)	
occurrences (all)	17	3	
Infections and infestations			
Bronchitis			
subjects affected / exposed	9 / 198 (4.55%)	6 / 95 (6.32%)	
occurrences (all)	10	8	
Nasopharyngitis			

subjects affected / exposed occurrences (all)	10 / 198 (5.05%) 12	6 / 95 (6.32%) 9	
Upper respiratory tract infection subjects affected / exposed occurrences (all)	23 / 198 (11.62%) 30	8 / 95 (8.42%) 9	
Urinary tract infection subjects affected / exposed occurrences (all)	13 / 198 (6.57%) 15	3 / 95 (3.16%) 4	
Metabolism and nutrition disorders			
Decreased appetite subjects affected / exposed occurrences (all)	26 / 198 (13.13%) 27	2 / 95 (2.11%) 2	
Dehydration subjects affected / exposed occurrences (all)	11 / 198 (5.56%) 12	0 / 95 (0.00%) 0	
Hypokalaemia subjects affected / exposed occurrences (all)	21 / 198 (10.61%) 22	4 / 95 (4.21%) 4	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 January 2013	<ul style="list-style-type: none">• Updated information regarding secondary and tertiary endpoints• Updated inclusion criteria relating to contraception to comply with the European Union (EU) health authority• Clarified that the IRC findings were primary for analyses of PFS and other tumor control endpoints• Updated plan to control Type I error rate for secondary endpoints• Increased washout period for previous cancer therapies from 3 to 6 weeks• Provided clarification on phototoxicity risk• Clarified duration of therapy for each study treatment group• Clarified that subjects in Groups A and B who prematurely discontinued 1 study drug could continue other study drug• Updated safety and clinical information in alignment with Version 7 of the Investigator's Brochure (IB)• Added new section to differentiate discontinuation from study versus discontinuation of study drug• Clarified language around dose modifications that are made for adverse events (AEs) or laboratory abnormalities that the investigator considered related to study drug• Changed the criteria for splenomegaly with a splenic longest vertical dimension from 10 cm to 12 cm based on expert radiology recommendations
17 September 2013	Revised text to add 1 additional formal interim efficacy analysis after ~50% of the expected number of PFS events have occurred and changed the 2nd interim analysis from 66% of the planned events occurring to 75%
22 October 2013	Added monitoring guidelines for Hep B reactivation
29 July 2014	Added a double-blind extension to allow eligible subjects to receive idelalisib monotherapy at the time of iNHL disease progression
31 October 2014	<ul style="list-style-type: none">• Updated the following information to align with investigator's brochure Edition 11.<ul style="list-style-type: none">- Guidance to investigators for evaluation, intervention, and drug interruption/discontinuation for specific adverse events.- Information regarding the interaction of idelalisib with CYP3A inhibitors, inducers, and substrates.
31 July 2015	Added an open-label extension to permit subjects randomized to Group B (Placebo + Rituximab) the opportunity to receive open-label IDL150 mg twice daily

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
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11 March 2016	An increased rate of deaths and serious adverse events (SAEs) among participants with front-line chronic lymphocytic leukemia (CLL) and early-line iNHL treated with idelalisib in combination with standard therapies was observed by the independent data monitoring committee (DMC) during regular review of 3 Gilead Phase 3 studies. Gilead reviewed the unblinded data and terminated this study in agreement with the DMC recommendation and in consultation with the US Food and Drug Administration (FDA). Due to the early termination of the study, efficacy data were not available for all participants, and therefore the prespecified analyses were not conducted.	-
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Notes:

Limitations and caveats

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

An unplanned review of unblinded clinical trial data was performed in this study that was not prospectively specified in the protocol. There was no impact on the overall integrity or conclusions of the study.

Notes: