



Clinical trial results: A Phase 2 Study of IPI-145 in Subjects with Refractory Indolent Non-Hodgkin Lymphoma Summary

EudraCT number	2013-004008-20
Trial protocol	GB IT HU CZ ES BE BG
Global end of trial date	18 November 2020

Results information

Result version number	v1
This version publication date	13 August 2023
First version publication date	13 August 2023

Trial information

Trial identification

Sponsor protocol code	IPI-145-06
-----------------------	------------

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01882803
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Secura Bio, Inc.
Sponsor organisation address	1995 Village Center Circle, Suite 128, Las Vegas, NV, United States, 89134
Public contact	Senior Director Medical Affairs, Secura Bio, Inc., +1 678-581-4536, bgregory@securabio.com
Scientific contact	Senior Director Medical Affairs, Secura Bio, Inc., +1 678-581-4536, bgregory@securabio.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	18 November 2020
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	18 November 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of this trial was to evaluate the therapeutic effect of duvelisib (IPI-145) administered to participants diagnosed with indolent non-Hodgkin lymphoma (defined as follicular lymphoma, marginal zone lymphoma [splenic, nodal and extranodal], or small lymphocytic lymphoma) whose disease was refractory to rituximab and to either chemotherapy or radioimmunotherapy.

Protection of trial subjects:

This study was conducted in accordance with 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	17 June 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	Belarus: 10
Country: Number of subjects enrolled	Canada: 9
Country: Number of subjects enrolled	Czechia: 9
Country: Number of subjects enrolled	Georgia: 1
Country: Number of subjects enrolled	United States: 46
Country: Number of subjects enrolled	Spain: 2
Country: Number of subjects enrolled	United Kingdom: 11
Country: Number of subjects enrolled	Belgium: 2
Country: Number of subjects enrolled	Bulgaria: 5
Country: Number of subjects enrolled	France: 6
Country: Number of subjects enrolled	Hungary: 7
Country: Number of subjects enrolled	Italy: 21
Worldwide total number of subjects	129
EEA total number of subjects	52

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)	64
From 65 to 84 years	62
85 years and over	3

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

This multicenter, multinational study enrolled participants at 56 medical clinics across 12 countries.

Period 1

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

Arms

Arm title	Duvelisib
------------------	-----------

Arm description:

Participants received a dose of 25 milligrams (mg) duvelisib twice daily (BID) over the course of 28-day treatment cycles until disease progression or unacceptable toxicity.

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:

Duvelisib was administered orally as a capsule.

Number of subjects in period 1	Duvelisib
Started	129
Received at Least 1 Dose of Study drug	129
Completed	0
Not completed	129
Consent withdrawn by subject	9
Physician decision	3
Disease progression	1
Death	68
Follow-up completed	39
Lost to follow-up	3
Study terminated by the Sponsor	6

Baseline characteristics

Reporting groups

Reporting group title	Overall Study
-----------------------	---------------

Reporting group description:

Full Analysis Set: all participants who received at least 1 dose of duvelisib.

Reporting group values	Overall Study	Total	
Number of subjects	129	129	
Age categorical			
Units: Subjects			
≤18 years	0	0	
Between 18 and 64 years	64	64	
≥65 years	65	65	
Age continuous			
Units: years			
arithmetic mean	63.6		
standard deviation	± 11.69	-	
Gender categorical			
Units: Subjects			
Female	41	41	
Male	88	88	
Ethnicity			
National Institutes of Health/Office of Management and Budget (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	3	3	
Not Hispanic or Latino	118	118	
Unknown or Not Reported	8	8	
Race			
Units: Subjects			
American Indian or Alaskan Native	1	1	
Asian	1	1	
Black or African American	6	6	
Native Hawaiian or other Pacific Islander	0	0	
White	116	116	
Other	1	1	
Unknown	2	2	
Missing	2	2	
Region of Enrollment			
Units: Subjects			
Hungary	7	7	
United States	46	46	
Czechia	9	9	
United Kingdom	11	11	
Belarus	10	10	
Spain	2	2	
Canada	9	9	
Belgium	2	2	

Italy	21	21	
Georgia	1	1	
France	6	6	
Bulgaria	5	5	

End points

End points reporting groups

Reporting group title	Duvelisib
Reporting group description: Participants received a dose of 25 milligrams (mg) duvelisib twice daily (BID) over the course of 28-day treatment cycles until disease progression or unacceptable toxicity.	
Subject analysis set title	IPI-656
Subject analysis set type	Sub-group analysis
Subject analysis set description: Participants who received at least 1 dose of duvelisib and with at least 1 adequate post-baseline blood sample for measuring concentrations of the main duvelisib metabolite, IPI-656.	
Subject analysis set title	Full Analysis Set
Subject analysis set type	Full analysis
Subject analysis set description: All participants who received at least 1 dose of duvelisib.	
Subject analysis set title	Pharmacokinetics Set
Subject analysis set type	Sub-group analysis
Subject analysis set description: All participants who received at least 1 dose of duvelisib and with at least 1 adequate post-baseline blood sample.	

Primary: Overall Response Rate (ORR)

End point title	Overall Response Rate (ORR) ^[1]
End point description: ORR, defined as the total percentage of participants who had a best overall response of either complete response (CR) or partial response (PR), was evaluated locally (investigator's assessment) and by an independent, third-party panel of radiologists and oncologists (Independent Review Committee [IRC]) according to the revised International Working Group (IWG) Response Criteria for Malignant Lymphoma. ORR is reported with a 2-sided 95% exact confidence interval. ORR was tested against the null ($\leq 30\%$) by 1-sided exact binomial test at 0.025 level. The p-value (≤ 0.0001) was calculated by 1-sided exact binomial test with the null hypothesis that ORR $\leq 30\%$.	
End point type	Primary
End point timeframe: Every 8-16 weeks while on treatment with duvelisib for up to 72 months	

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: Statistical analysis (p-value) located under 'End point description'.

End point values	Duvelisib			
Subject group type	Reporting group			
Number of subjects analysed	129 ^[2]			
Units: percent				
number (confidence interval 95%)	59.7 (50.7 to 68.2)			

Notes:

[2] - Full Analysis Set

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Treatment-emergent Adverse Events (TEAEs)

End point title	Number of Participants With Treatment-emergent Adverse Events (TEAEs)
-----------------	---

End point description:

An adverse event was defined as any untoward medical occurrence in a participant who received study drug without regard to possibility of causal relationship. A TEAE was defined as any adverse event that emerged or worsened in the period from the first dose of study treatment to 30 days after the last dose of study treatment. A summary of serious and all other non-serious adverse events regardless of causality is located in the Reported Adverse Events module.

End point type	Secondary
----------------	-----------

End point timeframe:

Every 2-8 weeks for up to 73 months

End point values	Duvelisib			
Subject group type	Reporting group			
Number of subjects analysed	129 ^[3]			
Units: Participant	128			

Notes:

[3] - Full Analysis Set

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR)

End point title	Duration of Response (DOR)
-----------------	----------------------------

End point description:

DOR, defined as the time from the first documentation of response to either progressive disease (PD) or death due to any cause, was evaluated locally (investigator's assessment) and by an independent, third-party panel of radiologists and oncologists (IRC) according to the revised IWG Response Criteria for Malignant Lymphoma.

End point type	Secondary
----------------	-----------

End point timeframe:

Every 8-16 weeks for up to 72 months

End point values	Duvelisib			
Subject group type	Reporting group			
Number of subjects analysed	129 ^[4]			
Units: month				
median (confidence interval 95%)	10.16 (8.78 to 13.61)			

Notes:

[4] - Full Analysis Set

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free Survival (PFS)

End point title	Progression-free Survival (PFS)
-----------------	---------------------------------

End point description:

PFS, defined as the time from the first dose of study treatment to the first documentation of either Investigator-assessed PD or death resulting from any cause, was evaluated locally (investigator's assessment) and by an independent, third-party panel of radiologists and oncologists (IRC) according to the revised IWG Response Criteria for Malignant Lymphoma.

End point type	Secondary
----------------	-----------

End point timeframe:

Every 8-16 weeks for up to 72 months

End point values	Duvelisib			
Subject group type	Reporting group			
Number of subjects analysed	129 ^[5]			
Units: month				
median (confidence interval 95%)	9.57 (8.35 to 11.70)			

Notes:

[5] - Full Analysis Set

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)
-----------------	-----------------------

End point description:

OS, defined as the time from the first dose of study treatment to the date of death, was evaluated locally (investigator's assessment) and by an independent, third-party panel of radiologists and oncologists (IRC) according to the revised IWG Response Criteria for Malignant Lymphoma.

End point type	Secondary
----------------	-----------

End point timeframe:

Every 16 weeks for up to 72 months

End point values	Duvelisib			
Subject group type	Reporting group			
Number of subjects analysed	129 ^[6]			
Units: month				
median (confidence interval 95%)	28.96 (21.37 to 37.02)			

Notes:

[6] - Full Analysis Set

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Concentration of Duvelisib and IPI-656

End point title	Plasma Concentration of Duvelisib and IPI-656
-----------------	---

End point description:

The serum concentration of duvelisib and its main metabolite, IPI-656, are reported for Day 15 of Cycle 1 (C1D15) and Day 1 of Cycle 2 (C2D1) and Day 1 of Cycle 3 (C3D1). Results are reported in nanograms/millilitre (ng/mL).

End point type	Secondary
----------------	-----------

End point timeframe:

Every 4 weeks for 12 weeks (C1D15: predose, 1 and 4 hours post dose; C2D1 and C3D1: anytime during study visit)

End point values	Duvelisib	IPI-656		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	129 ^[7]	129 ^[8]		
Units: ng/mL				
median (full range (min-max))				
C1D15 Predose	414 (19 to 4590)	648 (116 to 6010)		
C1D15 1 hour post dose	1175 (206 to 6820)	641 (160 to 5920)		
C1D15 4 hours post dose	852 (233 to 5170)	714 (230 to 6020)		
C2D1	631 (0000 to 4180)	704 (0000 to 10200)		
C3D1	696 (0000 to 3540)	664 (0000 to 6850)		

Notes:

[7] - Pharmacokinetics Set; N = 117, 118, 129, 129, 110

0000 = lower limit of quantification

[8] - Pharmacokinetics Set; N = 117, 118, 118, 117, 110

0000 = lower limit of quantification

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Response (TTR)

End point title	Time to Response (TTR)
-----------------	------------------------

End point description:

TTR, defined as the time from the first dose of study treatment to the first documentation of response, was evaluated locally (investigator's assessment) and by an independent, third-party panel of radiologists and oncologists (IRC) according to the revised IWG Response Criteria for Malignant Lymphoma.

End point type	Secondary
----------------	-----------

End point timeframe:

First dose to first documentation of complete or partial response (up to 6 months)

End point values	Duvelisib			
Subject group type	Reporting group			
Number of subjects analysed	59 ^[9]			
Units: month				
median (inter-quartile range (Q1-Q3))	1.87 (1.71 to 3.65)			

Notes:

[9] - Participants in the FAS who were responders (CR or PR) per IRC.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

73 months

Assessment type	Systematic
-----------------	------------

Dictionary used

Dictionary name	MedDRA
-----------------	--------

Dictionary version	16.1
--------------------	------

Reporting groups

Reporting group title	Duvelisib
-----------------------	-----------

Reporting group description:

Participants received a dose of 25 mg duvelisib BID over the course of 28-day treatment cycles until disease progression or unacceptable toxicity.

Serious adverse events	Duvelisib		
Total subjects affected by serious adverse events			
subjects affected / exposed	83 / 129 (64.34%)		
number of deaths (all causes)	68		
number of deaths resulting from adverse events	18		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Squamous cell carcinoma of skin			
subjects affected / exposed	3 / 129 (2.33%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Acute myeloid leukaemia			
subjects affected / exposed	1 / 129 (0.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Malignant melanoma			
subjects affected / exposed	1 / 129 (0.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Myelodysplastic syndrome			
subjects affected / exposed	1 / 129 (0.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Neuroendocrine carcinoma of the skin			
subjects affected / exposed	1 / 129 (0.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Non-small cell lung cancer			
subjects affected / exposed	1 / 129 (0.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Squamous cell carcinoma			
subjects affected / exposed	1 / 129 (0.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 129 (0.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Embolism			
subjects affected / exposed	1 / 129 (0.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Peripheral embolism			
subjects affected / exposed	1 / 129 (0.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Superior vena cava syndrome			
subjects affected / exposed	1 / 129 (0.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Disease progression			

subjects affected / exposed	9 / 129 (6.98%)		
occurrences causally related to treatment / all	0 / 9		
deaths causally related to treatment / all	0 / 9		
Pyrexia			
subjects affected / exposed	4 / 129 (3.10%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
General physical health deterioration			
subjects affected / exposed	2 / 129 (1.55%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Fatigue			
subjects affected / exposed	1 / 129 (0.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Pneumonitis			
subjects affected / exposed	4 / 129 (3.10%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 1		
Pleural effusion			
subjects affected / exposed	3 / 129 (2.33%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Respiratory failure			
subjects affected / exposed	2 / 129 (1.55%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 129 (0.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Dyspnoea			

subjects affected / exposed	1 / 129 (0.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory disorder			
subjects affected / exposed	1 / 129 (0.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 129 (0.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Amylase increased			
subjects affected / exposed	1 / 129 (0.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood creatinine increased			
subjects affected / exposed	1 / 129 (0.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lipase increased			
subjects affected / exposed	1 / 129 (0.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	1 / 129 (0.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Spinal compression fracture			
subjects affected / exposed	1 / 129 (0.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Traumatic fracture subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 129 (0.78%) 0 / 1 0 / 0		
Cardiac disorders Atrial fibrillation subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	2 / 129 (1.55%) 0 / 2 0 / 0		
Cardiac failure subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 129 (0.78%) 0 / 1 0 / 0		
Cardiac failure congestive subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 129 (0.78%) 0 / 1 0 / 1		
Cardio-respiratory arrest subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 129 (0.78%) 0 / 1 0 / 1		
Coronary artery occlusion subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 129 (0.78%) 0 / 1 0 / 0		
Pericarditis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 129 (0.78%) 0 / 1 0 / 0		
Nervous system disorders Transient ischaemic attack subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 129 (0.78%) 0 / 1 0 / 0		

Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	9 / 129 (6.98%)		
occurrences causally related to treatment / all	0 / 9		
deaths causally related to treatment / all	0 / 0		
Pancytopenia			
subjects affected / exposed	4 / 129 (3.10%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Anaemia			
subjects affected / exposed	2 / 129 (1.55%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Thrombocytopenia			
subjects affected / exposed	2 / 129 (1.55%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Lymphadenopathy			
subjects affected / exposed	1 / 129 (0.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Glaucoma			
subjects affected / exposed	1 / 129 (0.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	10 / 129 (7.75%)		
occurrences causally related to treatment / all	0 / 10		
deaths causally related to treatment / all	0 / 0		
Colitis			

subjects affected / exposed	6 / 129 (4.65%)			
occurrences causally related to treatment / all	0 / 6			
deaths causally related to treatment / all	0 / 1			
Enterocolitis				
subjects affected / exposed	2 / 129 (1.55%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Vomiting				
subjects affected / exposed	2 / 129 (1.55%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Abdominal mass				
subjects affected / exposed	1 / 129 (0.78%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Abdominal pain				
subjects affected / exposed	2 / 129 (1.55%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Duodenitis				
subjects affected / exposed	1 / 129 (0.78%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nausea				
subjects affected / exposed	1 / 129 (0.78%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Oesophagitis				
subjects affected / exposed	1 / 129 (0.78%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pancreatitis acute				

subjects affected / exposed	1 / 129 (0.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Small intestinal haemorrhage			
subjects affected / exposed	1 / 129 (0.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 129 (0.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hyperbilirubinaemia			
subjects affected / exposed	1 / 129 (0.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	3 / 129 (2.33%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Rash generalised			
subjects affected / exposed	2 / 129 (1.55%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Dermatitis allergic			
subjects affected / exposed	1 / 129 (0.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Dermatitis exfoliative			
subjects affected / exposed	1 / 129 (0.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Drug reaction with eosinophilia and			

systemic symptoms			
subjects affected / exposed	1 / 129 (0.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Toxic epidermal necrolysis			
subjects affected / exposed	1 / 129 (0.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Renal and urinary disorders			
Renal failure acute			
subjects affected / exposed	4 / 129 (3.10%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Renal failure			
subjects affected / exposed	2 / 129 (1.55%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Rhabdomyolysis			
subjects affected / exposed	1 / 129 (0.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Pneumonia			
subjects affected / exposed	7 / 129 (5.43%)		
occurrences causally related to treatment / all	0 / 7		
deaths causally related to treatment / all	0 / 1		
Bronchopneumonia			
subjects affected / exposed	4 / 129 (3.10%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Cellulitis			

subjects affected / exposed	3 / 129 (2.33%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Lower respiratory tract infection				
subjects affected / exposed	2 / 129 (1.55%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Oral candidiasis				
subjects affected / exposed	2 / 129 (1.55%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Pneumonia pseudomonas aeruginosa				
subjects affected / exposed	2 / 129 (1.55%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Bronchitis				
subjects affected / exposed	1 / 129 (0.78%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Bronchopulmonary aspergillosis				
subjects affected / exposed	1 / 129 (0.78%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Campylobacter gastroenteritis				
subjects affected / exposed	1 / 129 (0.78%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Campylobacter infection				
subjects affected / exposed	1 / 129 (0.78%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Clostridium difficile colitis				

subjects affected / exposed	1 / 129 (0.78%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cystitis pseudomonal				
subjects affected / exposed	1 / 129 (0.78%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Diverticulitis				
subjects affected / exposed	1 / 129 (0.78%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Enteritis infectious				
subjects affected / exposed	1 / 129 (0.78%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Escherichia sepsis				
subjects affected / exposed	1 / 129 (0.78%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis				
subjects affected / exposed	1 / 129 (0.78%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infective myositis				
subjects affected / exposed	1 / 129 (0.78%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Influenza				
subjects affected / exposed	1 / 129 (0.78%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Klebsiella sepsis				

subjects affected / exposed	1 / 129 (0.78%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Neutropenic sepsis				
subjects affected / exposed	1 / 129 (0.78%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Oropharyngeal candidiasis				
subjects affected / exposed	1 / 129 (0.78%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumocystis jirovecii pneumonia				
subjects affected / exposed	1 / 129 (0.78%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia cytomegaloviral				
subjects affected / exposed	1 / 129 (0.78%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia moraxella				
subjects affected / exposed	1 / 129 (0.78%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pseudomembranous colitis				
subjects affected / exposed	1 / 129 (0.78%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pseudomonal bacteraemia				
subjects affected / exposed	1 / 129 (0.78%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pseudomonal sepsis				

subjects affected / exposed	1 / 129 (0.78%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pyelonephritis acute				
subjects affected / exposed	1 / 129 (0.78%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Scrotal infection				
subjects affected / exposed ^[1]	1 / 88 (1.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Sepsis				
subjects affected / exposed	1 / 129 (0.78%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Sepsis syndrome				
subjects affected / exposed	1 / 129 (0.78%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Septic shock				
subjects affected / exposed	1 / 129 (0.78%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Urinary tract infection				
subjects affected / exposed	1 / 129 (0.78%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Viral infection				
subjects affected / exposed	1 / 129 (0.78%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Vulval cellulitis				

subjects affected / exposed ^[2]	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Hypercalcaemia			
subjects affected / exposed	2 / 129 (1.55%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Hypokalaemia			
subjects affected / exposed	2 / 129 (1.55%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Hyperkalaemia			
subjects affected / exposed	1 / 129 (0.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypoglycaemia			
subjects affected / exposed	1 / 129 (0.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hyponatraemia			
subjects affected / exposed	1 / 129 (0.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Notes:

[1] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.

Justification: This adverse event only affected male participants.

[2] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.

Justification: This adverse event only affected female participants.

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

Non-serious adverse events	Duvelisib		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	122 / 129 (94.57%)		
Investigations			

Alanine aminotransferase increased			
subjects affected / exposed	17 / 129 (13.18%)		
occurrences (all)	39		
Aspartate aminotransferase increased			
subjects affected / exposed	13 / 129 (10.08%)		
occurrences (all)	27		
Weight decreased			
subjects affected / exposed	13 / 129 (10.08%)		
occurrences (all)	17		
Lipase increased			
subjects affected / exposed	12 / 129 (9.30%)		
occurrences (all)	23		
Blood creatinine increased			
subjects affected / exposed	8 / 129 (6.20%)		
occurrences (all)	9		
Blood alkaline phosphatase increased			
subjects affected / exposed	7 / 129 (5.43%)		
occurrences (all)	9		
Blood lactate dehydrogenase increased			
subjects affected / exposed	7 / 129 (5.43%)		
occurrences (all)	7		
Neutrophil count decreased			
subjects affected / exposed	7 / 129 (5.43%)		
occurrences (all)	17		
Vascular disorders			
Hypertension			
subjects affected / exposed	7 / 129 (5.43%)		
occurrences (all)	7		
Hypotension			
subjects affected / exposed	7 / 129 (5.43%)		
occurrences (all)	8		
Nervous system disorders			
Headache			
subjects affected / exposed	21 / 129 (16.28%)		
occurrences (all)	25		
Dizziness			

subjects affected / exposed occurrences (all)	7 / 129 (5.43%) 7		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	36 / 129 (27.91%)		
occurrences (all)	78		
Neutropenia			
subjects affected / exposed	37 / 129 (28.68%)		
occurrences (all)	140		
Thrombocytopenia			
subjects affected / exposed	25 / 129 (19.38%)		
occurrences (all)	55		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	37 / 129 (28.68%)		
occurrences (all)	57		
Pyrexia			
subjects affected / exposed	32 / 129 (24.81%)		
occurrences (all)	50		
Oedema peripheral			
subjects affected / exposed	22 / 129 (17.05%)		
occurrences (all)	32		
Asthenia			
subjects affected / exposed	15 / 129 (11.63%)		
occurrences (all)	19		
Chills			
subjects affected / exposed	9 / 129 (6.98%)		
occurrences (all)	15		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	63 / 129 (48.84%)		
occurrences (all)	139		
Nausea			
subjects affected / exposed	38 / 129 (29.46%)		
occurrences (all)	46		
Vomiting			

subjects affected / exposed	22 / 129 (17.05%)		
occurrences (all)	25		
Abdominal pain			
subjects affected / exposed	20 / 129 (15.50%)		
occurrences (all)	24		
Constipation			
subjects affected / exposed	15 / 129 (11.63%)		
occurrences (all)	17		
Dry mouth			
subjects affected / exposed	9 / 129 (6.98%)		
occurrences (all)	12		
Stomatitis			
subjects affected / exposed	9 / 129 (6.98%)		
occurrences (all)	9		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	35 / 129 (27.13%)		
occurrences (all)	53		
Dyspnoea			
subjects affected / exposed	14 / 129 (10.85%)		
occurrences (all)	16		
Oropharyngeal pain			
subjects affected / exposed	8 / 129 (6.20%)		
occurrences (all)	11		
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	22 / 129 (17.05%)		
occurrences (all)	52		
Night sweats			
subjects affected / exposed	13 / 129 (10.08%)		
occurrences (all)	15		
Pruritus			
subjects affected / exposed	10 / 129 (7.75%)		
occurrences (all)	15		
Hyperhidrosis			

subjects affected / exposed occurrences (all)	7 / 129 (5.43%) 7		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	19 / 129 (14.73%)		
occurrences (all)	32		
Back pain			
subjects affected / exposed	18 / 129 (13.95%)		
occurrences (all)	19		
Pain in extremity			
subjects affected / exposed	13 / 129 (10.08%)		
occurrences (all)	17		
Musculoskeletal pain			
subjects affected / exposed	8 / 129 (6.20%)		
occurrences (all)	8		
Infections and infestations			
Oral candidiasis			
subjects affected / exposed	8 / 129 (6.20%)		
occurrences (all)	10		
Urinary tract infection			
subjects affected / exposed	7 / 129 (5.43%)		
occurrences (all)	9		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	19 / 129 (14.73%)		
occurrences (all)	30		
Hypokalaemia			
subjects affected / exposed	18 / 129 (13.95%)		
occurrences (all)	24		
Hyperuricaemia			
subjects affected / exposed	11 / 129 (8.53%)		
occurrences (all)	13		
Dehydration			
subjects affected / exposed	8 / 129 (6.20%)		
occurrences (all)	9		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 April 2014	- Added human immunodeficiency virus screening/history at Screening. - Added guidance regarding use of vaccines, specifically the prohibition of live and live attenuated vaccines prior to and during study treatment. - Prophylaxis for herpes simplex virus and herpes zoster virus was added as a requirement for all participants. In addition, cytomegalovirus (CMV) prophylaxis was added as a recommendation for participants with prior CMV infection that required treatment, and additional monitoring for reactivation was added as a recommendation for these participants. - Modified Exclusion #2 to prohibit any prior treatment with phosphoinositide-3-kinase (PI3K) inhibitors and to add prior treatment with Bruton's tyrosine kinase (BTK) inhibitors to exclusion criterion. - The statistical design of the study was updated from the previously used precision-based method to a group sequential design in the hypothesis testing framework. - Primary objective and endpoint definition were corrected to ORR, with overall response defined as best response of CR or PR. - TTR was added as a secondary endpoint. - Baseline corrected QT interval (QTc) measurements using the Fridericia's correction method exclusion criterion was changed from >480 milliseconds (ms) to >500 ms; treatment modifications (that is, dose interruptions/holds) were updated with treatment interruption for duvelisib-treated participants now based on new Grade 3 QTc >20 ms from baseline. - Exclusion criteria were added for certain cardiac events and for participants who have had gastric bypass or other procedures that may affect absorption of duvelisib. - The 25 mg once a day dose level was replaced with 10 mg BID for dose level -2. A new dose level of 5 mg BID (-3) was added. - Concomitant medication sections for antimicrobial prophylaxis, use of vaccines, immunosuppressants, PI3K and BTK inhibitors, and photosafety were added.
30 April 2015	- Changed to allow participants to continue to receive duvelisib treatment for an additional year after 13 cycles if they have documented evidence of response (CR or PR) or stable disease. This had been amended from the original language which required a CR or PR. - Changed to enroll approximately 80 follicular lymphoma participants, rather than at least 100. The amended estimate was based on the accrual pattern of the subtypes observed in the study. - Change to reflect that an independent data monitoring committee (DMC), rather than an internal DMC, was assembled to periodically review all available safety information and review efficacy data at the interim analysis.
03 November 2015	- Changed to state that participants who display evidence of clinical benefit after 1 year of treatment may continue to receive duvelisib until disease progression or unacceptable toxicity. This was amended from allowing participants to receive up to a total of 2 years of treatment. - The cautionary statements on concomitant use of cytochrome P450 substrates were strengthened. - An exploratory efficacy endpoint evaluating lymph node response rate was added.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported