Clinical trial results:
A randomized, double-blind Phase III study of copanlisib versus placebo in patients with rituximab-refractory indolent non-Hodgkin's lymphoma (iNHL) - CHRONOS-2

Summary

EudraCT number	2014-000925-19
Trial protocol	AT IE GR PL IT
Global end of trial date	26 October 2022

Results information

Result version number	v1 (current)
This version publication date	20 October 2023
First version publication date	20 October 2023

Trial information

Trial identification

Sponsor protocol code	BAY80-6946 / 17322

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02369016
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Bayer AG
Sponsor organisation address	Kaiser Wilhelm Allee, Leverkusen, Germany, D-51368
Public contact	Therapeutic Area Head, Bayer AG, clinical-trials-contact@bayer.com
Scientific contact	Therapeutic Area Head, Bayer AG, clinical-trials-contact@bayer.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	15 December 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	26 October 2022
Global end of trial reached?	Yes
Global end of trial date	26 October 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the safety of copanlisib.

Protection of trial subjects:

The conduct of this clinical study met all local legal and regulatory requirements. The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and the International Conference on Harmonization guideline E6: Good Clinical Practice. Before entering the study, the informed consent form was read by and explained to all subjects. Participating subjects signed informed consent form and could withdraw from the study at any time without any disadvantage and without having to provide a reason for this decision. Only investigators qualified by training and experience were selected as appropriate experts to investigate the study drug.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	22 September 2015
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	Brazil: 1
Country: Number of subjects enrolled	Bulgaria: 1
Country: Number of subjects enrolled	Greece: 2
Country: Number of subjects enrolled	Italy: 1
Country: Number of subjects enrolled	Poland: 3
Country: Number of subjects enrolled	Russian Federation: 7
Country: Number of subjects enrolled	Korea, Republic of: 6
Country: Number of subjects enrolled	Taiwan: 2
Country: Number of subjects enrolled	Turkey: 2
Worldwide total number of subjects	25
EEA total number of subjects	7

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)	17
From 65 to 84 years	8
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 20 study centers in 10 countries/regions: Brazil (2), Bulgaria (1), Greece (1), Italy (2), Poland (1), Russian Federation (5), South Africa (1), South Korea (5), Taiwan (1) and Turkey (1) between 22 September 2015 (first patient first visit) and 26 October 2022 (last patient last visit).

Pre-assignment

Screening details:

34 participants were screened. 9 participants were screening failures and 25 participants were randomized to study treatment: 17 to copanlisib and 8 to placebo. All randomized participants also received at least one dose of study treatment and were valid for safety analyses. After study unblinding 7 placebo participants switched to copanlisib.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Copanlisib (BAY80-6946, Aliqopa)

Arm description:

Participants who were randomized to copanlisib until end of the study

Arm type	Experimental
Investigational medicinal product name	Copanlisib 60 mg solution for infusion
Investigational medicinal product code	BAY80-6946
Other name	Aliqopa
Pharmaceutical forms	Solution for infusion
Routes of administration	Infusion

Dosage and administration details:

Copanlisib was administered IV over approximately 1 h on Days 1, 8, and 15 of each 28-day treatment cycle (3 weeks on/1 week off).

Arm title	Placebo

Arm description:

Participants who were randomized to placebo until switching from placebo to copanlisib after disease progression or after study unblinding

Arm type	Experimental
Investigational medicinal product name	placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Placebo was administered IV over approximately 1 h on Days 1, 8, and 15 of each 28-day treatment cycle (3 weeks on/1 week off).

Number of subjects in period 1	Copanlisib (BAY80-6946, Aliqopa)	Placebo
Started	17	8
Completed	0	0
Not completed	17	8
AE associated with clinical disease progression	2	1
AE not associated with clinical diseaseprogression	4	1
Progressive disease - clinical progression	1	4
withdrawal by patient	4	-
Progressive disease - radiological progression	6	2

Baseline characteristics

Reporting groups	
Reporting group title	overall

Reporting group description: -

Reporting group values	overall	Total	
Number of subjects	25	25	
Age categorical Units: Subjects			
Adults (18-64 years)	17	17	
From 65-84 years	8	8	
Gender categorical Units: Subjects			
Female	8	8	
Male	17	17	

Subject analysis sets	
Subject analysis set title	Safety analysis set
Subject analysis set type	Safety analysis

Subject analysis set description:

All participants with at least one administration of the study drug were included in the Safety analysis set.

Subject analysis set title	Full analysis set
Subject analysis set type	Full analysis

Subject analysis set description:

All participants who were randomized to the treatment arms at the start of the study were included in the FAS.

Subject analysis set title	Switched to copanlisib
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants who switched from placebo to copanlisib

Subject analysis set title	Treated with copanlisib
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants who were treated with copanlisib (randomized to copanlisib + switched from placebo to copanlisib)

Reporting group values	Safety analysis set	Full analysis set	Switched to copanlisib
Number of subjects	25	25	7
Age categorical Units: Subjects			
Adults (18-64 years)	17	17	4
From 65-84 years	8	8	3
Gender categorical Units: Subjects			
Female	8	8	1
Male	17	17	6

Reporting group values	Treated with copanlisib		
Number of subjects	24		
Age categorical Units: Subjects			
Adults (18-64 years)	16		
From 65-84 years	8		
Gender categorical Units: Subjects			
Female	8		
Male	16		

End points

End points reporting groups

Reporting group title	Copanlisib (BAY80-6946, Aliqopa)
Reporting group description: Participants who were randomized to copanlisib until end of the study	
Reporting group title	Placebo
Reporting group description: Participants who were randomized to placebo until switching from placebo to copanlisib after disease progression or after study unblinding	
Subject analysis set title	Safety analysis set
Subject analysis set type	Safety analysis
Subject analysis set description: All participants with at least one administration of the study drug were included in the Safety analysis set.	
Subject analysis set title	Full analysis set
Subject analysis set type	Full analysis
Subject analysis set description: All participants who were randomized to the treatment arms at the start of the study were included in the FAS.	
Subject analysis set title	Switched to copanlisib
Subject analysis set type	Sub-group analysis
Subject analysis set description: Participants who switched from placebo to copanlisib	
Subject analysis set title	Treated with copanlisib
Subject analysis set type	Sub-group analysis
Subject analysis set description: Participants who were treated with copanlisib (randomized to copanlisib + switched from placebo to copanlisib)	

Primary: Number of participants with treatment-emergent adverse events (TEAE)s

End point title	Number of participants with treatment-emergent adverse events (TEAE)s[1]
End point description: Adverse event data were collected after signing the informed consent until 30 days after the last study drug administration (end of safety follow-up)	
End point type	Primary
End point timeframe: up to 7 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: Due the limited number of patients, statistical analyses included in this study focused on descriptive statistics only.
Due to the short duration of placebo treatment before switching to copanlisib and the small number of patients receiving placebo, any comparisons between copanlisib and placebo treatment are not considered meaningful.

End point values	Copanlisib (BAY80-6946, Aliqopa)	Placebo	Switched to copanlisib	Treated with copanlisib
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	17	8	7	24
Units: patients	17	7	7	24

Statistical analyses

No statistical analyses for this end point

Primary: Number of participants with treatment-emergent serious adverse events

End point title	Number of participants with treatment-emergent serious adverse events[2]

End point description:

Serious Adverse event data were collected after signing the informed consent until 30 days after the last study drug administration (end of safety follow-up)

End point type	Primary

End point timeframe:

up to 7 years

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Due the limited number of patients, statistical analyses included in this study focused on descriptive statistics only.
Due to the short duration of placebo treatment before switching to copanlisib and the small number of patients receiving placebo, any comparisons between copanlisib and placebo treatment are not considered meaningful.

End point values	Copanlisib (BAY80-6946, Aliqopa)	Placebo	Switched to copanlisib	Treated with copanlisib
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	17	8	7	24
Units: patients	6	1	5	11

Statistical analyses

No statistical analyses for this end point

Primary: Participants with abnormal laboratory parameters

End point title	Participants with abnormal laboratory parameters[3]

End point description:

- Above threshold 10% and reported as TEAEs - - any event grade 1-4 -

End point type	Primary

End point timeframe:

up to 7 years

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Due the limited number of patients, statistical analyses included in this study focused on descriptive statistics only.
Due to the short duration of placebo treatment before switching to copanlisib and the small number of patients receiving placebo, any comparisons between copanlisib and placebo treatment are not considered meaningful.

End point values	Copanlisib (BAY80-6946, Aliqopa)	Placebo	Switched to copanlisib	Treated with copanlisib
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	17	8	7	24
Units: patients				
ANY	9	1	3	12
Hyperglycaemia	6	0	4	10
Neutropenia	6	0	1	7
Neutrophil count decreased	4	0	2	6
Anaemia	2	2	4	6
Platelet count decreased	3	0	2	5

Statistical analyses

No statistical analyses for this end point

Primary: Participants with abnormal vital signs

End point title	Participants with abnormal vital signs[4]

End point description:

- Reported as TEAEs - worst CTCAE grade 'total' -

End point type	Primary

End point timeframe:

up to 7 years

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Due the limited number of patients, statistical analyses included in this study focused on descriptive statistics only.
Due to the short duration of placebo treatment before switching to copanlisib and the small number of patients receiving placebo, any comparisons between copanlisib and placebo treatment are not considered meaningful.

End point values	Copanlisib (BAY80-6946, Aliqopa)	Placebo	Switched to copanlisib	Treated with copanlisib
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	17	8	7	24
Units: patients				
Blood pressure increased	2	0	1	3
Electrocardiogram QT prolonged	1	0	0	1

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
from the start of study drug administration until 30 days after the last study drug administraion, up to end of safety follow-up, approximately 7 years	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	25.1

Reporting groups	
Reporting group title	Randomized to copanlisib
Reporting group description:	
Participants who were randomized to copanlisib and continued copanlisib treatment after study unbilnding (randomized to copanlisib group)	
Reporting group title	Randomized to placebo
Reporting group description:	
Participants who were randomized to placebo until switching from placebo to copanlsib after disease progression or after study unblinding	
Reporting group title	Switched to copanlisib
Reporting group description:	
Participants who switched from placebo to copanlisib	
Reporting group title	Treated with copanlisib
Reporting group description:	
Participants who were treated with copanlisib (randomized to copanlisib + switched from placebo to copanlisib)	

Serious adverse events	Randomized to copanlisib	Randomized to placebo	Switched to copanlisib
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 17 (35.29%)	1 / 8 (12.50%)	5 / 7 (71.43%)
number of deaths (all causes)	2	1	2
number of deaths resulting from adverse events	0	0	2
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 17 (5.88%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Alanine aminotransferase increased			
subjects affected / exposed	1 / 17 (5.88%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration			

site conditions			
General physical health deterioration			
subjects affected / exposed	1 / 17 (5.88%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 17 (5.88%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 17 (0.00%)	0 / 8 (0.00%)	1 / 7 (14.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Skin and subcutaneous tissue disorders			
Skin ulcer			
subjects affected / exposed	0 / 17 (0.00%)	1 / 8 (12.50%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Cellulitis			
subjects affected / exposed	1 / 17 (5.88%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	1 / 17 (5.88%)	0 / 8 (0.00%)	2 / 7 (28.57%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Klebsiella bacteraemia			
subjects affected / exposed	0 / 17 (0.00%)	0 / 8 (0.00%)	1 / 7 (14.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Pneumocystis jirovecii pneumonia			

subjects affected / exposed	1 / 17 (5.88%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hyperglycaemic hyperosmolar nonketotic syndrome			
subjects affected / exposed	0 / 17 (0.00%)	0 / 8 (0.00%)	1 / 7 (14.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Treated with copanlisib		
Total subjects affected by serious adverse events			
subjects affected / exposed	11 / 24 (45.83%)		
number of deaths (all causes)	4		
number of deaths resulting from adverse events	2		
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Alanine aminotransferase increased			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
General physical health deterioration			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			

Dyspnoea				
subjects affected / exposed	1 / 24 (4.17%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Skin and subcutaneous tissue disorders				
Skin ulcer				
subjects affected / exposed	0 / 24 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Cellulitis				
subjects affected / exposed	1 / 24 (4.17%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	3 / 24 (12.50%)			
occurrences causally related to treatment / all	1 / 4			
deaths causally related to treatment / all	0 / 0			
Klebsiella bacteraemia				
subjects affected / exposed	1 / 24 (4.17%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Pneumocystis jirovecii pneumonia				
subjects affected / exposed	1 / 24 (4.17%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
Hyperglycaemic hyperosmolar nonketotic syndrome				
subjects affected / exposed	1 / 24 (4.17%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			

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

Non-serious adverse events	Randomized to copanlisib	Randomized to placebo	Switched to copanlisib
Total subjects affected by non-serious adverse events			
subjects affected / exposed	17 / 17 (100.00%)	7 / 8 (87.50%)	7 / 7 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Seborrhoeic keratosis			
subjects affected / exposed	0 / 17 (0.00%)	1 / 8 (12.50%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Cancer pain			
subjects affected / exposed	0 / 17 (0.00%)	0 / 8 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Vascular disorders			
Hypertension			
subjects affected / exposed	3 / 17 (17.65%)	1 / 8 (12.50%)	2 / 7 (28.57%)
occurrences (all)	32	1	19
Surgical and medical procedures			
Tooth extraction			
subjects affected / exposed	1 / 17 (5.88%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
General disorders and administration site conditions			
Extravasation			
subjects affected / exposed	1 / 17 (5.88%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Asthenia			
subjects affected / exposed	0 / 17 (0.00%)	1 / 8 (12.50%)	1 / 7 (14.29%)
occurrences (all)	0	1	2
Fatigue			
subjects affected / exposed	1 / 17 (5.88%)	0 / 8 (0.00%)	1 / 7 (14.29%)
occurrences (all)	3	0	1
Pain			
subjects affected / exposed	0 / 17 (0.00%)	0 / 8 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Injection site irritation			
subjects affected / exposed	1 / 17 (5.88%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Pyrexia			

subjects affected / exposed	2 / 17 (11.76%)	0 / 8 (0.00%)	3 / 7 (42.86%)
occurrences (all)	6	0	4
General physical health deterioration			
subjects affected / exposed	1 / 17 (5.88%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Non-cardiac chest pain			
subjects affected / exposed	0 / 17 (0.00%)	0 / 8 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 17 (5.88%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Immunodeficiency common variable			
subjects affected / exposed	0 / 17 (0.00%)	0 / 8 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	3 / 17 (17.65%)	1 / 8 (12.50%)	2 / 7 (28.57%)
occurrences (all)	3	1	4
Catarrh			
subjects affected / exposed	1 / 17 (5.88%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Upper-airway cough syndrome			
subjects affected / exposed	1 / 17 (5.88%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Organising pneumonia			
subjects affected / exposed	1 / 17 (5.88%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Sinus pain			
subjects affected / exposed	0 / 17 (0.00%)	0 / 8 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Rhinorrhoea			
subjects affected / exposed	2 / 17 (11.76%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences (all)	2	0	0
Productive cough			

subjects affected / exposed	1 / 17 (5.88%)	2 / 8 (25.00%)	1 / 7 (14.29%)
occurrences (all)	5	3	1
Lung disorder			
subjects affected / exposed	0 / 17 (0.00%)	0 / 8 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Dyspnoea			
subjects affected / exposed	1 / 17 (5.88%)	0 / 8 (0.00%)	2 / 7 (28.57%)
occurrences (all)	1	0	2
Psychiatric disorders			
Depressed mood			
subjects affected / exposed	1 / 17 (5.88%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Restlessness			
subjects affected / exposed	1 / 17 (5.88%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Insomnia			
subjects affected / exposed	2 / 17 (11.76%)	0 / 8 (0.00%)	1 / 7 (14.29%)
occurrences (all)	2	0	1
Investigations			
Blood bilirubin increased			
subjects affected / exposed	1 / 17 (5.88%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Blood creatinine increased			
subjects affected / exposed	1 / 17 (5.88%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Blood pressure increased			
subjects affected / exposed	2 / 17 (11.76%)	0 / 8 (0.00%)	1 / 7 (14.29%)
occurrences (all)	12	0	7
Electrocardiogram QT prolonged			
subjects affected / exposed	1 / 17 (5.88%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Platelet count decreased			
subjects affected / exposed	3 / 17 (17.65%)	0 / 8 (0.00%)	2 / 7 (28.57%)
occurrences (all)	5	0	4
Neutrophil count decreased			

subjects affected / exposed	4 / 17 (23.53%)	0 / 8 (0.00%)	2 / 7 (28.57%)
occurrences (all)	9	0	4
N-terminal prohormone brain natriuretic peptide increased			
subjects affected / exposed	0 / 17 (0.00%)	0 / 8 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 17 (0.00%)	0 / 8 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Cytomegalovirus test positive			
subjects affected / exposed	1 / 17 (5.88%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Weight increased			
subjects affected / exposed	1 / 17 (5.88%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Weight decreased			
subjects affected / exposed	2 / 17 (11.76%)	1 / 8 (12.50%)	1 / 7 (14.29%)
occurrences (all)	4	1	1
Lipase increased			
subjects affected / exposed	1 / 17 (5.88%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	1 / 17 (5.88%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences (all)	2	0	0
Accidental overdose			
subjects affected / exposed	1 / 17 (5.88%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Cervical vertebral fracture			
subjects affected / exposed	1 / 17 (5.88%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Lumbar vertebral fracture			
subjects affected / exposed	1 / 17 (5.88%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Thoracic vertebral fracture			

subjects affected / exposed	1 / 17 (5.88%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Limb injury			
subjects affected / exposed	0 / 17 (0.00%)	0 / 8 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Cardiac disorders			
Tachycardia			
subjects affected / exposed	0 / 17 (0.00%)	1 / 8 (12.50%)	1 / 7 (14.29%)
occurrences (all)	0	6	3
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 17 (17.65%)	0 / 8 (0.00%)	1 / 7 (14.29%)
occurrences (all)	5	0	1
Dizziness			
subjects affected / exposed	3 / 17 (17.65%)	1 / 8 (12.50%)	0 / 7 (0.00%)
occurrences (all)	8	1	0
Ataxia			
subjects affected / exposed	0 / 17 (0.00%)	1 / 8 (12.50%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Muscle contractions involuntary			
subjects affected / exposed	1 / 17 (5.88%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Paraesthesia			
subjects affected / exposed	1 / 17 (5.88%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences (all)	4	0	0
Somnolence			
subjects affected / exposed	1 / 17 (5.88%)	0 / 8 (0.00%)	1 / 7 (14.29%)
occurrences (all)	1	0	1
Neuralgia			
subjects affected / exposed	1 / 17 (5.88%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Tremor			
subjects affected / exposed	1 / 17 (5.88%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Blood and lymphatic system disorders			

Neutropenia			
subjects affected / exposed	6 / 17 (35.29%)	0 / 8 (0.00%)	1 / 7 (14.29%)
occurrences (all)	14	0	4
Thrombocytopenia			
subjects affected / exposed	1 / 17 (5.88%)	0 / 8 (0.00%)	2 / 7 (28.57%)
occurrences (all)	1	0	2
Lymphopenia			
subjects affected / exposed	1 / 17 (5.88%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences (all)	11	0	0
Anaemia			
subjects affected / exposed	2 / 17 (11.76%)	2 / 8 (25.00%)	4 / 7 (57.14%)
occurrences (all)	2	2	11
Hyperviscosity syndrome			
subjects affected / exposed	1 / 17 (5.88%)	1 / 8 (12.50%)	0 / 7 (0.00%)
occurrences (all)	1	1	0
Ear and labyrinth disorders			
External ear inflammation			
subjects affected / exposed	1 / 17 (5.88%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Eye disorders			
Conjunctivitis allergic			
subjects affected / exposed	1 / 17 (5.88%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences (all)	2	0	0
Conjunctival hyperaemia			
subjects affected / exposed	1 / 17 (5.88%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Lacrimation increased			
subjects affected / exposed	1 / 17 (5.88%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	1 / 17 (5.88%)	1 / 8 (12.50%)	1 / 7 (14.29%)
occurrences (all)	1	1	1
Abdominal pain			
subjects affected / exposed	2 / 17 (11.76%)	2 / 8 (25.00%)	0 / 7 (0.00%)
occurrences (all)	2	2	0
Abdominal pain upper			

subjects affected / exposed	1 / 17 (5.88%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Anal fissure			
subjects affected / exposed	0 / 17 (0.00%)	0 / 8 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Constipation			
subjects affected / exposed	0 / 17 (0.00%)	2 / 8 (25.00%)	0 / 7 (0.00%)
occurrences (all)	0	2	0
Dental caries			
subjects affected / exposed	1 / 17 (5.88%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Diarrhoea			
subjects affected / exposed	3 / 17 (17.65%)	0 / 8 (0.00%)	1 / 7 (14.29%)
occurrences (all)	12	0	6
Dyspepsia			
subjects affected / exposed	0 / 17 (0.00%)	0 / 8 (0.00%)	2 / 7 (28.57%)
occurrences (all)	0	0	2
Gastric ulcer			
subjects affected / exposed	2 / 17 (11.76%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences (all)	2	0	0
Gastritis			
subjects affected / exposed	0 / 17 (0.00%)	0 / 8 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Gastrointestinal pain			
subjects affected / exposed	1 / 17 (5.88%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Gingival pain			
subjects affected / exposed	2 / 17 (11.76%)	0 / 8 (0.00%)	1 / 7 (14.29%)
occurrences (all)	2	0	1
Haemorrhoids			
subjects affected / exposed	0 / 17 (0.00%)	0 / 8 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Mouth ulceration			
subjects affected / exposed	1 / 17 (5.88%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences (all)	2	0	0
Stomatitis			

subjects affected / exposed	3 / 17 (17.65%)	0 / 8 (0.00%)	2 / 7 (28.57%)
occurrences (all)	5	0	2
Proctalgia			
subjects affected / exposed	1 / 17 (5.88%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Nausea			
subjects affected / exposed	2 / 17 (11.76%)	1 / 8 (12.50%)	0 / 7 (0.00%)
occurrences (all)	6	1	0
Hepatobiliary disorders			
Hepatotoxicity			
subjects affected / exposed	0 / 17 (0.00%)	0 / 8 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Skin and subcutaneous tissue disorders			
Dermatitis			
subjects affected / exposed	0 / 17 (0.00%)	0 / 8 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Rash			
subjects affected / exposed	0 / 17 (0.00%)	0 / 8 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Pruritus			
subjects affected / exposed	1 / 17 (5.88%)	1 / 8 (12.50%)	0 / 7 (0.00%)
occurrences (all)	1	1	0
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	1 / 17 (5.88%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Dry skin			
subjects affected / exposed	1 / 17 (5.88%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Dermatitis bullous			
subjects affected / exposed	1 / 17 (5.88%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Dermatitis atopic			
subjects affected / exposed	1 / 17 (5.88%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Paraneoplastic rash			

subjects affected / exposed	1 / 17 (5.88%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Urticaria			
subjects affected / exposed	1 / 17 (5.88%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences (all)	3	0	0
Skin ulcer			
subjects affected / exposed	0 / 17 (0.00%)	1 / 8 (12.50%)	1 / 7 (14.29%)
occurrences (all)	0	1	1
Skin reaction			
subjects affected / exposed	1 / 17 (5.88%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Rash maculo-papular			
subjects affected / exposed	1 / 17 (5.88%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Renal and urinary disorders			
Renal colic			
subjects affected / exposed	1 / 17 (5.88%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal and connective tissue disorders			
Bone pain			
subjects affected / exposed	1 / 17 (5.88%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Arthralgia			
subjects affected / exposed	0 / 17 (0.00%)	1 / 8 (12.50%)	1 / 7 (14.29%)
occurrences (all)	0	1	1
Joint contracture			
subjects affected / exposed	0 / 17 (0.00%)	0 / 8 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Muscular weakness			
subjects affected / exposed	1 / 17 (5.88%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Myalgia			
subjects affected / exposed	2 / 17 (11.76%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences (all)	3	0	0
Musculoskeletal chest pain			

subjects affected / exposed	1 / 17 (5.88%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal stiffness			
subjects affected / exposed	1 / 17 (5.88%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences (all)	2	0	0
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 17 (0.00%)	0 / 8 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Cellulitis			
subjects affected / exposed	1 / 17 (5.88%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Clostridium difficile colitis			
subjects affected / exposed	0 / 17 (0.00%)	0 / 8 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Conjunctivitis			
subjects affected / exposed	1 / 17 (5.88%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Herpes zoster			
subjects affected / exposed	1 / 17 (5.88%)	0 / 8 (0.00%)	1 / 7 (14.29%)
occurrences (all)	1	0	1
Herpes simplex			
subjects affected / exposed	1 / 17 (5.88%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Nasopharyngitis			
subjects affected / exposed	1 / 17 (5.88%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Pneumonia			
subjects affected / exposed	1 / 17 (5.88%)	0 / 8 (0.00%)	2 / 7 (28.57%)
occurrences (all)	1	0	2
Periodontitis			
subjects affected / exposed	1 / 17 (5.88%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Scrub typhus			
subjects affected / exposed	1 / 17 (5.88%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0

Sinusitis			
subjects affected / exposed	1 / 17 (5.88%)	0 / 8 (0.00%)	1 / 7 (14.29%)
occurrences (all)	3	0	2
Upper respiratory tract infection			
subjects affected / exposed	1 / 17 (5.88%)	0 / 8 (0.00%)	3 / 7 (42.86%)
occurrences (all)	1	0	4
Urinary tract infection			
subjects affected / exposed	3 / 17 (17.65%)	1 / 8 (12.50%)	0 / 7 (0.00%)
occurrences (all)	3	1	0
Oral infection			
subjects affected / exposed	1 / 17 (5.88%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Respiratory tract infection viral			
subjects affected / exposed	0 / 17 (0.00%)	0 / 8 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Alveolar osteitis			
subjects affected / exposed	0 / 17 (0.00%)	0 / 8 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Pneumocystis jirovecii pneumonia			
subjects affected / exposed	1 / 17 (5.88%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Herpes zoster reactivation			
subjects affected / exposed	0 / 17 (0.00%)	0 / 8 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Metabolism and nutrition disorders			
Hyperuricaemia			
subjects affected / exposed	2 / 17 (11.76%)	1 / 8 (12.50%)	0 / 7 (0.00%)
occurrences (all)	3	1	0
Hypermagnesaemia			
subjects affected / exposed	1 / 17 (5.88%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Hyperglycaemia			
subjects affected / exposed	6 / 17 (35.29%)	0 / 8 (0.00%)	4 / 7 (57.14%)
occurrences (all)	107	0	59
Hypercholesterolaemia			

subjects affected / exposed	1 / 17 (5.88%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences (all)	2	0	0
Hypercalcaemia			
subjects affected / exposed	0 / 17 (0.00%)	0 / 8 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Cachexia			
subjects affected / exposed	0 / 17 (0.00%)	1 / 8 (12.50%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Hypocalcaemia			
subjects affected / exposed	0 / 17 (0.00%)	0 / 8 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Hypophosphataemia			
subjects affected / exposed	0 / 17 (0.00%)	1 / 8 (12.50%)	2 / 7 (28.57%)
occurrences (all)	0	1	3
Hypomagnesaemia			
subjects affected / exposed	1 / 17 (5.88%)	0 / 8 (0.00%)	1 / 7 (14.29%)
occurrences (all)	2	0	1
Hypokalaemia			
subjects affected / exposed	0 / 17 (0.00%)	0 / 8 (0.00%)	2 / 7 (28.57%)
occurrences (all)	0	0	3
Lactic acidosis			
subjects affected / exposed	0 / 17 (0.00%)	1 / 8 (12.50%)	1 / 7 (14.29%)
occurrences (all)	0	1	1
Decreased appetite			
subjects affected / exposed	2 / 17 (11.76%)	1 / 8 (12.50%)	1 / 7 (14.29%)
occurrences (all)	2	1	1
Dyslipidaemia			
subjects affected / exposed	1 / 17 (5.88%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0

Non-serious adverse events	Treated with copanlisib		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	24 / 24 (100.00%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			

Seborrhoeic keratosis subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0		
Cancer pain subjects affected / exposed occurrences (all)	1 / 24 (4.17%) 1		
Vascular disorders Hypertension subjects affected / exposed occurrences (all)	5 / 24 (20.83%) 51		
Surgical and medical procedures Tooth extraction subjects affected / exposed occurrences (all)	1 / 24 (4.17%) 1		
General disorders and administration site conditions Extravasation subjects affected / exposed occurrences (all)	1 / 24 (4.17%) 1		
Asthenia subjects affected / exposed occurrences (all)	1 / 24 (4.17%) 2		
Fatigue subjects affected / exposed occurrences (all)	2 / 24 (8.33%) 4		
Pain subjects affected / exposed occurrences (all)	1 / 24 (4.17%) 1		
Injection site irritation subjects affected / exposed occurrences (all)	1 / 24 (4.17%) 1		
Pyrexia subjects affected / exposed occurrences (all)	5 / 24 (20.83%) 10		
General physical health deterioration subjects affected / exposed occurrences (all)	1 / 24 (4.17%) 1		

Non-cardiac chest pain			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Immunodeficiency common variable			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	5 / 24 (20.83%)		
occurrences (all)	7		
Catarrh			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Upper-airway cough syndrome			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Organising pneumonia			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Sinus pain			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Rhinorrhoea			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	2		
Productive cough			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	6		
Lung disorder			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Dyspnoea			

subjects affected / exposed	3 / 24 (12.50%)		
occurrences (all)	3		
Psychiatric disorders			
Depressed mood			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Restlessness			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Insomnia			
subjects affected / exposed	3 / 24 (12.50%)		
occurrences (all)	3		
Investigations			
Blood bilirubin increased			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Blood creatinine increased			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Blood pressure increased			
subjects affected / exposed	3 / 24 (12.50%)		
occurrences (all)	19		
Electrocardiogram QT prolonged			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Platelet count decreased			
subjects affected / exposed	5 / 24 (20.83%)		
occurrences (all)	9		
Neutrophil count decreased			
subjects affected / exposed	6 / 24 (25.00%)		
occurrences (all)	13		
N-terminal prohormone brain natriuretic peptide increased			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Blood alkaline phosphatase increased			

subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Cytomegalovirus test positive			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Weight increased			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Weight decreased			
subjects affected / exposed	3 / 24 (12.50%)		
occurrences (all)	5		
Lipase increased			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	2		
Accidental overdose			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Cervical vertebral fracture			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Lumbar vertebral fracture			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Thoracic vertebral fracture			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Limb injury			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Cardiac disorders			

Tachycardia subjects affected / exposed occurrences (all)	1 / 24 (4.17%) 3		
Nervous system disorders Headache subjects affected / exposed occurrences (all) Dizziness subjects affected / exposed occurrences (all) Ataxia subjects affected / exposed occurrences (all) Muscle contractions involuntary subjects affected / exposed occurrences (all) Paraesthesia subjects affected / exposed occurrences (all) Somnolence subjects affected / exposed occurrences (all) Neuralgia subjects affected / exposed occurrences (all) Tremor subjects affected / exposed occurrences (all)	 4 / 24 (16.67%) 6 3 / 24 (12.50%) 8 0 / 24 (0.00%) 0 1 / 24 (4.17%) 1 1 / 24 (4.17%) 4 2 / 24 (8.33%) 2 1 / 24 (4.17%) 1 1 / 24 (4.17%) 1		
Blood and lymphatic system disorders Neutropenia subjects affected / exposed occurrences (all) Thrombocytopenia subjects affected / exposed occurrences (all) Lymphopenia	 7 / 24 (29.17%) 18 3 / 24 (12.50%) 3		

subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	11		
Anaemia			
subjects affected / exposed	6 / 24 (25.00%)		
occurrences (all)	13		
Hyperviscosity syndrome			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Ear and labyrinth disorders			
External ear inflammation			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Eye disorders			
Conjunctivitis allergic			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	2		
Conjunctival hyperaemia			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Lacrimation increased			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	2		
Abdominal pain			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	2		
Abdominal pain upper			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Anal fissure			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Constipation			

subjects affected / exposed	0 / 24 (0.00%)			
occurrences (all)	0			
Dental caries				
subjects affected / exposed	1 / 24 (4.17%)			
occurrences (all)	1			
Diarrhoea				
subjects affected / exposed	4 / 24 (16.67%)			
occurrences (all)	18			
Dyspepsia				
subjects affected / exposed	2 / 24 (8.33%)			
occurrences (all)	2			
Gastric ulcer				
subjects affected / exposed	2 / 24 (8.33%)			
occurrences (all)	2			
Gastritis				
subjects affected / exposed	1 / 24 (4.17%)			
occurrences (all)	1			
Gastrointestinal pain				
subjects affected / exposed	1 / 24 (4.17%)			
occurrences (all)	1			
Gingival pain				
subjects affected / exposed	3 / 24 (12.50%)			
occurrences (all)	3			
Haemorrhoids				
subjects affected / exposed	1 / 24 (4.17%)			
occurrences (all)	1			
Mouth ulceration				
subjects affected / exposed	1 / 24 (4.17%)			
occurrences (all)	2			
Stomatitis				
subjects affected / exposed	5 / 24 (20.83%)			
occurrences (all)	7			
Proctalgia				
subjects affected / exposed	1 / 24 (4.17%)			
occurrences (all)	1			
Nausea				

subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	6		
Hepatobiliary disorders			
Hepatotoxicity			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Dermatitis			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Rash			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Pruritus			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Dry skin			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Dermatitis bullous			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Dermatitis atopic			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Paraneoplastic rash			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Urticaria			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	3		
Skin ulcer			

subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Skin reaction			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Rash maculo-papular			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Renal and urinary disorders			
Renal colic			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Bone pain			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Arthralgia			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Joint contracture			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Muscular weakness			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Myalgia			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	3		
Musculoskeletal chest pain			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Musculoskeletal stiffness			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	2		
Infections and infestations			

Bronchitis				
subjects affected / exposed	1 / 24 (4.17%)			
occurrences (all)	1			
Cellulitis				
subjects affected / exposed	1 / 24 (4.17%)			
occurrences (all)	1			
Clostridium difficile colitis				
subjects affected / exposed	1 / 24 (4.17%)			
occurrences (all)	1			
Conjunctivitis				
subjects affected / exposed	1 / 24 (4.17%)			
occurrences (all)	1			
Herpes zoster				
subjects affected / exposed	2 / 24 (8.33%)			
occurrences (all)	2			
Herpes simplex				
subjects affected / exposed	1 / 24 (4.17%)			
occurrences (all)	1			
Nasopharyngitis				
subjects affected / exposed	1 / 24 (4.17%)			
occurrences (all)	1			
Pneumonia				
subjects affected / exposed	3 / 24 (12.50%)			
occurrences (all)	3			
Periodontitis				
subjects affected / exposed	1 / 24 (4.17%)			
occurrences (all)	1			
Scrub typhus				
subjects affected / exposed	1 / 24 (4.17%)			
occurrences (all)	1			
Sinusitis				
subjects affected / exposed	2 / 24 (8.33%)			
occurrences (all)	5			
Upper respiratory tract infection				
subjects affected / exposed	4 / 24 (16.67%)			
occurrences (all)	5			

Urinary tract infection subjects affected / exposed occurrences (all)	3 / 24 (12.50%) 3			
Oral infection subjects affected / exposed occurrences (all)	1 / 24 (4.17%) 1			
Respiratory tract infection viral subjects affected / exposed occurrences (all)	1 / 24 (4.17%) 1			
Alveolar osteitis subjects affected / exposed occurrences (all)	1 / 24 (4.17%) 1			
Pneumocystis jirovecii pneumonia subjects affected / exposed occurrences (all)	1 / 24 (4.17%) 1			
Herpes zoster reactivation subjects affected / exposed occurrences (all)	1 / 24 (4.17%) 1			
Metabolism and nutrition disorders Hyperuricaemia subjects affected / exposed occurrences (all)	2 / 24 (8.33%) 3			
Hypermagnesaemia subjects affected / exposed occurrences (all)	1 / 24 (4.17%) 1			
Hyperglycaemia subjects affected / exposed occurrences (all)	10 / 24 (41.67%) 166			
Hypercholesterolaemia subjects affected / exposed occurrences (all)	1 / 24 (4.17%) 2			
Hypercalcaemia subjects affected / exposed occurrences (all)	1 / 24 (4.17%) 1			
Cachexia				

subjects affected / exposed	0 / 24 (0.00%)		
occurrences (all)	0		
Hypocalcaemia			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Hypophosphataemia			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	3		
Hypomagnesaemia			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	3		
Hypokalaemia			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	3		
Lactic acidosis			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Decreased appetite			
subjects affected / exposed	3 / 24 (12.50%)		
occurrences (all)	3		
Dyslipidaemia			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 November 2014	• Several inclusion/exclusion and withdrawal criteria were modified. • The study target population for efficacy analysis was changed from iNHL to FL patients. • Randomization ratio was changed from 1:1 to 2:1 and prior treatment with PI3K inhibitors was added as a new stratification factor. • Time to improvement in disease-related symptoms physical (subscale) (DRS-P) and secondary PFS (PFS2) were added as efficacy variables.
16 February 2016	• Several inclusion/exclusion criteria were modified. • Guidance for the management of noninfectious pneumonitis (NIP), glucose and BP increases were updated.
21 July 2016	• Several inclusion/exclusion criteria were modified. • Withdrawal criteria of study treatment due to cytomegalovirus (CMV) infection was added. • Guidance for monitoring and prophylaxis of opportunistic infections was added.
31 March 2017	Changes were made following the sponsor's decision to stop enrollment due to a lack of feasibility to complete this study in a reasonable time frame: • Study design was modified from a randomized, double-blind, placebo-controlled study to an open-label, single arm study. • Statistical analyses and efficacy endpoints were revised. Primary efficacy endpoint was changed from PFS to objective response rate and several secondary efficacy endpoints were removed. • Central imaging review was removed, and bone marrow biopsy was changed to local standard of care.
01 December 2017	The study design was further modified due to the limited number of participants to be included in the analyses: • Primary endpoint was changed to safety and other study objectives were removed. • Active and survival follow-up periods were removed. • Several withdrawal criteria were modified. • Timing of statistical analysis and guidance for tumor assessments were changed.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported