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

Summary

EudraCT number	2012-001236-65
Trial protocol	BE IE GB SE ES DK FR
Global end of trial date	15 August 2018

Results information

Result version number	v1 (current)
This version publication date	21 August 2019
First version publication date	21 August 2019

Trial information

Trial identification

Sponsor protocol code	GS-US-312-0119

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01659021
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	Gilead Clinical Study Information Center, Gilead Sciences, GileadClinicalTrials@gilead.com
Scientific contact	Gilead Clinical Study Information Center, Gilead Sciences, GileadClinicalTrials@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	15 August 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 August 2018
Global end of trial reached?	Yes
Global end of trial date	15 August 2018
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 ofatumumab on progression-free survival (PFS) in participants with previously treated chronic lymphocytic leukemia (CLL).

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	04 December 2012
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	5 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 36
Country: Number of subjects enrolled	Spain: 13
Country: Number of subjects enrolled	Sweden: 6
Country: Number of subjects enrolled	United Kingdom: 17
Country: Number of subjects enrolled	Belgium: 6
Country: Number of subjects enrolled	Denmark: 4
Country: Number of subjects enrolled	France: 24
Country: Number of subjects enrolled	Ireland: 11
Country: Number of subjects enrolled	United States: 93
Country: Number of subjects enrolled	Australia: 29
Country: Number of subjects enrolled	Canada: 22

Worldwide total number of subjects	261
EEA total number of subjects	117

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)	94
From 65 to 84 years	166
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled at study sites in North America, Europe, and Australia. The first participant was screened on 04 December 2012. The last study visit occurred on 15 August 2018.

Pre-assignment

Screening details:

310 participants were screened.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Idelalisib+Ofatumumab

Arm description:

Randomized Initial Therapy (24 weeks): Idelalisib 150 mg tablets twice daily + ofatumumab for a total of 12 infusions (300 mg on Day 1, followed by 1000 mg weekly for 7 weeks, and then 1000 mg every 4 weeks for 4 doses);

Continuing Therapy/Observation: Idelalisib 150 mg tablets twice daily until the earliest of subject withdrawal from study, definitive progression of CLL, intolerable idelalisib-related toxicity, pregnancy or initiation of breast feeding, substantial noncompliance with study procedures, or study discontinuation.

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

Dosage and administration details:

150 mg administered twice daily

Investigational medicinal product name	Ofatumumab
Investigational medicinal product code	
Other name	Arzerra®
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Total of 12 infusions (300 mg on Day 1, followed by 2000 mg weekly for 7 weeks, and then 2000 mg every 4 weeks for 4 doses)

Arm title	Ofatumumab

Arm description:

Randomized Initial Therapy (24 weeks): Ofatumumab for a total of 12 infusions (300 mg on Day 1, followed by 2000 mg weekly for 7 weeks, and then 2000 mg every 4 weeks for 4 doses);

Continuing Therapy/Observation: Observation until the earliest of subject withdrawal from study, definitive progression of CLL, intolerable idelalisib-related toxicity, pregnancy or initiation of breast feeding, substantial noncompliance with study procedures, or study discontinuation.

Arm type	Active comparator

Investigational medicinal product name	Ofatumumab
Investigational medicinal product code	
Other name	Arzerra®
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Total of 12 infusions (300 mg on Day 1, followed by 2000 mg weekly for 7 weeks, and then 2000 mg every 4 weeks for 4 doses)

Number of subjects in period 1	Idelalisib+Ofatumumab	Ofatumumab
Started	174	87
Randomized and Treated	173	86
Completed: Disease Progression or Death	100	50
Completed	100	50
Not completed	74	37
Physician decision	34	16
Adverse Event	2	3
Unknown Reasons	2	1
Withdrawal by Subject	19	16
Study Terminated by Sponsor	16	1
Lost to follow-up	1	-

Period 2

Period 2 title	Long-Term Follow Up
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

The arms in the LTFU period are mutually exclusive, but due to system restrictions, "No" was entered for this field to allow entry of appropriate data.

Arms

Are arms mutually exclusive?	No
Arm title	Idelalisib+Ofatumumab (LTFU)

Arm description:

Long-Term Follow-up (LTFU): Participants were followed for up to 5 years. Information on medical status, anti-tumor treatments, secondary malignancies, and survival status were collected annually during a routine clinic visit or other contact, such as telephone.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	Ofatumumab (LTFU)

Arm description:
LTFU: Participants were followed for up to 5 years. Information on medical status, anti-tumor treatments, secondary malignancies, and survival status were collected annually during a routine clinic visit or other contact, such as telephone.

Arm type	No intervention
No investigational medicinal product assigned in this arm	

Number of subjects in period 2	Idelalisib+Ofatumumab (LTFU)	Ofatumumab (LTFU)
Started	138	69
Completed	133	65
Not completed	5	4
Withdrawal by Subject	2	1
Lost to follow-up	3	3

Baseline characteristics

Reporting groups	
Reporting group title	Idelalisib+Ofatumumab

Reporting group description:

Randomized Initial Therapy (24 weeks): Idelalisib 150 mg tablets twice daily + ofatumumab for a total of 12 infusions (300 mg on Day 1, followed by 1000 mg weekly for 7 weeks, and then 1000 mg every 4 weeks for 4 doses);

Continuing Therapy/Observation: Idelalisib 150 mg tablets twice daily until the earliest of subject withdrawal from study, definitive progression of CLL, intolerable idelalisib-related toxicity, pregnancy or initiation of breast feeding, substantial noncompliance with study procedures, or study discontinuation.

Reporting group title	Ofatumumab

Reporting group description:

Randomized Initial Therapy (24 weeks): Ofatumumab for a total of 12 infusions (300 mg on Day 1, followed by 2000 mg weekly for 7 weeks, and then 2000 mg every 4 weeks for 4 doses);

Continuing Therapy/Observation: Observation until the earliest of subject withdrawal from study, definitive progression of CLL, intolerable idelalisib-related toxicity, pregnancy or initiation of breast feeding, substantial noncompliance with study procedures, or study discontinuation.

Reporting group values	Idelalisib+Ofatumumab	Ofatumumab	Total
Number of subjects	174	87	261
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	67	67	
standard deviation	± 9.0	± 9.7	-
Gender categorical Units: Subjects			
Female	50	25	75
Male	124	62	186
Ethnicity Units: Subjects			
Hispanic or Latino	7	3	10
Not Hispanic or Latino	141	74	215
Unknown or Not Reported	26	10	36
Race Units: Subjects			
White	149	71	220
Black or African American	0	4	4
Native Hawaiian or Other Pacific Islander	1	0	1
Asian	2	0	2
Other	2	3	5
Not Permitted	20	9	29
17p deletion and/ or TP53 mutation Units: Subjects			

Either	70	33	103
Neither	104	54	158
Immunoglobulin heavy chain variable region (IGHV) mutation status Units: Subjects			
Mutated	37	19	56
Unmutated	137	68	205
Disease Status			
Refractory: CLL progression < 6 months from completion of prior therapy; Relapsed: CLL progression ≥ 6 months from completion of prior therapy.			
Units: Subjects			
Refractory	82	47	129
Relapsed	92	40	132
Time Since Diagnosis			
Only participants who were randomized and treated are included. Idelalisib+Ofatumumab = 173 participants; Ofatumumab = 86 participants			
Units: months			
arithmetic mean	101.0	94.3	
standard deviation	± 60.21	± 52.51	-

End points

End points reporting groups

Reporting group title	Idelalisib+Ofatumumab

Reporting group description:

Randomized Initial Therapy (24 weeks): Idelalisib 150 mg tablets twice daily + ofatumumab for a total of 12 infusions (300 mg on Day 1, followed by 1000 mg weekly for 7 weeks, and then 1000 mg every 4 weeks for 4 doses);

Continuing Therapy/Observation: Idelalisib 150 mg tablets twice daily until the earliest of subject withdrawal from study, definitive progression of CLL, intolerable idelalisib-related toxicity, pregnancy or initiation of breast feeding, substantial noncompliance with study procedures, or study discontinuation.

Reporting group title	Ofatumumab

Reporting group description:

Randomized Initial Therapy (24 weeks): Ofatumumab for a total of 12 infusions (300 mg on Day 1, followed by 2000 mg weekly for 7 weeks, and then 2000 mg every 4 weeks for 4 doses);

Continuing Therapy/Observation: Observation until the earliest of subject withdrawal from study, definitive progression of CLL, intolerable idelalisib-related toxicity, pregnancy or initiation of breast feeding, substantial noncompliance with study procedures, or study discontinuation.

Reporting group title	Idelalisib+Ofatumumab (LTFU)

Reporting group description:

Long-Term Follow-up (LTFU): Participants were followed for up to 5 years. Information on medical status, anti-tumor treatments, secondary malignancies, and survival status were collected annually during a routine clinic visit or other contact, such as telephone.

Reporting group title	Ofatumumab (LTFU)

Reporting group description:

LTFU: Participants were followed for up to 5 years. Information on medical status, anti-tumor treatments, secondary malignancies, and survival status were collected annually during a routine clinic visit or other contact, such as telephone.

Primary: Progression-Free Survival (PFS)

End point title	Progression-Free Survival (PFS)

End point description:

PFS 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. PFS was analyzed using Kaplan-Meier (KM) estimates. Intent-to-Treat (ITT) Analysis Set included participants who were randomized regardless of whether they received any study drug(s), or received a different regimen from that to which they were randomized. Treatment was according to randomization.

End point type	Primary

End point timeframe:

Randomization to End of Study (up to 60 months)

End point values	Idelalisib+Ofatumumab	Ofatumumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	174	87		
Units: months				
median (confidence interval 95%)	16.6 (13.7 to 19.6)	8.0 (5.7 to 8.4)		

Statistical analyses

Statistical analysis title	Statistical Analysis for Progression-Free Survival
Comparison groups	Idelalisib+Ofatumumab v Ofatumumab
Number of subjects included in analysis	261
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [1]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.26
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.18
upper limit	0.37

Notes:

[1] - P-value: stratified log-rank test, adjusted for randomization stratification factors (17p deletion/TP53 mutation, IGHV mutation, and disease status). Hazard Ratio & 95% CIs: proportional hazard model, 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.

Overall response rate was analyzed using KM estimates. Participants in the ITT Analysis Set were analyzed.

End point type	Secondary

End point timeframe:

Randomization to End of Study (up to 60 months)

End point values	Idelalisib+Ofatumumab	Ofatumumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	174	87		
Units: percentage of participants				
number (confidence interval 95%)	75.3 (68.2 to 81.5)	17.2 (10.0 to 26.8)		

Statistical analyses

Statistical analysis title	Statistical Analysis for Overall Response Rate
Comparison groups	Ofatumumab v Idelalisib+Ofatumumab
Number of subjects included in analysis	261
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [2]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	16.85
Confidence interval	
level	95 %
sides	2-sided
lower limit	8.17
upper limit	34.76

Notes:

[2] - P-value, odds ratio, and 95% CIs were calculated from the Cochran-Mantel-Haenszel (CMH) Chi-square test stratified by stratification factors.

Secondary: Lymph Node Response Rate

End point title	Lymph Node Response Rate

End point description:

Lymph node response rate was defined as the proportion of participants who achieved a ≥ 50% decrease from baseline in the sum of the products of the greatest perpendicular diameters (SPD) of index lymph nodes. Participants in the ITT Analysis Set with available data were analyzed.

End point type	Secondary

End point timeframe:

Randomization to End of Study (up to 60 months)

End point values	Idelalisib+Ofatumumab	Ofatumumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	164	81		
Units: percentage of participants				
number (confidence interval 95%)	92.7 (87.6 to 96.2)	4.9 (1.4 to 12.2)		

Statistical analyses

Statistical analysis title	Statistical Analysis for Lymph Node Response Rate
Comparison groups	Idelalisib+Ofatumumab v Ofatumumab
Number of subjects included in analysis	245
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [3]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	483.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	94.63
upper limit	2467.02

Notes:

[3] - P-value, odds ratio, and 95% CI were calculated from the CMH Chi-square test stratified by stratification factors.

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. Overall survival was analyzed using KM estimates. Participants in the ITT Analysis Set were analyzed. 999 = Not applicable, too few events to estimate the upper limit of the confidence interval.

End point type	Secondary

End point timeframe:

Randomization to Last Long-Term Follow-Up Visit (up to maximum of 5 years)

End point values	Idelalisib+Ofatumumab	Ofatumumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	174	87		
Units: months				
median (confidence interval 95%)	45.2 (34.1 to 999)	39 (23.0 to 999)		

Statistical analyses

Statistical analysis title	Statistical Analysis for Overall Survival
Comparison groups	Idelalisib+Ofatumumab v Ofatumumab

Number of subjects included in analysis	261
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.247 [4]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.79
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.54
upper limit	1.15

Notes:

[4] - P-value is from stratified log-rank test, adjusted for randomization stratification factors (17p deletion/TP53 mutation, IGHV mutation, and disease status).

Secondary: Progression-Free Survival in Subgroup of Participants With Chromosome 17p Deletion and/or TP53 Mutation

End point title	Progression-Free Survival in Subgroup of Participants With Chromosome 17p Deletion and/or TP53 Mutation

End point description:

Progression-free survival in subgroup of participants with chromosome 17p deletion and/or TP53 mutation was analyzed using KM estimates. Participants in the ITT Analysis Set with chromosome 17p deletion and/or TP53 mutation were analyzed.

End point type	Secondary

End point timeframe:

Randomization to End of Study (up to 60 months)

End point values	Idelalisib+Ofatumumab	Ofatumumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	70	33		
Units: months				
median (confidence interval 95%)	16.2 (11.1 to 19.1)	5.8 (4.5 to 8.4)		

Statistical analyses

Statistical analysis title	Statistical Analysis for PFS in Subgroup
Comparison groups	Idelalisib+Ofatumumab v Ofatumumab
Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	other[5]
Parameter estimate	Hazard ratio (HR)
Point estimate	0.3

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.17
upper limit	0.51

Notes:

[5] - Hazard ratio and 95% CIs were calculated using the Cox proportional hazards model without any adjustments.

Secondary: Complete Response Rate

End point title	Complete Response Rate

End point description:

Complete response rate was defined as the percentage of participants who achieve a complete response and maintain their response for at least 8 weeks (with a 1-week window). Participants in the ITT Analysis Set were analyzed.

End point type	Secondary

End point timeframe:

Randomization to End of Study (up to 60 months)

End point values	Idelalisib+Ofatumumab	Ofatumumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	174	87		
Units: percentage of participants				
number (not applicable)	1.1	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events: Start of Treatment to End of Treatment (up to 60 months) plus 30 days; All-Cause Mortality: Baseline to Last Long-Term Follow-Up Visit (up to maximum of 5 years)

Adverse event reporting additional description:

All-Cause Mortality was assessed in all randomized participants. All other adverse events were assessed in the Safety Analysis Set (participants who received ≥ 1 dose of study treatment, with treatment assignments designated according to the actual treatment received).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups

Reporting group title	Idelalisib+Ofatumumab

Reporting group description:

Randomized Initial Therapy (24 weeks): Idelalisib 150 mg tablets twice daily + ofatumumab for a total of 12 infusions (300 mg on Day 1, followed by 1000 mg weekly for 7 weeks, and then 1000 mg every 4 weeks for 4 doses);

Continuing Therapy/Observation: Idelalisib 150 mg tablets twice daily until the earliest of subject withdrawal from study, definitive progression of CLL, intolerable idelalisib-related toxicity, pregnancy or initiation of breast feeding, substantial noncompliance with study procedures, or study discontinuation

Long-Term Follow-up: Participants were followed for up to 5 years. Information on medical status, anti-tumor treatments, secondary malignancies, and survival status were collected annually during a routine clinic visit or other contact, such as telephone.

Reporting group title	Ofatumumab

Reporting group description:

Randomized Initial Therapy (24 weeks): Ofatumumab for a total of 12 infusions (300 mg on Day 1, followed by 2000 mg weekly for 7 weeks, and then 2000 mg every 4 weeks for 4 doses);

Continuing Therapy/Observation: Observation until the earliest of subject withdrawal from study, definitive progression of CLL, intolerable idelalisib-related toxicity, pregnancy or initiation of breast feeding, substantial noncompliance with study procedures, or study discontinuation

Long-Term Follow-up: Participants were followed for up to 5 years. Information on medical status, anti-tumor treatments, secondary malignancies, and survival status were collected annually during a routine clinic visit or other contact, such as telephone.

Serious adverse events	Idelalisib+Ofatumumab	Ofatumumab	
Total subjects affected by serious adverse events			
subjects affected / exposed	136 / 173 (78.61%)	36 / 86 (41.86%)	
number of deaths (all causes)	87	40	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			

subjects affected / exposed	2 / 173 (1.16%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-small cell lung cancer			
subjects affected / exposed	2 / 173 (1.16%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma			
subjects affected / exposed	2 / 173 (1.16%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adenocarcinoma of colon			
subjects affected / exposed	1 / 173 (0.58%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anogenital warts			
subjects affected / exposed	1 / 173 (0.58%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Central nervous system leukaemia			
subjects affected / exposed	0 / 173 (0.00%)	1 / 86 (1.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Colon cancer metastatic			
subjects affected / exposed	1 / 173 (0.58%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Invasive lobular breast carcinoma			
subjects affected / exposed	1 / 173 (0.58%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant ascites			

subjects affected / exposed	1 / 173 (0.58%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant melanoma			
subjects affected / exposed	0 / 173 (0.00%)	1 / 86 (1.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mycosis fungoides			
subjects affected / exposed	1 / 173 (0.58%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer			
subjects affected / exposed	1 / 173 (0.58%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal neoplasm			
subjects affected / exposed	1 / 173 (0.58%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypotension			
subjects affected / exposed	7 / 173 (4.05%)	1 / 86 (1.16%)	
occurrences causally related to treatment / all	2 / 7	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematoma			
subjects affected / exposed	1 / 173 (0.58%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral artery aneurysm			
subjects affected / exposed	1 / 173 (0.58%)	0 / 86 (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			

Pyrexia			
subjects affected / exposed	23 / 173 (13.29%)	1 / 86 (1.16%)	
occurrences causally related to treatment / all	17 / 37	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthenia			
subjects affected / exposed	2 / 173 (1.16%)	1 / 86 (1.16%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	2 / 173 (1.16%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	1 / 173 (0.58%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
General physical health deterioration			
subjects affected / exposed	1 / 173 (0.58%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Generalised oedema			
subjects affected / exposed	0 / 173 (0.00%)	1 / 86 (1.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Impaired self-care			
subjects affected / exposed	1 / 173 (0.58%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza like illness			
subjects affected / exposed	1 / 173 (0.58%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Strangulated hernia			

subjects affected / exposed	1 / 173 (0.58%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Systemic inflammatory response syndrome			
subjects affected / exposed	1 / 173 (0.58%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Anaphylactic shock			
subjects affected / exposed	0 / 173 (0.00%)	1 / 86 (1.16%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pneumonitis			
subjects affected / exposed	7 / 173 (4.05%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	7 / 7	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Respiratory failure			
subjects affected / exposed	6 / 173 (3.47%)	1 / 86 (1.16%)	
occurrences causally related to treatment / all	4 / 6	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Dyspnoea			
subjects affected / exposed	4 / 173 (2.31%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	1 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory failure			
subjects affected / exposed	2 / 173 (1.16%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cough			
subjects affected / exposed	2 / 173 (1.16%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Interstitial lung disease				
subjects affected / exposed	2 / 173 (1.16%)	0 / 86 (0.00%)		
occurrences causally related to treatment / all	2 / 2	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Pleural effusion				
subjects affected / exposed	2 / 173 (1.16%)	0 / 86 (0.00%)		
occurrences causally related to treatment / all	0 / 3	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Pulmonary embolism				
subjects affected / exposed	2 / 173 (1.16%)	0 / 86 (0.00%)		
occurrences causally related to treatment / all	0 / 2	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Aspiration				
subjects affected / exposed	1 / 173 (0.58%)	0 / 86 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Bronchitis chronic				
subjects affected / exposed	1 / 173 (0.58%)	0 / 86 (0.00%)		
occurrences causally related to treatment / all	0 / 2	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Chronic obstructive pulmonary disease				
subjects affected / exposed	1 / 173 (0.58%)	0 / 86 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 1	0 / 0		
Lower respiratory tract inflammation				
subjects affected / exposed	1 / 173 (0.58%)	0 / 86 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Lung disorder				
subjects affected / exposed	1 / 173 (0.58%)	0 / 86 (0.00%)		
occurrences causally related to treatment / all	0 / 2	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Pneumonia aspiration				

subjects affected / exposed	1 / 173 (0.58%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary fibrosis			
subjects affected / exposed	1 / 173 (0.58%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pulmonary haemorrhage			
subjects affected / exposed	1 / 173 (0.58%)	0 / 86 (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 / 173 (0.00%)	1 / 86 (1.16%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory arrest			
subjects affected / exposed	1 / 173 (0.58%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Bipolar I disorder			
subjects affected / exposed	0 / 173 (0.00%)	1 / 86 (1.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Confusional state			
subjects affected / exposed	1 / 173 (0.58%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mania			
subjects affected / exposed	1 / 173 (0.58%)	0 / 86 (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	1 / 173 (0.58%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Device occlusion			
subjects affected / exposed	1 / 173 (0.58%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Neutrophil count decreased			
subjects affected / exposed	6 / 173 (3.47%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	6 / 6	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Weight decreased			
subjects affected / exposed	1 / 173 (0.58%)	1 / 86 (1.16%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Alanine aminotransferase increased			
subjects affected / exposed	1 / 173 (0.58%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 173 (0.58%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
C-reactive protein increased			
subjects affected / exposed	1 / 173 (0.58%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphocyte count decreased			
subjects affected / exposed	1 / 173 (0.58%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Platelet count decreased			
subjects affected / exposed	1 / 173 (0.58%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transaminases increased			
subjects affected / exposed	1 / 173 (0.58%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Troponin increased			
subjects affected / exposed	0 / 173 (0.00%)	1 / 86 (1.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
White blood cell count decreased			
subjects affected / exposed	1 / 173 (0.58%)	0 / 86 (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			
Infusion related reaction			
subjects affected / exposed	3 / 173 (1.73%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Overdose			
subjects affected / exposed	2 / 173 (1.16%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral neck fracture			
subjects affected / exposed	0 / 173 (0.00%)	1 / 86 (1.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	0 / 173 (0.00%)	1 / 86 (1.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Upper limb fracture			
subjects affected / exposed	0 / 173 (0.00%)	1 / 86 (1.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	3 / 173 (1.73%)	2 / 86 (2.33%)	
occurrences causally related to treatment / all	0 / 3	1 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	2 / 173 (1.16%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Cardiogenic shock			
subjects affected / exposed	2 / 173 (1.16%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Myocardial infarction			
subjects affected / exposed	2 / 173 (1.16%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Acute coronary syndrome			
subjects affected / exposed	0 / 173 (0.00%)	1 / 86 (1.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic valve disease			
subjects affected / exposed	1 / 173 (0.58%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arrhythmia			
subjects affected / exposed	1 / 173 (0.58%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Bradycardia			

subjects affected / exposed	1 / 173 (0.58%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	1 / 173 (0.58%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac failure			
subjects affected / exposed	1 / 173 (0.58%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Myocardial ischaemia			
subjects affected / exposed	1 / 173 (0.58%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Palpitations			
subjects affected / exposed	0 / 173 (0.00%)	1 / 86 (1.16%)	
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 / 173 (0.58%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Hemiparesis			
subjects affected / exposed	2 / 173 (1.16%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	2 / 173 (1.16%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aphasia			

subjects affected / exposed	1 / 173 (0.58%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral infarction			
subjects affected / exposed	1 / 173 (0.58%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	1 / 173 (0.58%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolic stroke			
subjects affected / exposed	1 / 173 (0.58%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial paralysis			
subjects affected / exposed	1 / 173 (0.58%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotonia			
subjects affected / exposed	1 / 173 (0.58%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Locked-in syndrome			
subjects affected / exposed	1 / 173 (0.58%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peroneal nerve palsy			
subjects affected / exposed	1 / 173 (0.58%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sciatica			

subjects affected / exposed	1 / 173 (0.58%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	19 / 173 (10.98%)	3 / 86 (3.49%)	
occurrences causally related to treatment / all	19 / 25	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	13 / 173 (7.51%)	2 / 86 (2.33%)	
occurrences causally related to treatment / all	10 / 18	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			
subjects affected / exposed	8 / 173 (4.62%)	2 / 86 (2.33%)	
occurrences causally related to treatment / all	2 / 8	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	5 / 173 (2.89%)	2 / 86 (2.33%)	
occurrences causally related to treatment / all	0 / 9	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Granulocytopenia			
subjects affected / exposed	2 / 173 (1.16%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	2 / 173 (1.16%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Autoimmune haemolytic anaemia			
subjects affected / exposed	1 / 173 (0.58%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disseminated intravascular coagulation			

subjects affected / exposed	1 / 173 (0.58%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukocytosis			
subjects affected / exposed	1 / 173 (0.58%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphadenopathy			
subjects affected / exposed	0 / 173 (0.00%)	1 / 86 (1.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
External ear inflammation			
subjects affected / exposed	1 / 173 (0.58%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vertigo			
subjects affected / exposed	1 / 173 (0.58%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	23 / 173 (13.29%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	25 / 32	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	13 / 173 (7.51%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	14 / 15	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	7 / 173 (4.05%)	1 / 86 (1.16%)	
occurrences causally related to treatment / all	4 / 7	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			

subjects affected / exposed	3 / 173 (1.73%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	3 / 173 (1.73%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			
subjects affected / exposed	2 / 173 (1.16%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	0 / 173 (0.00%)	1 / 86 (1.16%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal wall haematoma			
subjects affected / exposed	1 / 173 (0.58%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal fistula			
subjects affected / exposed	0 / 173 (0.00%)	1 / 86 (1.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis ulcerative			
subjects affected / exposed	1 / 173 (0.58%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	1 / 173 (0.58%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric haemorrhage			

subjects affected / exposed	1 / 173 (0.58%)	0 / 86 (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 / 173 (0.00%)	1 / 86 (1.16%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine perforation			
subjects affected / exposed	1 / 173 (0.58%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mouth haemorrhage			
subjects affected / exposed	1 / 173 (0.58%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	2 / 173 (1.16%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bile duct obstruction			
subjects affected / exposed	1 / 173 (0.58%)	0 / 86 (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			
Dermatitis allergic			
subjects affected / exposed	1 / 173 (0.58%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash			
subjects affected / exposed	1 / 173 (0.58%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			

Acute kidney injury			
subjects affected / exposed	5 / 173 (2.89%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	1 / 6	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	3 / 173 (1.73%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	2 / 173 (1.16%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic kidney disease			
subjects affected / exposed	1 / 173 (0.58%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	1 / 173 (0.58%)	0 / 86 (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	2 / 173 (1.16%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemarthrosis			
subjects affected / exposed	1 / 173 (0.58%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscle haemorrhage			
subjects affected / exposed	1 / 173 (0.58%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Myalgia			
subjects affected / exposed	1 / 173 (0.58%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	1 / 173 (0.58%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polyarthritis			
subjects affected / exposed	1 / 173 (0.58%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Soft tissue necrosis			
subjects affected / exposed	1 / 173 (0.58%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tenosynovitis			
subjects affected / exposed	1 / 173 (0.58%)	0 / 86 (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			
Pneumonia			
subjects affected / exposed	27 / 173 (15.61%)	9 / 86 (10.47%)	
occurrences causally related to treatment / all	13 / 35	2 / 9	
deaths causally related to treatment / all	3 / 7	1 / 2	
Sepsis			
subjects affected / exposed	11 / 173 (6.36%)	1 / 86 (1.16%)	
occurrences causally related to treatment / all	6 / 13	0 / 1	
deaths causally related to treatment / all	1 / 3	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	7 / 173 (4.05%)	2 / 86 (2.33%)	
occurrences causally related to treatment / all	4 / 10	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumocystis jirovecii pneumonia			

subjects affected / exposed	8 / 173 (4.62%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	6 / 8	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	7 / 173 (4.05%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	0 / 8	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic sepsis			
subjects affected / exposed	4 / 173 (2.31%)	2 / 86 (2.33%)	
occurrences causally related to treatment / all	1 / 4	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	5 / 173 (2.89%)	1 / 86 (1.16%)	
occurrences causally related to treatment / all	2 / 5	0 / 1	
deaths causally related to treatment / all	1 / 4	0 / 1	
Respiratory tract infection			
subjects affected / exposed	3 / 173 (1.73%)	2 / 86 (2.33%)	
occurrences causally related to treatment / all	1 / 3	1 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Bronchitis			
subjects affected / exposed	4 / 173 (2.31%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	2 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	4 / 173 (2.31%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	2 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atypical pneumonia			
subjects affected / exposed	2 / 173 (1.16%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			

subjects affected / exposed	2 / 173 (1.16%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	2 / 173 (1.16%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumocystis jirovecii infection			
subjects affected / exposed	1 / 173 (0.58%)	1 / 86 (1.16%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Progressive multifocal leukoencephalopathy			
subjects affected / exposed	0 / 173 (0.00%)	2 / 86 (2.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	1 / 2	
Pseudomonal bacteraemia			
subjects affected / exposed	2 / 173 (1.16%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinusitis			
subjects affected / exposed	2 / 173 (1.16%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess			
subjects affected / exposed	0 / 173 (0.00%)	1 / 86 (1.16%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspergillus infection			
subjects affected / exposed	1 / 173 (0.58%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial sepsis			

subjects affected / exposed	1 / 173 (0.58%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biliary sepsis			
subjects affected / exposed	1 / 173 (0.58%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Bronchopulmonary aspergillosis			
subjects affected / exposed	1 / 173 (0.58%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Candida infection			
subjects affected / exposed	1 / 173 (0.58%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Candida pneumonia			
subjects affected / exposed	0 / 173 (0.00%)	1 / 86 (1.16%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Candida sepsis			
subjects affected / exposed	1 / 173 (0.58%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Chronic sinusitis			
subjects affected / exposed	1 / 173 (0.58%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus colitis			
subjects affected / exposed	1 / 173 (0.58%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			

subjects affected / exposed	0 / 173 (0.00%)	1 / 86 (1.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia bacteraemia			
subjects affected / exposed	0 / 173 (0.00%)	1 / 86 (1.16%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia sepsis			
subjects affected / exposed	1 / 173 (0.58%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia urinary tract infection			
subjects affected / exposed	0 / 173 (0.00%)	1 / 86 (1.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Folliculitis			
subjects affected / exposed	1 / 173 (0.58%)	0 / 86 (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 / 173 (0.58%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis salmonella			
subjects affected / exposed	1 / 173 (0.58%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Genital herpes			
subjects affected / exposed	1 / 173 (0.58%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
H1N1 influenza			

subjects affected / exposed	0 / 173 (0.00%)	1 / 86 (1.16%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes simplex			
subjects affected / exposed	1 / 173 (0.58%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	1 / 173 (0.58%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster disseminated			
subjects affected / exposed	1 / 173 (0.58%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infective exacerbation of chronic obstructive airways disease			
subjects affected / exposed	1 / 173 (0.58%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	1 / 173 (0.58%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Listeria sepsis			
subjects affected / exposed	0 / 173 (0.00%)	1 / 86 (1.16%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pseudomonal sepsis			
subjects affected / exposed	1 / 173 (0.58%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pseudomonas infection			

subjects affected / exposed	0 / 173 (0.00%)	1 / 86 (1.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory syncytial virus bronchiolitis			
subjects affected / exposed	1 / 173 (0.58%)	0 / 86 (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 bacterial			
subjects affected / exposed	1 / 173 (0.58%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhinovirus infection			
subjects affected / exposed	1 / 173 (0.58%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Salmonellosis			
subjects affected / exposed	1 / 173 (0.58%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin infection			
subjects affected / exposed	0 / 173 (0.00%)	1 / 86 (1.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	1 / 173 (0.58%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Varicella			
subjects affected / exposed	0 / 173 (0.00%)	1 / 86 (1.16%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular device infection			

subjects affected / exposed	1 / 173 (0.58%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			
subjects affected / exposed	1 / 173 (0.58%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral sepsis			
subjects affected / exposed	1 / 173 (0.58%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	6 / 173 (3.47%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	2 / 11	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia			
subjects affected / exposed	3 / 173 (1.73%)	1 / 86 (1.16%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	3 / 173 (1.73%)	1 / 86 (1.16%)	
occurrences causally related to treatment / all	1 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	4 / 173 (2.31%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	2 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	2 / 173 (1.16%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypophosphataemia			

subjects affected / exposed	2 / 173 (1.16%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cachexia			
subjects affected / exposed	1 / 173 (0.58%)	0 / 86 (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 / 173 (0.58%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pseudohyperkalaemia			
subjects affected / exposed	1 / 173 (0.58%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour lysis syndrome			
subjects affected / exposed	1 / 173 (0.58%)	0 / 86 (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+Ofatumumab	Ofatumumab	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	167 / 173 (96.53%)	79 / 86 (91.86%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Squamous cell carcinoma			
subjects affected / exposed	11 / 173 (6.36%)	3 / 86 (3.49%)	
occurrences (all)	20	3	
Vascular disorders			
Hypertension			
subjects affected / exposed	21 / 173 (12.14%)	6 / 86 (6.98%)	
occurrences (all)	23	7	
Hypotension			

subjects affected / exposed	14 / 173 (8.09%)	5 / 86 (5.81%)	
occurrences (all)	18	7	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	60 / 173 (34.68%)	24 / 86 (27.91%)	
occurrences (all)	82	25	
Pyrexia			
subjects affected / exposed	55 / 173 (31.79%)	19 / 86 (22.09%)	
occurrences (all)	106	28	
Oedema peripheral			
subjects affected / exposed	35 / 173 (20.23%)	9 / 86 (10.47%)	
occurrences (all)	41	11	
Chills			
subjects affected / exposed	27 / 173 (15.61%)	13 / 86 (15.12%)	
occurrences (all)	31	17	
Asthenia			
subjects affected / exposed	27 / 173 (15.61%)	9 / 86 (10.47%)	
occurrences (all)	30	9	
Influenza like illness			
subjects affected / exposed	14 / 173 (8.09%)	1 / 86 (1.16%)	
occurrences (all)	18	1	
Pain			
subjects affected / exposed	13 / 173 (7.51%)	2 / 86 (2.33%)	
occurrences (all)	16	2	
Peripheral swelling			
subjects affected / exposed	12 / 173 (6.94%)	1 / 86 (1.16%)	
occurrences (all)	13	1	
Chest pain			
subjects affected / exposed	9 / 173 (5.20%)	2 / 86 (2.33%)	
occurrences (all)	10	2	
Malaise			
subjects affected / exposed	10 / 173 (5.78%)	1 / 86 (1.16%)	
occurrences (all)	11	1	
Immune system disorders			

Hypogammaglobulinaemia			
subjects affected / exposed	11 / 173 (6.36%)	3 / 86 (3.49%)	
occurrences (all)	12	3	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	60 / 173 (34.68%)	18 / 86 (20.93%)	
occurrences (all)	89	21	
Dyspnoea			
subjects affected / exposed	34 / 173 (19.65%)	11 / 86 (12.79%)	
occurrences (all)	45	15	
Oropharyngeal pain			
subjects affected / exposed	17 / 173 (9.83%)	3 / 86 (3.49%)	
occurrences (all)	20	3	
Nasal congestion			
subjects affected / exposed	11 / 173 (6.36%)	6 / 86 (6.98%)	
occurrences (all)	13	6	
Productive cough			
subjects affected / exposed	17 / 173 (9.83%)	0 / 86 (0.00%)	
occurrences (all)	23	0	
Epistaxis			
subjects affected / exposed	9 / 173 (5.20%)	6 / 86 (6.98%)	
occurrences (all)	11	6	
Rhinorrhoea			
subjects affected / exposed	12 / 173 (6.94%)	1 / 86 (1.16%)	
occurrences (all)	12	1	
Dysphonia			
subjects affected / exposed	9 / 173 (5.20%)	1 / 86 (1.16%)	
occurrences (all)	11	1	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	30 / 173 (17.34%)	12 / 86 (13.95%)	
occurrences (all)	36	12	
Anxiety			
subjects affected / exposed	15 / 173 (8.67%)	2 / 86 (2.33%)	
occurrences (all)	15	2	
Confusional state			

subjects affected / exposed	10 / 173 (5.78%)	0 / 86 (0.00%)	
occurrences (all)	16	0	
Investigations			
Weight decreased			
subjects affected / exposed	28 / 173 (16.18%)	5 / 86 (5.81%)	
occurrences (all)	31	5	
Alanine aminotransferase increased			
subjects affected / exposed	19 / 173 (10.98%)	2 / 86 (2.33%)	
occurrences (all)	32	2	
Neutrophil count decreased			
subjects affected / exposed	16 / 173 (9.25%)	2 / 86 (2.33%)	
occurrences (all)	29	2	
Aspartate aminotransferase increased			
subjects affected / exposed	14 / 173 (8.09%)	2 / 86 (2.33%)	
occurrences (all)	22	2	
Platelet count decreased			
subjects affected / exposed	9 / 173 (5.20%)	1 / 86 (1.16%)	
occurrences (all)	10	1	
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	30 / 173 (17.34%)	23 / 86 (26.74%)	
occurrences (all)	40	35	
Contusion			
subjects affected / exposed	18 / 173 (10.40%)	3 / 86 (3.49%)	
occurrences (all)	21	3	
Cardiac disorders			
Tachycardia			
subjects affected / exposed	10 / 173 (5.78%)	2 / 86 (2.33%)	
occurrences (all)	12	2	
Nervous system disorders			
Headache			
subjects affected / exposed	37 / 173 (21.39%)	9 / 86 (10.47%)	
occurrences (all)	67	10	
Dizziness			
subjects affected / exposed	17 / 173 (9.83%)	5 / 86 (5.81%)	
occurrences (all)	20	6	

Neuropathy peripheral			
subjects affected / exposed	11 / 173 (6.36%)	6 / 86 (6.98%)	
occurrences (all)	11	6	
Paraesthesia			
subjects affected / exposed	11 / 173 (6.36%)	4 / 86 (4.65%)	
occurrences (all)	11	4	
Dysgeusia			
subjects affected / exposed	11 / 173 (6.36%)	3 / 86 (3.49%)	
occurrences (all)	13	3	
Hypoaesthesia			
subjects affected / exposed	10 / 173 (5.78%)	1 / 86 (1.16%)	
occurrences (all)	13	1	
Peripheral sensory neuropathy			
subjects affected / exposed	6 / 173 (3.47%)	5 / 86 (5.81%)	
occurrences (all)	7	5	
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	57 / 173 (32.95%)	14 / 86 (16.28%)	
occurrences (all)	136	21	
Anaemia			
subjects affected / exposed	38 / 173 (21.97%)	7 / 86 (8.14%)	
occurrences (all)	50	7	
Thrombocytopenia			
subjects affected / exposed	25 / 173 (14.45%)	5 / 86 (5.81%)	
occurrences (all)	26	5	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	96 / 173 (55.49%)	21 / 86 (24.42%)	
occurrences (all)	196	33	
Nausea			
subjects affected / exposed	62 / 173 (35.84%)	23 / 86 (26.74%)	
occurrences (all)	93	25	
Constipation			
subjects affected / exposed	39 / 173 (22.54%)	13 / 86 (15.12%)	
occurrences (all)	54	13	
Vomiting			

subjects affected / exposed	29 / 173 (16.76%)	12 / 86 (13.95%)	
occurrences (all)	43	13	
Abdominal pain			
subjects affected / exposed	28 / 173 (16.18%)	5 / 86 (5.81%)	
occurrences (all)	37	6	
Abdominal pain upper			
subjects affected / exposed	15 / 173 (8.67%)	4 / 86 (4.65%)	
occurrences (all)	19	4	
Gastrooesophageal reflux disease			
subjects affected / exposed	15 / 173 (8.67%)	3 / 86 (3.49%)	
occurrences (all)	16	3	
Colitis			
subjects affected / exposed	17 / 173 (9.83%)	0 / 86 (0.00%)	
occurrences (all)	19	0	
Dyspepsia			
subjects affected / exposed	13 / 173 (7.51%)	3 / 86 (3.49%)	
occurrences (all)	15	3	
Stomatitis			
subjects affected / exposed	9 / 173 (5.20%)	0 / 86 (0.00%)	
occurrences (all)	9	0	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	36 / 173 (20.81%)	7 / 86 (8.14%)	
occurrences (all)	50	10	
Night sweats			
subjects affected / exposed	17 / 173 (9.83%)	10 / 86 (11.63%)	
occurrences (all)	19	10	
Pruritus			
subjects affected / exposed	21 / 173 (12.14%)	6 / 86 (6.98%)	
occurrences (all)	23	6	
Dry skin			
subjects affected / exposed	11 / 173 (6.36%)	1 / 86 (1.16%)	
occurrences (all)	12	1	
Rash maculo-papular			
subjects affected / exposed	12 / 173 (6.94%)	0 / 86 (0.00%)	
occurrences (all)	14	0	

Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	28 / 173 (16.18%)	11 / 86 (12.79%)	
occurrences (all)	33	12	
Arthralgia			
subjects affected / exposed	19 / 173 (10.98%)	5 / 86 (5.81%)	
occurrences (all)	26	5	
Pain in extremity			
subjects affected / exposed	19 / 173 (10.98%)	5 / 86 (5.81%)	
occurrences (all)	21	5	
Muscle spasms			
subjects affected / exposed	18 / 173 (10.40%)	2 / 86 (2.33%)	
occurrences (all)	22	2	
Myalgia			
subjects affected / exposed	15 / 173 (8.67%)	1 / 86 (1.16%)	
occurrences (all)	16	1	
Musculoskeletal pain			
subjects affected / exposed	13 / 173 (7.51%)	1 / 86 (1.16%)	
occurrences (all)	13	1	
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	47 / 173 (27.17%)	9 / 86 (10.47%)	
occurrences (all)	61	9	
Sinusitis			
subjects affected / exposed	23 / 173 (13.29%)	3 / 86 (3.49%)	
occurrences (all)	33	3	
Bronchitis			
subjects affected / exposed	25 / 173 (14.45%)	0 / 86 (0.00%)	
occurrences (all)	31	0	
Urinary tract infection			
subjects affected / exposed	18 / 173 (10.40%)	6 / 86 (6.98%)	
occurrences (all)	26	6	
Pneumonia			
subjects affected / exposed	21 / 173 (12.14%)	2 / 86 (2.33%)	
occurrences (all)	23	2	
Oral candidiasis			

subjects affected / exposed	15 / 173 (8.67%)	0 / 86 (0.00%)	
occurrences (all)	18	0	
Lower respiratory tract infection			
subjects affected / exposed	11 / 173 (6.36%)	2 / 86 (2.33%)	
occurrences (all)	19	2	
Oral herpes			
subjects affected / exposed	10 / 173 (5.78%)	2 / 86 (2.33%)	
occurrences (all)	14	2	
Respiratory tract infection			
subjects affected / exposed	9 / 173 (5.20%)	1 / 86 (1.16%)	
occurrences (all)	13	1	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	37 / 173 (21.39%)	7 / 86 (8.14%)	
occurrences (all)	42	8	
Hypokalaemia			
subjects affected / exposed	32 / 173 (18.50%)	4 / 86 (4.65%)	
occurrences (all)	55	5	
Hyperglycaemia			
subjects affected / exposed	15 / 173 (8.67%)	1 / 86 (1.16%)	
occurrences (all)	18	1	
Dehydration			
subjects affected / exposed	14 / 173 (8.09%)	0 / 86 (0.00%)	
occurrences (all)	22	0	
Hypomagnesaemia			
subjects affected / exposed	11 / 173 (6.36%)	3 / 86 (3.49%)	
occurrences (all)	15	3	
Hyponatraemia			
subjects affected / exposed	12 / 173 (6.94%)	1 / 86 (1.16%)	
occurrences (all)	15	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 November 2012	• Added the exclusion criterion "Prior participation in a GS-1101 clinical trial" • Updated information regarding secondary and tertiary/exploratory endpoints • Clarified that the IRC findings would be primary for analyses of PFS and other tumor control endpoints • Updated plan to control Type I error rate for secondary endpoints • Increased washout period to 6 weeks • Provided clarification on phototoxicity risk • Added details regarding diagnosis/management of progressive multifocal leukoencephalopathy (PML) consistent with Arzerra product label • Added guidelines for monitoring participants for ofatumumab infusion toxicity • Added urine pregnancy testing at intervals ≤ 6 weeks after Week 48 • Clarified timing of scans in participants who had a temporary cessation of therapy • Clarified duration of therapy for each study treatment in Group A of the study • Clarified that participants in Group B who prematurely discontinued 1 drug could continue the other • Increased number of participating centers and study locations • Updated safety and clinical information to align with IB Ed. 7 • Added new references regarding modifications in the assessment of absolute lymphocyte counts (ALC) in determining disease response and progression in participants with CLL • Modified protocol to achieve 129 events with planned sample size • Added new section to differentiate discontinuation from study versus discontinuation of drug • Clarified that modifications were to be made for AEs or laboratory abnormalities that the investigator considered related to study drug • Provided description of the standard accountability procedures because Gilead was supplying ofatumumab • Modified protocol to allow enrollment of individuals with a positive HBV antibody if HBV DNA was undetectable by quantitative polymerase chain reaction (PCR) • Updated inclusion criteria relating to contraception • Added the Per Protocol Analysis Set • Modified the spleen ULN from 10 cm to 12 cm
17 October 2013	• Increased planned sample size to 255 participants to ensure PFS events would be met in a timely manner; up to 270 participants could be enrolled to permit eligible participants who were in screening at the time of enrollment closure to join the study • Updated "Hepatic Events" section to add monitoring guidelines for participants who were HBc antibody positive at screening • Updated order of key secondary endpoints • Updated the nonclinical toxicology and clinical pharmacology sections to align with current understanding and to simplify and remove redundancy with the investigator's brochure (IB), Edition 8 • Updated data for the recently completed Phase 1 monotherapy study (101-02) in participants with hematologic malignancies • Removed AEs as a reason for discontinuation from study • Updated the clinical response section to align with the criteria for the independent review committee (IRC) • Updated the pregnancy risk language based on current nonclinical toxicology • Updated AE reporting to align with Gilead guidelines
13 January 2014	• Updated response sections for consistency with central reader rules and to align across Gilead oncology studies • Added "Sample Storage" section to request tissue samples collected as part of standard of care • Updated the "Long-Term Follow-Up" section to change the interval to annual and to describe the data to be collected

04 March 2014	• Added a formal interim efficacy analysis to be conducted when approximately 50% of the planned 129 events occurred and a second interim to be performed when approximately 75% of expected events occurred • Gave participants in Group B (ofatumumab monotherapy) the option to receive idelalisib (IDL) in the event that the data monitoring committee (DMC) observed substantial evidence of benefit in Group A (IDL + ofatumumab) based on the interim data
26 September 2014	• Added secondary objective "To evaluate the effect of the addition of IDL to ofatumumab on the onset, magnitude, and duration of tumor control for participants with 17p deletion and/or TP53 mutation" • Added information regarding the possible crossover of Group B participants to IDL in the event that the data monitoring committee (DMC) and Gilead decided to stop the study after the first interim or second interim analysis
17 December 2014	Removed crossover study allowance
28 March 2016	Updated the safety information and guidelines for toxicity management to be consistent across IDL study protocols; the specific changes included mandating prophylaxis for Pneumocystis jirovecii pneumonia, cytomegalovirus surveillance, and increased monitoring
04 August 2016	• Clarified the definition of recommended versus required actions related to dose modifications for AEs • Modified the safety measures to require monitoring of subjects for Pneumocystis jirovecii pneumonia prophylaxis for 2 to 6 months after the last dose of IDL
24 October 2016	In order to provide clear guidance for IDL administration in the event of pneumonitis, the language around actions to be taken was revised.
30 August 2017	Organizing pneumonia emerged as a potential safety signal during routine signal detection monitoring. This protocol was amended to add organizing pneumonia as a potential risk.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
15 August 2018	This study was terminated by the sponsor. The last subject last observation occurred on 15 August 2018.	-

Notes:

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/28257752