Clinical trial results:
A Phase 3 Study of Duvelisib (IPI-145) vs Ofatumumab in Patients with Relapsed or Refractory Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

Summary

EudraCT number	2013-002405-61
Trial protocol	ES HU IT GB BE AT DE LV GR
Global end of trial date	23 December 2020

Results information

Result version number	v1
This version publication date	15 December 2022
First version publication date	15 December 2022

Trial information

Trial identification

Sponsor protocol code	IPI-145-07

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02004522
WHO universal trial number (UTN)	U1111-1138-8603

Notes:

Sponsors

Sponsor organisation name	Secura Bio
Sponsor organisation address	1995 Village Center Circle, Suite 128, Las Vegas, NV, United States, 89134
Public contact	NgocDiep Le, Verastem, Inc., 001 7812924200, dle@verastem.com
Scientific contact	NgocDiep Le, Verastem, Inc., 001 7812924200, dle@verastem.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	25 June 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	19 May 2017
Global end of trial reached?	Yes
Global end of trial date	23 December 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

A phase 3 clinical trial to examine the efficacy of duvelisib monotherapy versus ofatumumab monotherapy in subjects with relapsed or refractory chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL).

Protection of trial subjects:

This study was conducted in accordance with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice, and the principles of the Declaration of Helsinki, in addition to following the laws and regulations of the country or countries in which a study is conducted.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 November 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	Spain: 40
Country: Number of subjects enrolled	United Kingdom: 17
Country: Number of subjects enrolled	Austria: 11
Country: Number of subjects enrolled	Belgium: 27
Country: Number of subjects enrolled	France: 30
Country: Number of subjects enrolled	Germany: 4
Country: Number of subjects enrolled	Hungary: 65
Country: Number of subjects enrolled	Italy: 41
Country: Number of subjects enrolled	Australia: 21
Country: Number of subjects enrolled	New Zealand: 12
Country: Number of subjects enrolled	United States: 51
Worldwide total number of subjects	319
EEA total number of subjects	218

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)	102
From 65 to 84 years	211
85 years and over	6

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Screening was performed at least 30 days prior to dosing (Cycle 1 Day 1).

Period 1

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

Arms

Are arms mutually exclusive?	No
Arm title	Duvelisib

Arm description:

Duvelisib is administered orally and supplied as 5 mg and 25 mg formulated capsules.

Arm type	Experimental
Investigational medicinal product name	Duvelisib
Investigational medicinal product code	
Other name	Copiktra, IPI-145, PI3K Inhibitor
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Subjects received starting dose of 25 mg duvelisib twice a day initially over the course of 21-day treatment cycle followed by 28-day treatment cycles for up to 18 cycles or until disease progression or unacceptable toxicity (whichever comes first).

Arm title	Ofatumumab

Arm description:

Ofatumumab is administered as an intravenous (IV) infusion and is supplied in single-use vials at two strengths, 100 mg/5 mL and 1000 mg/50 mL.

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

Dosage and administration details:

Subjects received ofatumumab at the dose and schedule outlined in the approved product labelling for monotherapy in relapsed CLL at the time the study was initiated.

Number of subjects in period 1	Duvelisib	Ofatumumab
Started	160	159
Completed	34	0
Not completed	126	159
Consent withdrawn by subject	13	7
Physician decision	3	4
Disease progression	35	31
Adverse event, non-fatal	55	6
Death	12	3
Other reason listed by PI	4	1
Completed treatment cycles per protocol	1	103
Never dosed	2	4
Protocol deviation	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Duvelisib
Reporting group description:	
Duvelisib is administered orally and supplied as 5 mg and 25 mg formulated capsules.	
Reporting group title	Ofatumumab
Reporting group description:	
Ofatumumab is administered as an intravenous (IV) infusion and is supplied in single-use vials at two strengths, 100 mg/5 mL and 1000 mg/50 mL.	

Reporting group values	Duvelisib	Ofatumumab	Total
Number of subjects	160	159	319
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	48	54	102
From 65-84 years	109	102	211
85 years and over	3	3	6
Gender categorical Units: Subjects			
Female	64	64	128
Male	96	95	191

End points

End points reporting groups

Reporting group title	Duvelisib
Reporting group description:	
Duvelisib is administered orally and supplied as 5 mg and 25 mg formulated capsules.	
Reporting group title	Ofatumumab
Reporting group description:	
Ofatumumab is administered as an intravenous (IV) infusion and is supplied in single-use vials at two strengths, 100 mg/5 mL and 1000 mg/50 mL.	
Subject analysis set title	Intent to Treat
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All randomized subjects with treatment group designated according to randomization.	
Subject analysis set title	Subjects With Abnormal Hematologic Values at Baseline
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Subjects with abnormally high values for neutrophil count, haemoglobin, or platelet count at Baseline.	

Primary: Progression-free Survival (PFS)

End point title	Progression-free Survival (PFS)[1]
End point description:	
The primary efficacy endpoint for the study was PFS, defined as time from randomization to the first documentation of PD as determined by blinded independent review or death due to any cause.	
End point type	Primary
End point timeframe:	
From date of randomization until the date of first documented progression or date of death from any cause, whichever came first, assessed up to 3 years	

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: Only descriptive statistics (median plus confidence interval) are reported for PFS.

End point values	Duvelisib	Ofatumumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	160[2]	159[3]		
Units: Months				
median (confidence interval 95%)	13.3 (12.1 to 16.8)	9.9 (9.2 to 11.3)		

Notes:

[2] - Intent to Treat

[3] - Intent to Treat

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Response Rate (ORR)

End point title	Overall Response Rate (ORR)
End point description:	
ORR is a key secondary efficacy endpoint with overall response defined as best response of CR, CRi, PR, or PRwL, according to the modified IWCLL/IWG Response Criteria, with modification for treatment-	

related lymphocytosis as defined in the protocol.

End point type	Secondary

End point timeframe:

Until disease progression or unacceptable toxicity assessed up to 6 years

End point values	Duvelisib	Ofatumumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	160[4]	159[5]		
Units: Count of participants	118	72		

Notes:

[4] - Intent to Treat

[5] - Intent to Treat

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Hematologic Improvements

End point title	Number of Subjects With Hematologic Improvements

End point description:

Subjects with hematologic improvement included those subjects with abnormally high values for neutrophil count, haemoglobin, or platelet count at Baseline determined to have consistently met the criteria of an improvement for those parameters for a period of at least 60 days during which the subject did not have a transfusion or exogenous cytokines.

End point type	Secondary

End point timeframe:

3 years

End point values	Duvelisib	Ofatumumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	94[6]	95[7]		
Units: Count of participants	56	51		

Notes:

[6] - Subjects With Abnormal Hematologic Values at Baseline

[7] - Subjects With Abnormal Hematologic Values at Baseline

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival

End point title	Overall Survival

End point description:

A stratified Cox regression analysis was used to test for any treatment effect. 9999 = Upper limit not estimable due to an insufficient number of events at the time of analysis.

End point type	Secondary

End point timeframe:

Every 6 months for up to 3 years after first dose

End point values	Duvelisib	Ofatumumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	160[8]	159[9]		
Units: Months				
median (confidence interval 95%)	54.94 (43.00 to 67.99)	63.25 (44.15 to 9999)		

Notes:

[8] - Intent to Treat

[9] - Intent to Treat

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 defined as greater than or equal to 50% decrease in the SPD of target lymph nodes.

End point type	Secondary

End point timeframe:

3 years

End point values	Duvelisib	Ofatumumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	160[10]	159[11]		
Units: Count of participants	136	25		

Notes:

[10] - Intent to Treat

[11] - Intent to Treat

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR)

End point title	Duration of Response (DOR)

End point description:

Duration of response is defined only for subjects demonstrating a response (eg, CR, CRi, PR, PRwL), with the response and progression statuses both determined by the blinded, central independent review. The analysis will be descriptive for each treatment group only.

End point type	Secondary

End point timeframe:

Time from the first documentation of response to first documentation of progressive disease or death

due to any cause

End point values	Duvelisib	Ofatumumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	160[12]	159[13]		
Units: Months				
median (confidence interval 95%)	11.1 (9.2 to 18.3)	9.3 (7.7 to 11.0)		

Notes:

[12] - Intent to Treat

[13] - Intent to Treat

Statistical analyses

No statistical analyses for this end point

Secondary: Treatment-Emergent Adverse Events (TEAEs) and Changes in Safety Laboratory Values

End point title	Treatment-Emergent Adverse Events (TEAEs) and Changes in Safety Laboratory Values

End point description:

An analysis of TEAEs with an onset within the first 24 weeks of treatment was performed to examine and compare the incidence of events across an equal period for each treatment arm. Twenty-four weeks was anticipated to be the median exposure to ofatumumab.

End point type	Secondary

End point timeframe:

From 04 Feb 2014 until 19 June 2018

End point values	Duvelisib	Ofatumumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	160[14]	159[15]		
Units: Count of participants	150	143		

Notes:

[14] - Intent to Treat

[15] - Intent to Treat

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Samples Available for Duvelisib Pharmacokinetics (PK)

End point title	Number of Subjects With Samples Available for Duvelisib Pharmacokinetics (PK)[16]

End point description:

Number of subjects with samples available for duvelisib Pharmacokinetics (PK).

End point type	Secondary

End point timeframe:

Cycle 2, Cycle 3, and Cycle 7

Notes:

[16] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No PK samples were collected for ofatumumab subjects.

End point values	Duvelisib			
Subject group type	Reporting group			
Number of subjects analysed	160			
Units: Number of participants	158			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
39 months	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups	
Reporting group title	Duvelisib
Reporting group description:	
Duvelisib is administered orally and supplied as 5 mg and 25 mg formulated capsules.	
Reporting group title	Ofatumumab
Reporting group description:	
Ofatumumab is administered as an IV infusion and is supplied in single-use vials at two strengths, 100 mg/5 mL and 1000 mg/50 mL.	

Serious adverse events	Duvelisib	Ofatumumab	
Total subjects affected by serious adverse events			
subjects affected / exposed	124 / 158 (78.48%)	50 / 155 (32.26%)	
number of deaths (all causes)	78	70	
number of deaths resulting from adverse events	24	7	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Glioblastoma multiforme			
subjects affected / exposed	0 / 158 (0.00%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Intestinal adenocarcinoma			
subjects affected / exposed	1 / 158 (0.63%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Malignant melanoma			
subjects affected / exposed	1 / 158 (0.63%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant pleural effusion			

subjects affected / exposed	0 / 158 (0.00%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuroendocrine carcinoma of the skin			
subjects affected / exposed	1 / 158 (0.63%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuroendocrine tumour			
subjects affected / exposed	1 / 158 (0.63%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Richter’s syndrome			
subjects affected / exposed	1 / 158 (0.63%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma			
subjects affected / exposed	0 / 158 (0.00%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Squamous cell carcinoma of lung			
subjects affected / exposed	0 / 158 (0.00%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transitional cell carcinoma			
subjects affected / exposed	1 / 158 (0.63%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	2 / 158 (1.27%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			

subjects affected / exposed	1 / 158 (0.63%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral embolism			
subjects affected / exposed	0 / 158 (0.00%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombosis			
subjects affected / exposed	1 / 158 (0.63%)	0 / 155 (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			
Death			
subjects affected / exposed	2 / 158 (1.27%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Disease progression			
subjects affected / exposed	0 / 158 (0.00%)	2 / 155 (1.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Fatigue			
subjects affected / exposed	0 / 158 (0.00%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	4 / 158 (2.53%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	1 / 4	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Infusion site extravasation			
subjects affected / exposed	0 / 158 (0.00%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucosal inflammation			

subjects affected / exposed	1 / 158 (0.63%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multi-organ failure			
subjects affected / exposed	1 / 158 (0.63%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Oedema peripheral			
subjects affected / exposed	1 / 158 (0.63%)	0 / 155 (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	7 / 158 (4.43%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	3 / 9	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden death			
subjects affected / exposed	1 / 158 (0.63%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Immune system disorders			
Contrast media allergy			
subjects affected / exposed	0 / 158 (0.00%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug hypersensitivity			
subjects affected / exposed	0 / 158 (0.00%)	1 / 155 (0.65%)	
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			
Acute respiratory distress syndrome			
subjects affected / exposed	1 / 158 (0.63%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Acute respiratory failure			
subjects affected / exposed	1 / 158 (0.63%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 158 (0.63%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Dyspnoea			
subjects affected / exposed	2 / 158 (1.27%)	0 / 155 (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	2 / 158 (1.27%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngeal stenosis			
subjects affected / exposed	0 / 158 (0.00%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung disorder			
subjects affected / exposed	1 / 158 (0.63%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 158 (0.63%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural haemorrhage			
subjects affected / exposed	1 / 158 (0.63%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			

subjects affected / exposed	1 / 158 (0.63%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	6 / 158 (3.80%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	6 / 6	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	3 / 158 (1.90%)	2 / 155 (1.29%)	
occurrences causally related to treatment / all	1 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	2 / 158 (1.27%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 158 (0.63%)	0 / 155 (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 / 158 (0.63%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lipase increased			
subjects affected / exposed	1 / 158 (0.63%)	0 / 155 (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			
Accidental overdose			
subjects affected / exposed	1 / 158 (0.63%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Cervical vertebral fracture			
subjects affected / exposed	1 / 158 (0.63%)	0 / 155 (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	0 / 158 (0.00%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Femur fracture			
subjects affected / exposed	1 / 158 (0.63%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infusion related reaction			
subjects affected / exposed	0 / 158 (0.00%)	3 / 155 (1.94%)	
occurrences causally related to treatment / all	0 / 0	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Splenic rupture			
subjects affected / exposed	1 / 158 (0.63%)	0 / 155 (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 / 158 (0.63%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Traumatic haematoma			
subjects affected / exposed	1 / 158 (0.63%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	0 / 158 (0.00%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			

subjects affected / exposed	2 / 158 (1.27%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	3 / 158 (1.90%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	2 / 158 (1.27%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	1 / 158 (0.63%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericarditis			
subjects affected / exposed	1 / 158 (0.63%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia			
subjects affected / exposed	0 / 158 (0.00%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular tachycardia			
subjects affected / exposed	1 / 158 (0.63%)	0 / 155 (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			
Brain stem haemorrhage			
subjects affected / exposed	1 / 158 (0.63%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dementia			

subjects affected / exposed	1 / 158 (0.63%)	0 / 155 (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	0 / 158 (0.00%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic stroke			
subjects affected / exposed	2 / 158 (1.27%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Headache			
subjects affected / exposed	0 / 158 (0.00%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	0 / 158 (0.00%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental impairment			
subjects affected / exposed	1 / 158 (0.63%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 158 (1.27%)	2 / 155 (1.29%)	
occurrences causally related to treatment / all	1 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	10 / 158 (6.33%)	3 / 155 (1.94%)	
occurrences causally related to treatment / all	6 / 12	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemolytic anaemia			

subjects affected / exposed	2 / 158 (1.27%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymph node pain			
subjects affected / exposed	0 / 158 (0.00%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	1 / 158 (0.63%)	0 / 155 (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	3 / 158 (1.90%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	1 / 158 (0.63%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 158 (0.63%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	1 / 158 (0.63%)	0 / 155 (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	20 / 158 (12.66%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	20 / 21	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis ischaemic			

subjects affected / exposed	1 / 158 (0.63%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	18 / 158 (11.39%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	17 / 20	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteritis			
subjects affected / exposed	1 / 158 (0.63%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis			
subjects affected / exposed	2 / 158 (1.27%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	2 / 2	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	3 / 158 (1.90%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	3 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileal ulcer			
subjects affected / exposed	1 / 158 (0.63%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mallory-Weiss syndrome			
subjects affected / exposed	1 / 158 (0.63%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal ulcer			
subjects affected / exposed	0 / 158 (0.00%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			

subjects affected / exposed	1 / 158 (0.63%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Portal hypertensive gastropathy			
subjects affected / exposed	0 / 158 (0.00%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Proctitis			
subjects affected / exposed	1 / 158 (0.63%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	2 / 158 (1.27%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 158 (0.00%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic failure			
subjects affected / exposed	0 / 158 (0.00%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Skin and subcutaneous tissue disorders			
Dermatitis allergic			
subjects affected / exposed	1 / 158 (0.63%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dermatitis exfoliative			
subjects affected / exposed	2 / 158 (1.27%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash			

subjects affected / exposed	2 / 158 (1.27%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash erythematous			
subjects affected / exposed	2 / 158 (1.27%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash maculo-papular			
subjects affected / exposed	2 / 158 (1.27%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	5 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxic skin eruption			
subjects affected / exposed	4 / 158 (2.53%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	4 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	1 / 158 (0.63%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal colic			
subjects affected / exposed	1 / 158 (0.63%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	1 / 158 (0.63%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure acute			
subjects affected / exposed	4 / 158 (2.53%)	2 / 155 (1.29%)	
occurrences causally related to treatment / all	1 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Renal failure chronic			

subjects affected / exposed	1 / 158 (0.63%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthritis			
subjects affected / exposed	1 / 158 (0.63%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone pain			
subjects affected / exposed	1 / 158 (0.63%)	0 / 155 (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			
Aspergillus infection			
subjects affected / exposed	2 / 158 (1.27%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Bronchiolitis			
subjects affected / exposed	1 / 158 (0.63%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	5 / 158 (3.16%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	2 / 5	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Bronchitis viral			
subjects affected / exposed	1 / 158 (0.63%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopneumonia			
subjects affected / exposed	1 / 158 (0.63%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Bronchopulmonary aspergillosis			
subjects affected / exposed	2 / 158 (1.27%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Campylobacter gastroenteritis			
subjects affected / exposed	2 / 158 (1.27%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic sinusitis			
subjects affected / exposed	0 / 158 (0.00%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	2 / 158 (1.27%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile infection			
subjects affected / exposed	0 / 158 (0.00%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus colitis			
subjects affected / exposed	1 / 158 (0.63%)	0 / 155 (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 / 158 (0.00%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	1 / 158 (0.63%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterococcal infection			

subjects affected / exposed	1 / 158 (0.63%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterococcal sepsis			
subjects affected / exposed	1 / 158 (0.63%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Escherichia sepsis			
subjects affected / exposed	1 / 158 (0.63%)	3 / 155 (1.94%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 0	
Escherichia urinary tract infection			
subjects affected / exposed	1 / 158 (0.63%)	2 / 155 (1.29%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fungal infection			
subjects affected / exposed	2 / 158 (1.27%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	4 / 158 (2.53%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis viral			
subjects affected / exposed	1 / 158 (0.63%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemophilus infection			
subjects affected / exposed	1 / 158 (0.63%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes virus infection			

subjects affected / exposed	0 / 158 (0.00%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	1 / 158 (0.63%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Influenza			
subjects affected / exposed	2 / 158 (1.27%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infusion site cellulitis			
subjects affected / exposed	1 / 158 (0.63%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lobar pneumonia			
subjects affected / exposed	1 / 158 (0.63%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	2 / 158 (1.27%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	1 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection viral			
subjects affected / exposed	1 / 158 (0.63%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	1 / 158 (0.63%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumocystis jirovecii pneumonia			

subjects affected / exposed	3 / 158 (1.90%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	25 / 158 (15.82%)	5 / 155 (3.23%)	
occurrences causally related to treatment / all	13 / 28	3 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia bacterial			
subjects affected / exposed	2 / 158 (1.27%)	2 / 155 (1.29%)	
occurrences causally related to treatment / all	1 / 2	1 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pneumonia bordetella			
subjects affected / exposed	1 / 158 (0.63%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia cytomegaloviral			
subjects affected / exposed	1 / 158 (0.63%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia escherichia			
subjects affected / exposed	1 / 158 (0.63%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia fungal			
subjects affected / exposed	1 / 158 (0.63%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia klebsiella			
subjects affected / exposed	1 / 158 (0.63%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia mycoplasmal			

subjects affected / exposed	1 / 158 (0.63%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia pneumococcal			
subjects affected / exposed	3 / 158 (1.90%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia pseudomonas aeruginosa			
subjects affected / exposed	3 / 158 (1.90%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pneumonia respiratory syncytial viral			
subjects affected / exposed	1 / 158 (0.63%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia staphylococcal			
subjects affected / exposed	2 / 158 (1.27%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	2 / 2	0 / 0	
Pneumonia streptococcal			
subjects affected / exposed	1 / 158 (0.63%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia viral			
subjects affected / exposed	0 / 158 (0.00%)	1 / 155 (0.65%)	
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	2 / 158 (1.27%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pseudomonas bronchitis			

subjects affected / exposed	1 / 158 (0.63%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	1 / 158 (0.63%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	1 / 158 (0.63%)	0 / 155 (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 / 158 (0.63%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	3 / 158 (1.90%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	1 / 1	0 / 0	
Septic shock			
subjects affected / exposed	2 / 158 (1.27%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Skin infection			
subjects affected / exposed	2 / 158 (1.27%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal bacteraemia			
subjects affected / exposed	1 / 158 (0.63%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Streptococcal bacteraemia			

subjects affected / exposed	1 / 158 (0.63%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Streptococcal sepsis			
subjects affected / exposed	1 / 158 (0.63%)	0 / 155 (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	3 / 158 (1.90%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	2 / 158 (1.27%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection staphylococcal			
subjects affected / exposed	1 / 158 (0.63%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hypercalcaemia			
subjects affected / exposed	0 / 158 (0.00%)	2 / 155 (1.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	0 / 158 (0.00%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	0 / 158 (0.00%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypervolaemia			

subjects affected / exposed	0 / 158 (0.00%)	2 / 155 (1.29%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	1 / 158 (0.63%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	1 / 158 (0.63%)	1 / 155 (0.65%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malnutrition			
subjects affected / exposed	1 / 158 (0.63%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour lysis syndrome			
subjects affected / exposed	1 / 158 (0.63%)	0 / 155 (0.00%)	
occurrences causally related to treatment / all	0 / 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	Duvelisib	Ofatumumab	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	149 / 158 (94.30%)	130 / 155 (83.87%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	13 / 158 (8.23%)	4 / 155 (2.58%)	
occurrences (all)	18	4	
Hypotension			
subjects affected / exposed	4 / 158 (2.53%)	8 / 155 (5.16%)	
occurrences (all)	5	8	
General disorders and administration site conditions			

Asthenia			
subjects affected / exposed	20 / 158 (12.66%)	17 / 155 (10.97%)	
occurrences (all)	37	19	
Fatigue			
subjects affected / exposed	25 / 158 (15.82%)	18 / 155 (11.61%)	
occurrences (all)	38	21	
Oedema peripheral			
subjects affected / exposed	16 / 158 (10.13%)	7 / 155 (4.52%)	
occurrences (all)	22	7	
Pyrexia			
subjects affected / exposed	46 / 158 (29.11%)	15 / 155 (9.68%)	
occurrences (all)	76	18	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	36 / 158 (22.78%)	22 / 155 (14.19%)	
occurrences (all)	69	28	
Dyspnoea			
subjects affected / exposed	14 / 158 (8.86%)	9 / 155 (5.81%)	
occurrences (all)	15	11	
Productive cough			
subjects affected / exposed	8 / 158 (5.06%)	2 / 155 (1.29%)	
occurrences (all)	8	2	
Rhinorrhoea			
subjects affected / exposed	9 / 158 (5.70%)	3 / 155 (1.94%)	
occurrences (all)	10	3	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	8 / 158 (5.06%)	9 / 155 (5.81%)	
occurrences (all)	9	10	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	13 / 158 (8.23%)	3 / 155 (1.94%)	
occurrences (all)	25	3	
Aspartate aminotransferase increased			
subjects affected / exposed	15 / 158 (9.49%)	3 / 155 (1.94%)	
occurrences (all)	26	3	

Weight decreased			
subjects affected / exposed	21 / 158 (13.29%)	3 / 155 (1.94%)	
occurrences (all)	22	3	
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	2 / 158 (1.27%)	28 / 155 (18.06%)	
occurrences (all)	2	35	
Nervous system disorders			
Dizziness			
subjects affected / exposed	13 / 158 (8.23%)	5 / 155 (3.23%)	
occurrences (all)	14	6	
Headache			
subjects affected / exposed	13 / 158 (8.23%)	13 / 155 (8.39%)	
occurrences (all)	17	14	
Paraesthesia			
subjects affected / exposed	7 / 158 (4.43%)	15 / 155 (9.68%)	
occurrences (all)	7	20	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	39 / 158 (24.68%)	16 / 155 (10.32%)	
occurrences (all)	89	30	
Neutropenia			
subjects affected / exposed	53 / 158 (33.54%)	32 / 155 (20.65%)	
occurrences (all)	177	68	
Thrombocytopenia			
subjects affected / exposed	27 / 158 (17.09%)	9 / 155 (5.81%)	
occurrences (all)	45	12	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	17 / 158 (10.76%)	3 / 155 (1.94%)	
occurrences (all)	19	3	
Abdominal pain upper			
subjects affected / exposed	9 / 158 (5.70%)	5 / 155 (3.23%)	
occurrences (all)	9	6	
Colitis			

subjects affected / exposed	8 / 158 (5.06%)	1 / 155 (0.65%)	
occurrences (all)	8	1	
Constipation			
subjects affected / exposed	27 / 158 (17.09%)	12 / 155 (7.74%)	
occurrences (all)	36	12	
Diarrhoea			
subjects affected / exposed	79 / 158 (50.00%)	19 / 155 (12.26%)	
occurrences (all)	196	24	
Dry mouth			
subjects affected / exposed	8 / 158 (5.06%)	1 / 155 (0.65%)	
occurrences (all)	8	1	
Dyspepsia			
subjects affected / exposed	9 / 158 (5.70%)	4 / 155 (2.58%)	
occurrences (all)	10	5	
Nausea			
subjects affected / exposed	38 / 158 (24.05%)	17 / 155 (10.97%)	
occurrences (all)	49	20	
Paraesthesia oral			
subjects affected / exposed	0 / 158 (0.00%)	10 / 155 (6.45%)	
occurrences (all)	0	11	
Vomiting			
subjects affected / exposed	23 / 158 (14.56%)	10 / 155 (6.45%)	
occurrences (all)	29	12	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	11 / 158 (6.96%)	9 / 155 (5.81%)	
occurrences (all)	14	11	
Rash			
subjects affected / exposed	17 / 158 (10.76%)	18 / 155 (11.61%)	
occurrences (all)	22	23	
Rash maculo-papular			
subjects affected / exposed	9 / 158 (5.70%)	2 / 155 (1.29%)	
occurrences (all)	14	2	
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	11 / 158 (6.96%)	5 / 155 (3.23%)	
occurrences (all)	14	5	
Back pain			
subjects affected / exposed	12 / 158 (7.59%)	8 / 155 (5.16%)	
occurrences (all)	16	10	
Muscle spasms			
subjects affected / exposed	7 / 158 (4.43%)	8 / 155 (5.16%)	
occurrences (all)	7	10	
Pain in extremity			
subjects affected / exposed	9 / 158 (5.70%)	3 / 155 (1.94%)	
occurrences (all)	11	3	
Infections and infestations			
Bronchitis			
subjects affected / exposed	20 / 158 (12.66%)	12 / 155 (7.74%)	
occurrences (all)	29	16	
Nasopharyngitis			
subjects affected / exposed	13 / 158 (8.23%)	4 / 155 (2.58%)	
occurrences (all)	17	4	
Pneumonia			
subjects affected / exposed	8 / 158 (5.06%)	4 / 155 (2.58%)	
occurrences (all)	8	5	
Respiratory tract infection			
subjects affected / exposed	11 / 158 (6.96%)	3 / 155 (1.94%)	
occurrences (all)	18	4	
Upper respiratory tract infection			
subjects affected / exposed	22 / 158 (13.92%)	12 / 155 (7.74%)	
occurrences (all)	29	13	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	24 / 158 (15.19%)	5 / 155 (3.23%)	
occurrences (all)	37	5	
Dehydration			
subjects affected / exposed	8 / 158 (5.06%)	1 / 155 (0.65%)	
occurrences (all)	10	1	
Hyperkalaemia			

subjects affected / exposed	11 / 158 (6.96%)	5 / 155 (3.23%)	
occurrences (all)	12	5	
Hypokalaemia			
subjects affected / exposed	16 / 158 (10.13%)	3 / 155 (1.94%)	
occurrences (all)	32	3	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 April 2014	• Modified Inclusion criterion #3 to more clearly define eligibility around previous purine-analogue therapy. This change included the addition of a timeframe regarding relapse following previous therapy. • Revised exclusions for use of medications or procedures within a specified timeframe to add the use of live or live attenuated vaccines within 30 days prior to randomization. Other investigational therapy was also modified to remove the following: – "subjects who have received investigational agents with a half-life > 3 days or of unknown length may be allowed on a case by case basis after discussion with the medical monitor". • Changed Baseline QTcF exclusion criterion from > 480 ms to > 500 ms. • Updated treatment modifications (ie, dose interruptions/holds) with treatment interruption for duvelisib-treated subjects now based on new Grade 3 QTc > 20 ms from Baseline. • Added an additional secondary endpoint of lymph node response rate. • Reordered secondary endpoints based on re-examination of statistical assumptions. • Changed the statistical sections to improve the overall design of the trial: - Changed the efficacy boundaries for testing the primary endpoint of PFS from Pocock type to O'Brien-Fleming type for the following reasons: • The superiority of duvelisib compared to ofatumumab in PFS will not be declared by an independent data monitoring committee at an interim analysis unless very convincing evidence for efficacy is presented. • After this change, the criterion of stopping for efficacy was a one-sided p-value of 0.0015 (corresponding approximately to a HR of 0.540). Assuming the median PFS for ofatumumab arm is 9 months, the stopping rule will not be met unless the median PFS for duvelisib arm is approximately 16.7 months. • For the same number of events as the previous design (185 events), the overall power is greater than the previous design (93% vs 87%).
02 March 2015	• Changed the QTcF exclusion criteria from QTcF > 500 ms to > 480 ms; revised the "Dose Interruption/Hold/Modification Guidelines" to interrupt treatment for all QTcF prolongation ≥Grade 3 (≥ 500 ms). • Extended the length of survival follow-up from 3 to 6 years from randomization.
09 February 2017	• The Sponsor of Study IPI-145-07 was changed from Infinity to Verastem. • The maximum number of duvelisib treatment cycles (39 cycles) was removed to permit subjects experiencing clinical benefit after 39 cycles to continue duvelisib treatment until disease progression or unacceptable toxicity. • The criteria for receiving additional duvelisib beyond Cycle 19 was modified to reflect potential clinical benefit of a stable disease (SD) response.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported