Clinical trial results:
A Phase III, randomized, double-blind, placebo-controlled study evaluating the efficacy and safety of copanlisib in combination with rituximab in patients with relapsed indolent B-cell non-Hodgkin's lymphoma (iNHL) – CHRONOS-3

Summary

EudraCT number	2013-003893-29
Trial protocol	IE PT DE ES BE LT HU AT DK FR BG LU GR SK IT RO
Global end of trial date	15 November 2024

Results information

Result version number	v3 (current)
This version publication date	04 September 2025
First version publication date	12 September 2021
Version creation reason	• New data added to full data set data from final analysis

Trial information

Trial identification

Sponsor protocol code	BAY80-6946/17067

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02367040
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, +49 30 300139003, clinical-trials-contact@bayer.com
Scientific contact	Therapeutic Area Head, Bayer AG, +49 30 300139003, 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 November 2024
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	15 November 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate whether copanlisib in combination with rituximab is superior to placebo in combination with rituximab in prolonging progression-free survival (PFS) in patients with relapsed iNHL who have received one or more lines of treatment, including rituximab, and who either had a treatment-free interval of ≥ 12 months after completion of the last rituximab-containing treatment, or who are unwilling to receive chemotherapy/for whom chemotherapy is contraindicated on reason of age, comorbidities, and/or residual toxicity.

Protection of trial subjects:

The conduct of this clinical study met all local legal and regulatory requirements. The study was conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki and the International Council for Harmonization guideline E6: Good Clinical Practice. Before entering the study, the informed consent was read by and explained to all the participants (or their legally authorized representative according to local legislation). Participating participants (or their legally authorized representative according to local legislation) 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	03 August 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	Argentina: 6
Country: Number of subjects enrolled	Australia: 9
Country: Number of subjects enrolled	Brazil: 28
Country: Number of subjects enrolled	Austria: 7
Country: Number of subjects enrolled	Belgium: 1
Country: Number of subjects enrolled	Bulgaria: 13
Country: Number of subjects enrolled	Chile: 8
Country: Number of subjects enrolled	China: 81
Country: Number of subjects enrolled	Colombia: 9
Country: Number of subjects enrolled	France: 17
Country: Number of subjects enrolled	Germany: 8
Country: Number of subjects enrolled	Greece: 11
Country: Number of subjects enrolled	Hong Kong: 2

Country: Number of subjects enrolled	Hungary: 18
Country: Number of subjects enrolled	Ireland: 5
Country: Number of subjects enrolled	Italy: 4
Country: Number of subjects enrolled	Japan: 37
Country: Number of subjects enrolled	Malaysia: 9
Country: Number of subjects enrolled	Mexico: 5
Country: Number of subjects enrolled	Philippines: 4
Country: Number of subjects enrolled	Portugal: 2
Country: Number of subjects enrolled	Poland: 15
Country: Number of subjects enrolled	Romania: 16
Country: Number of subjects enrolled	Russian Federation: 25
Country: Number of subjects enrolled	Singapore: 6
Country: Number of subjects enrolled	Slovakia: 2
Country: Number of subjects enrolled	South Africa: 2
Country: Number of subjects enrolled	Korea, Republic of: 13
Country: Number of subjects enrolled	Spain: 11
Country: Number of subjects enrolled	Taiwan: 15
Country: Number of subjects enrolled	Thailand: 6
Country: Number of subjects enrolled	Turkey: 26
Country: Number of subjects enrolled	Ukraine: 15
Country: Number of subjects enrolled	United States: 18
Country: Number of subjects enrolled	Viet Nam: 4
Worldwide total number of subjects	458
EEA total number of subjects	130

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)	255
From 65 to 84 years	197
85 years and over	6

Subject disposition

Recruitment

Recruitment details:

The study was conducted at multiple centers in North America, South America, South Africa, Europe, Asia, and Australia between 03 August 2015 (first subject first visit) and 15 November 2024 (last subject first visit).

Pre-assignment

Screening details:

Overall, 652 were screened and total of 458 subjects were randomized in a 2:1 ratio to study treatment: 307 subjects to copanlisib/rituximab and 151 subjects to placebo/rituximab.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Copanlisib + Rituximab

Arm description:

Copanlisib (60 mg) was administered intravenously (IV) (over approximately 1 h) on Days 1, 8, and 15 of each 28-day cycle. Rituximab (375 mg/m^2) was administered weekly during Cycle 1 on Days 1, 8, 15, and 22, and then on Day 1 of Cycles 3, 5, 7, and 9. Copanlisib was administered before rituximab.

Arm type	Experimental
Investigational medicinal product name	Copanlisib
Investigational medicinal product code	BAY80-6946
Other name	
Pharmaceutical forms	Concentrate for emulsion for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Copanlisib was supplied as lyophilized preparation in a 6 ml injection vial. The total amount of copanlisib per vial was 60 mg. The solution for IV infusions was obtained after reconstitution with normal saline solution. Dosing was administered on Days 1, 8 and 15 of each 28-day cycle. Copanlisib was administered before rituximab.

Investigational medicinal product name	Rituximab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Rituximab dose 375 mg/m^2 body surface weekly during Cycle 1 on Days 1, 8, 15 and 22, and then on Day 1 of Cycles 3, 5, 7 and 9. The solution for IV infusions was obtained after reconstitution of a calculated concentration of 1 to 4 mg/ml rituximab into an infusion bag containing sterile, pyrogen-free sodium chloride 9 mg/ml (0.9%) solution for injection or 5% D-Glucose in water.

Arm title	Placebo + Rituximab

Arm description:

Placebo was administered intravenously (IV) (over approximately 1 h) on Days 1, 8, and 15 of each 28-day cycle. Rituximab (375 mg/m^2) was administered weekly during Cycle 1 on Days 1, 8, 15, and 22, and then on Day 1 of Cycles 3, 5, 7, and 9. Placebo was administered before rituximab.

Arm type	Experimental

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for emulsion for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Placebo was supplied as lyophilized preparation in a 6 ml injection vial. The developed placebo lyophilisate was equivalent to the 60 mg copanlisib formulation, with regard to the composition of excipients and the instructions for reconstitution and dose preparation. Placebo dosing was administered on Days 1, 8 and 15 of each 28-day cycle. Placebo was administered before rituximab.

Number of subjects in period 1	Copanlisib + Rituximab	Placebo + Rituximab
Started	307	151
Received treatment	304	149
Completed	0	4
Not completed	307	147
Progressive disease – radiological progression	54	80
Adverse event, serious fatal	2	-
AE associated with clinical disease progression	1	4
Physician decision	2	8
Non-compliance to study drug	1	-
Drug not administered	3	2
Study terminated by sponsor	19	2
Randomized by mistake with study treatment	1	-
AE not associated clinical disease progression	117	12
Failure to meet continuation criteria	1	-
Progressive disease – clinical progression	6	6
Other reason: Covid-19 pandemic related	1	-
Consent withdrawn by subject	51	16
Patient decision	40	14
Switching to other therapy	2	-
Lost to follow-up	1	1
Patient decision: COVID-19 pandemic related	1	-
Required procedure failed	1	-
Progressive disease	-	1
Lack of efficacy	1	-
Additional primary malignancy	1	1
Protocol deviation	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Copanlisib + Rituximab
Reporting group description:	
Copanlisib (60 mg) was administered intravenously (IV) (over approximately 1 h) on Days 1, 8, and 15 of each 28-day cycle. Rituximab (375 mg/m^2) was administered weekly during Cycle 1 on Days 1, 8, 15, and 22, and then on Day 1 of Cycles 3, 5, 7, and 9. Copanlisib was administered before rituximab.	
Reporting group title	Placebo + Rituximab
Reporting group description:	
Placebo was administered intravenously (IV) (over approximately 1 h) on Days 1, 8, and 15 of each 28-day cycle. Rituximab (375 mg/m^2) was administered weekly during Cycle 1 on Days 1, 8, 15, and 22, and then on Day 1 of Cycles 3, 5, 7, and 9. Placebo was administered before rituximab.	

Reporting group values	Copanlisib + Rituximab	Placebo + Rituximab	Total
Number of subjects	307	151	458
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	167	88	255
From 65-84 years	140	63	203
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	62.0	61.5	
standard deviation	± 12.1	± 11.0	-
Sex: Female, Male Units: Participants			
Female	154	66	220
Male	153	85	238
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	3	4	7
Asian	125	50	175
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	4	1	5
White	164	89	253
More than one race	0	0	0
Unknown or Not Reported	11	7	18
Eastern cooperative oncology group (ECOG) Performance Status (PS)			
ECOG PS was measured in a scale from 0 (best) to grade 2, where 0=Fully active, able to carry on all pre-diseases performance without restriction, 1=Restricted in physically strenuous activity but			

ambulatory and able to carry out work of a light or sedentary nature, 2=Ambulatory and capable of all self-care but unable to carry out any work activities, up and about more than 50 percent (%) waking hours (h).			
Units: Subjects			
0 – Fully active	182	95	277
1 – Restricted active	113	55	168
2 – Ambulatory and capable of all self-care	12	1	13
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	29	26	55
Not Hispanic or Latino	262	118	380
Unknown or Not Reported	16	7	23

End points

End points reporting groups

Reporting group title	Copanlisib + Rituximab
Reporting group description:	
Copanlisib (60 mg) was administered intravenously (IV) (over approximately 1 h) on Days 1, 8, and 15 of each 28-day cycle. Rituximab (375 mg/m^2) was administered weekly during Cycle 1 on Days 1, 8, 15, and 22, and then on Day 1 of Cycles 3, 5, 7, and 9. Copanlisib was administered before rituximab.	
Reporting group title	Placebo + Rituximab
Reporting group description:	
Placebo was administered intravenously (IV) (over approximately 1 h) on Days 1, 8, and 15 of each 28-day cycle. Rituximab (375 mg/m^2) was administered weekly during Cycle 1 on Days 1, 8, 15, and 22, and then on Day 1 of Cycles 3, 5, 7, and 9. Placebo was administered before rituximab.	
Subject analysis set title	Full analysis set (FAS)
Subject analysis set type	Full analysis
Subject analysis set description:	
All randomized subjects were included.	
Subject analysis set title	Safety analysis set (SAF)
Subject analysis set type	Safety analysis
Subject analysis set description:	
All FAS subjects with at least one intake of copanlisib/placebo or rituximab.	

Primary: Progression free survival (PFS) based on independent central review.

End point title	Progression free survival (PFS) based on independent central review.
End point description:	
Progression-free survival (PFS) was defined as the time from randomization to progressive disease (PD) or death due to any cause, whichever was earlier according to the Lugano Classification and Response criteria in patients affected by Waldenström macroglobulinemia.	
End point type	Primary
End point timeframe:	
From first participant randomization (20-Aug-2015) up to data cut-off date at primary completion (31-Aug-2020), approximately 5 years and 2-year follow-up after primary completion at 31-Aug-2022, up to 7 years and final analysis at 15-Nov-2024	

End point values	Copanlisib + Rituximab	Placebo + Rituximab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	307	151		
Units: Months				
median (confidence interval 95%)				
At data cut-off=31-Aug-2020	21.5 (17.8 to 33.0)	13.8 (10.2 to 17.5)		
At data cut-off=31-Aug-2022	23.2 (19.4 to 33.0)	13.8 (10.8 to 17.5)		
At data cut-off=15-Nov-2024	22.4 (19.7 to 30.7)	14.0 (11.4 to 19.2)		

Statistical analyses

Statistical analysis title	Progression free survival (PFS)
Statistical analysis description:	
At 2-year follow-up cut-off date	
Comparison groups	Copanlisib + Rituximab v Placebo + Rituximab
Number of subjects included in analysis	458
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.000003 [2]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.557
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.431
upper limit	0.722

Notes:

[1] - PFS was evaluated with the stratified log-rank test. HR and 95% CI were based on stratified Cox Regression Model.
[2] - 1-sided p-value

Statistical analysis title	Progression free survival (PFS)
Statistical analysis description:	
At primary completion date	
Comparison groups	Copanlisib + Rituximab v Placebo + Rituximab
Number of subjects included in analysis	458
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.000002 [4]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.52
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.393
upper limit	0.688

Notes:

[3] - PFS was evaluated with the stratified log-rank test. HR and 95% CI were based on stratified Cox Regression Model.
[4] - 1-sided p-value

Statistical analysis title	Progression free survival (PFS)
Statistical analysis description:	
At final analysis	
Comparison groups	Copanlisib + Rituximab v Placebo + Rituximab

Number of subjects included in analysis	458
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	= 0.000199 [6]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.643
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.502
upper limit	0.823

Notes:

[5] - PFS was evaluated with the stratified log-rank test. HR and 95% CI were based on stratified Cox Regression Model.
[6] - 1-sided p-value

Secondary: Objective response rate (ORR)

End point title	Objective response rate (ORR)

End point description:

Objective response rate (ORR) was defined as the percentage of subjects who have a best response rating over the whole duration of the study (i.e. until time of analysis of PFS) of complete response (CR) or partial response (PR) according to the Lugano Classification and for patients with Waldenström macroglobulinemia (WM) a response rating of CR, very good partial response (VGPR), PR, or minor response (MR) according to the Owen Criteria.

End point type	Secondary

End point timeframe:

From first subject randomization up to approximately 7 years at data cut-off date

End point values	Copanlisib + Rituximab	Placebo + Rituximab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	307	151		
Units: Percentage of subjects				
number (not applicable)				
At primary completion date	80.8	47.7		
At 2-year follow-up cut-off date	80.5	49.7		

Statistical analyses

Statistical analysis title	Objective response rate (ORR)

Statistical analysis description:

At 2-year follow-up cut-off date

Comparison groups	Copanlisib + Rituximab v Placebo + Rituximab

Number of subjects included in analysis	458
Analysis specification	Pre-specified
Analysis type	superiority[7]
P-value	< 0.000001 [8]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in ORR
Point estimate	30.67
Confidence interval	
level	95 %
sides	2-sided
lower limit	21.63
upper limit	39.72

Notes:

[7] - P-value from Cochran-Mantel-Haenszel (CMH) test stratified

[8] - 1-sided p-value

Statistical analysis title	Objective response rate (ORR)

Statistical analysis description:

At primary completion date

Comparison groups	Copanlisib + Rituximab v Placebo + Rituximab
Number of subjects included in analysis	458
Analysis specification	Pre-specified
Analysis type	superiority[9]
P-value	< 0.000001 [10]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in ORR
Point estimate	32.99
Confidence interval	
level	95 %
sides	2-sided
lower limit	23.95
upper limit	42.03

Notes:

[9] - P-value from Cochran-Mantel-Haenszel (CMH) test stratified

[10] - 1-sided p-value

Secondary: Complete response rate (CRR)

End point title	Complete response rate (CRR)

End point description:

Complete response rate (CRR) was defined as the percentage of subjects who had a best response rating over the whole duration of the study (i.e., until the time of analysis of PFS) according to the Lugano Classification and for patients with Waldenström macroglobulinemia (WM) a response rating of Complete Response according to the Owen Criteria.

End point type	Secondary

End point timeframe:

From first subject randomization up to approximately 7 years at data cut-off date

End point values	Copanlisib + Rituximab	Placebo + Rituximab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	307	151		
Units: Percentage of subjects				
number (not applicable)				
At primary completion date	33.9	14.6		
At 2-year follow-up cut-off date	34.2	15.2		

Statistical analyses

Statistical analysis title	Complete response rate (CRR)
Statistical analysis description:	
At 2-year follow-up cut-off date	
Comparison groups	Copanlisib + Rituximab v Placebo + Rituximab
Number of subjects included in analysis	458
Analysis specification	Pre-specified
Analysis type	superiority[11]
P-value	= 0.000001 [12]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in CRR
Point estimate	18.92
Confidence interval	
level	95 %
sides	2-sided
lower limit	11.11
upper limit	26.73

Notes:

[11] - P-value from Cochran-Mantel-Haenszel (CMH) test stratified

[12] - 1-sided p-value

Statistical analysis title	Complete response rate (CRR)
Statistical analysis description:	
At primary completion date	
Comparison groups	Copanlisib + Rituximab v Placebo + Rituximab
Number of subjects included in analysis	458
Analysis specification	Pre-specified
Analysis type	superiority[13]
P-value	< 0.000001 [14]
Method	Logrank
Parameter estimate	Difference in CRR
Point estimate	19.27
Confidence interval	
level	95 %
sides	2-sided
lower limit	11.57
upper limit	26.96

Notes:

[13] - P-value from Cochran-Mantel-Haenszel (CMH) test stratified.

[14] - 1-sided p-value

Secondary: Duration of response (DOR)

End point title	Duration of response (DOR)

End point description:

Duration of response (DOR) was defined as the time (in days) from first observed tumor response Complete Response (CR), Very good partial response (VGPR), Partial Response (PR) or Minor Response (MR) until progression or death from any cause, whichever occurred earlier according to the Owen Criteria. Only patients with response in FAS were included in the analysis.

End point type	Secondary

End point timeframe:

From first subject randomization up to approximately 7 years at data cut-off date

End point values	Copanlisib + Rituximab	Placebo + Rituximab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	307	151		
Units: Months				
median (confidence interval 95%)				
At primary completion date	20.4 (17.0 to 30.8)	17.3 (11.8 to 25.3)		
At 2-year follow-up cut-off date	25.9 (17.7 to 31.5)	15.2 (12.3 to 25.3)		

Statistical analyses

Statistical analysis title	Duration of response (DOR)

Statistical analysis description:

At 2-year follow-up cut-off date

Comparison groups	Copanlisib + Rituximab v Placebo + Rituximab
Number of subjects included in analysis	458
Analysis specification	Pre-specified
Analysis type	superiority[15]
P-value	= 0.051976 [16]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.761
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.547
upper limit	1.059

Notes:

[15] - DOR was evaluated with the stratified log-rank test. HR and 95% CI were based on stratified Cox Regression Model.

[16] - 1-sided p-value

Statistical analysis title	Duration of response (DOR)
Statistical analysis description:	
At primary completion date	
Comparison groups	Copanlisib + Rituximab v Placebo + Rituximab
Number of subjects included in analysis	458
Analysis specification	Pre-specified
Analysis type	superiority[17]
P-value	= 0.058262 [18]
Method	Logrank
Parameter estimate	Difference in DOR
Point estimate	0.741
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.508
upper limit	1.079

Notes:

[17] - DOR was evaluated with the stratified log-rank test. HR and 95% CI were based on stratified Cox Regression Model.
[18] - 1-sided p-value

Secondary: Disease control rate (DCR)

End point title	Disease control rate (DCR)

End point description:

Disease control rate was defined as the percentage of subjects who had a best response rating as Complete Response (CR), Partial Response (PR) or stable disease (SD) according to the Lugano Classification and for patients with Waldenström macroglobulinemia (WM) as a response rating of CR, very good partial response (VGPR), PR, minor response (MR) or stable disease (SD) according to the Owen Criteria.

End point type	Secondary

End point timeframe:

From first subject randomization up to approximately 7 years at data cut-off date

End point values	Copanlisib + Rituximab	Placebo + Rituximab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	307	151		
Units: Percentage of subjects				
number (not applicable)				
At primary completion date	89.3	84.8		
At 2-year follow-up cut-off date	89.3	84.8		

Statistical analyses

Statistical analysis title	Disease control rate (DCR)
Statistical analysis description:	
At 2-year follow-up cut-off date	
Comparison groups	Copanlisib + Rituximab v Placebo + Rituximab

Number of subjects included in analysis	458
Analysis specification	Pre-specified
Analysis type	superiority[19]
P-value	= 0.097339 [20]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in DCR
Point estimate	4.43
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.26
upper limit	11.12

Notes:

[19] - P-value from Cochran-Mantel-Haenszel (CMH) test stratified

[20] - 1-sided p-value

Statistical analysis title	Disease control rate (DCR)

Statistical analysis description:

At primary completion date

Comparison groups	Copanlisib + Rituximab v Placebo + Rituximab
Number of subjects included in analysis	458
Analysis specification	Pre-specified
Analysis type	superiority[21]
P-value	= 0.097339 [22]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in DCR
Point estimate	4.43
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.26
upper limit	11.12

Notes:

[21] - P-value from Cochran-Mantel-Haenszel (CMH) test stratified

[22] - 1-sided p-value

Secondary: Time to progression (TTP)

End point title	Time to progression (TTP)

End point description:

Time to progression (TTP) was defined as the time (days) from date of randomization to date of first observed disease progression according to the Lugano Classification and Response criteria in patients affected by Waldenström macroglobulinemia.

End point type	Secondary

End point timeframe:

From first subject randomization up to approximately 7 years at data cut-off date

End point values	Copanlisib + Rituximab	Placebo + Rituximab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	307	151		
Units: Months				
median (confidence interval 95%)				
At primary completion date	22.3 (19.4 to 33.2)	13.8 (10.8 to 18.7)		
At 2-year follow-up cut-off date	27.7 (21.9 to 33.3)	13.8 (11.0 to 18.7)		

Statistical analyses

Statistical analysis title	Time to progression (TTP)
Statistical analysis description:	
At primary completion date	
Comparison groups	Copanlisib + Rituximab v Placebo + Rituximab
Number of subjects included in analysis	458
Analysis specification	Pre-specified
Analysis type	superiority[23]
P-value	< 0.000001 [24]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.476
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.357
upper limit	0.635

Notes:

[23] - TTP was evaluated with the stratified log-rank test. HR and 95% CI were based on Cox Regression Model.
[24] - 1-sided p-value

Statistical analysis title	Time to progression (TTP)
Statistical analysis description:	
At 2-year follow-up cut-off date	
Comparison groups	Copanlisib + Rituximab v Placebo + Rituximab
Number of subjects included in analysis	458
Analysis specification	Pre-specified
Analysis type	superiority[25]
P-value	< 0.000001 [26]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.505
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.387
upper limit	0.659

Notes:

[25] - TTP was evaluated with the stratified log-rank test. HR and 95% CI were based on Cox Regression Model.
[26] - 1-sided p-value

Secondary: Overall survival (OS)

End point title	Overall survival (OS)

End point description:

Overall survival (OS) was defined as the time (in days) from randomization until death from any cause.

End point type	Secondary

End point timeframe:

From randomization up to the final analysis at 15-Nov-2024

End point values	Copanlisib + Rituximab	Placebo + Rituximab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	307[27]	151[28]		
Units: Months				
median (confidence interval 95%)	99999 (82.2 to 99999)	99999 (77.3 to 99999)		

Notes:

[27] - 99999 - value cannot be estimated due to censored data (insufficient number of events).

[28] - 99999 - value cannot be estimated due to censored data (insufficient number of events).

Statistical analyses

Statistical analysis title	Overall survival (OS)
Comparison groups	Copanlisib + Rituximab v Placebo + Rituximab
Number of subjects included in analysis	458
Analysis specification	Pre-specified
Analysis type	superiority[29]
P-value	= 0.436458 [30]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.972
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.691
upper limit	1.368

Notes:

[29] - OS was evaluated with the stratified log-rank test. HR and 95% CI were based on Cox Regression Model.
[30] - 1-sided p-value

Secondary: Time to deterioration in DRS-P (Disease-Related Symptoms – Physical) of at least three points, as measured by the Functional Assessment of Cancer Therapy Lymphoma Symptom Index-18 (FLymSI-18) questionnaire.

End point title	Time to deterioration in DRS-P (Disease-Related Symptoms – Physical) of at least three points, as measured by the Functional Assessment of Cancer Therapy Lymphoma Symptom Index-18 (FLymSI-18) questionnaire.

End point description:

Time to deterioration in DRS-P (Disease-Related Symptoms – Physical) of at least three points was defined as the time (in days) from randomization to DRS-P decline, progression, or death due to any reason, whichever occurred earlier. The Lymphoma Symptom Index-18 (FLymSI-18) questionnaire contains 18 items, each of which utilizes a Likert scale with 5 possible responses ranging from 0 'Not at all' to 4 'Very much' and was divided into a total score.

End point type	Secondary

End point timeframe:

From first subject randomization up to approximately 7 years at data cut-off date

End point values	Copanlisib + Rituximab	Placebo + Rituximab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	307	151		
Units: Months				
median (confidence interval 95%)				
At primary completion date	5.5 (4.2 to 5.9)	5.5 (4.0 to 7.4)		
At 2-year follow-up cut-off date	5.5 (4.2 to 5.9)	5.5 (4.1 to 7.4)		

Statistical analyses

Statistical analysis title	Time to deterioration in DRS-P

Statistical analysis description:

At 2-year follow-up cut-off date

Comparison groups	Copanlisib + Rituximab v Placebo + Rituximab
Number of subjects included in analysis	458
Analysis specification	Pre-specified
Analysis type	superiority[31]
P-value	= 0.661145 [32]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.047
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.841
upper limit	1.302

Notes:

[31] - Time to deterioration in DRS-P was evaluated with the stratified log-rank test. HR and 95% CI were based on Cox Regression Model.
[32] - 1-sided p-value

Statistical analysis title	Time to deterioration in DRS-P

Statistical analysis description:

At primary completion date

Comparison groups	Copanlisib + Rituximab v Placebo + Rituximab

Number of subjects included in analysis	458
Analysis specification	Pre-specified
Analysis type	superiority[33]
P-value	= 0.69261 [34]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.843
upper limit	1.331

Notes:

[33] - Time to deterioration in DRS-P was evaluated with the stratified log-rank test. HR and 95% CI were based on Cox Regression Model.
[34] - 1-sided p-value

Secondary: Time to improvement in DRS-P (Disease-Related Symptoms – Physical) of at least 3 points, as measured by the Functional Assessment of Cancer Therapy Lymphoma Symptom Index-18 (FLymSI-18) questionnaire.

End point title	Time to improvement in DRS-P (Disease-Related Symptoms – Physical) of at least 3 points, as measured by the Functional Assessment of Cancer Therapy Lymphoma Symptom Index-18 (FLymSI-18) questionnaire.

End point description:

Time to improvement in DRS-P (Disease-Related Symptoms – Physical) was defined as the time (in days) from randomization to DRS-P improvement of at least three points. The Lymphoma Symptom Index-18 (FLymSI-18) questionnaire contains 18 items, each of which utilizes a Likert scale with 5 possible responses ranging from 0 'Not at all' to 4 'Very much' and was divided into a total score.

End point type	Secondary

End point timeframe:

From first subject randomization up to approximately 7 years at data cut-off date

End point values	Copanlisib + Rituximab	Placebo + Rituximab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	307[35]	151[36]		
Units: Months				
median (confidence interval 95%)				
At primary completion date	99999 (8.3 to 99999)	99999 (6.0 to 99999)		
At 2-year follow-up cut-off date	38.5 (8.2 to 99999)	35.7 (5.9 to 99999)		

Notes:

[35] - 99999 - value cannot be estimated due to censored data (insufficient number of events).

[36] - 99999 - value cannot be estimated due to censored data (insufficient number of events).

Statistical analyses

Statistical analysis title	Time to improvement in DRS-P

Statistical analysis description:

At primary completion date

Comparison groups	Copanlisib + Rituximab v Placebo + Rituximab

Number of subjects included in analysis	458
Analysis specification	Pre-specified
Analysis type	superiority[37]
P-value	= 0.510038 [38]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.996
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.732
upper limit	1.355

Notes:

[37] - Time to improvement in DRS-P was evaluated with the stratified log-rank test. HR and 95% CI were based on Cox Regression Model.
[38] - 1-sided p-value

Statistical analysis title	Time to improvement in DRS-P

Statistical analysis description:

At 2-year follow-up cut-off date

Comparison groups	Copanlisib + Rituximab v Placebo + Rituximab
Number of subjects included in analysis	458
Analysis specification	Pre-specified
Analysis type	superiority[39]
P-value	= 0.40597 [40]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.036
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.768
upper limit	1.398

Notes:

[39] - Time to improvement in DRS-P was evaluated with the stratified log-rank test. HR and 95% CI were based on Cox Regression Model.
[40] - 1-sided p-value

Secondary: Number of subjects with treatment-emergent adverse events (TEAEs) at primary completion date.

End point title	Number of subjects with treatment-emergent adverse events (TEAEs) at primary completion date.

End point description:

Adverse events were considered to be treatment-emergent if they have started or worsened after first application of study medication up to 30 days after end of treatment with study medication.

End point type	Secondary

End point timeframe:

Up to 30 days after end of treatment with study drug, data reporting cut-off at 5 years from the first subject randomization date

End point values	Copanlisib + Rituximab	Placebo + Rituximab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	307	146		
Units: Subjects				
Any TEAEs	307	134		
Any copanlisib- or placebo-related TEAE	293	95		
Any rituximab-related TEAE	218	92		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with treatment-emergent adverse events (TEAEs) at 2-year follow-up cut-off date.

End point title	Number of subjects with treatment-emergent adverse events (TEAEs) at 2-year follow-up cut-off date.

End point description:

Adverse events were considered to be treatment-emergent if they have started or worsened after first application of study medication up to 30 days after end of treatment with study medication.

End point type	Secondary

End point timeframe:

Up to 30 days after end of treatment with study drug, data reporting cut-off at 7 years from the first subject randomization date

End point values	Copanlisib + Rituximab	Placebo + Rituximab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	307	146		
Units: Subjects				
Any TEAEs	307	137		
Any copanlisib- or placebo-related TEAE	295	98		
Any rituximab-related TEAE	218	93		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with treatment-emergent adverse events (TEAEs) at final analysis

End point title	Number of subjects with treatment-emergent adverse events (TEAEs) at final analysis

End point description:

Adverse events were considered to be treatment-emergent if they have started or worsened after first application of study medication up to 30 days after end of treatment with study medication.

End point type	Secondary

End point timeframe:

Up to 30 days after end of treatment with study drug, data reporting cut-off at final analysis

End point values	Copanlisib + Rituximab	Placebo + Rituximab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	307	146		
Units: Subjects				
Any TEAEs	307	137		
Any copanlisib- or placebo-related TEAE	295	98		
Any rituximab-related TEAE	218	93		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Time frame for Serious and Other Adverse Events - from first administration of study drug until 30 days after the last study drug intake / Time frame for number of death (all causes) - from randomization up to approximately 9 years.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	27.1

Reporting groups

Reporting group title	Placebo + Rituximab

Reporting group description:

Placebo was administered intravenously (IV) (over approximately 1 h) on Days 1, 8, and 15 of each 28-day cycle. Rituximab (375 mg/m^2) was administered weekly during Cycle 1 on Days 1, 8, 15, and 22, and then on Day 1 of Cycles 3, 5, 7, and 9. Placebo was administered before rituximab.

Reporting group title	Copanlisib + Rituximab

Reporting group description:

Copanlisib (60 mg) was administered intravenously (IV) (over approximately 1 h) on Days 1, 8, and 15 of each 28-day cycle. Rituximab (375 mg/m^2) was administered weekly during Cycle 1 on Days 1, 8, 15, and 22, and then on Day 1 of Cycles 3, 5, 7, and 9. Copanlisib was administered before rituximab.

Serious adverse events	Placebo + Rituximab	Copanlisib + Rituximab	
Total subjects affected by serious adverse events			
subjects affected / exposed	32 / 146 (21.92%)	161 / 307 (52.44%)	
number of deaths (all causes)	50	99	
number of deaths resulting from adverse events	1	9	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma gastric			
subjects affected / exposed	0 / 146 (0.00%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Basosquamous carcinoma			
subjects affected / exposed	1 / 146 (0.68%)	0 / 307 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Basal cell carcinoma			

subjects affected / exposed	1 / 146 (0.68%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma of skin			
subjects affected / exposed	1 / 146 (0.68%)	0 / 307 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour pain			
subjects affected / exposed	0 / 146 (0.00%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer			
subjects affected / exposed	0 / 146 (0.00%)	3 / 307 (0.98%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colorectal adenoma			
subjects affected / exposed	0 / 146 (0.00%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma			
subjects affected / exposed	0 / 146 (0.00%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung adenocarcinoma			
subjects affected / exposed	1 / 146 (0.68%)	0 / 307 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 146 (0.00%)	4 / 307 (1.30%)	
occurrences causally related to treatment / all	0 / 0	5 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombosis			

subjects affected / exposed	0 / 146 (0.00%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	0 / 146 (0.00%)	2 / 307 (0.65%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Arthrodesis			
subjects affected / exposed	0 / 146 (0.00%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Central venous catheterisation			
subjects affected / exposed	0 / 146 (0.00%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureteral stent removal			
subjects affected / exposed	0 / 146 (0.00%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia repair			
subjects affected / exposed	0 / 146 (0.00%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 146 (0.00%)	2 / 307 (0.65%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	0 / 146 (0.00%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	

Asthenia			
subjects affected / exposed	0 / 146 (0.00%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Administration site extravasation			
subjects affected / exposed	0 / 146 (0.00%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	0 / 146 (0.00%)	5 / 307 (1.63%)	
occurrences causally related to treatment / all	0 / 0	3 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	0 / 146 (0.00%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucosal inflammation			
subjects affected / exposed	0 / 146 (0.00%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Generalised oedema			
subjects affected / exposed	1 / 146 (0.68%)	0 / 307 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	0 / 146 (0.00%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypersensitivity			
subjects affected / exposed	0 / 146 (0.00%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast			

disorders			
Uterine prolapse			
subjects affected / exposed	1 / 146 (0.68%)	0 / 307 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	0 / 146 (0.00%)	4 / 307 (1.30%)	
occurrences causally related to treatment / all	0 / 0	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	0 / 146 (0.00%)	15 / 307 (4.89%)	
occurrences causally related to treatment / all	0 / 0	15 / 15	
deaths causally related to treatment / all	0 / 0	1 / 1	
Pleural effusion			
subjects affected / exposed	4 / 146 (2.74%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	1 / 6	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial lung disease			
subjects affected / exposed	0 / 146 (0.00%)	6 / 307 (1.95%)	
occurrences causally related to treatment / all	0 / 0	6 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 146 (0.00%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	1 / 146 (0.68%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			

subjects affected / exposed	0 / 146 (0.00%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis chronic			
subjects affected / exposed	0 / 146 (0.00%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Idiopathic interstitial pneumonia			
subjects affected / exposed	0 / 146 (0.00%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	0 / 146 (0.00%)	2 / 307 (0.65%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Investigations			
Amylase increased			
subjects affected / exposed	0 / 146 (0.00%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood calcium increased			
subjects affected / exposed	0 / 146 (0.00%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lipase increased			
subjects affected / exposed	0 / 146 (0.00%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutrophil count decreased			
subjects affected / exposed	1 / 146 (0.68%)	5 / 307 (1.63%)	
occurrences causally related to treatment / all	1 / 1	6 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza A virus test positive			

subjects affected / exposed	0 / 146 (0.00%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 146 (0.00%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dislocation of vertebra			
subjects affected / exposed	0 / 146 (0.00%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hyphaema			
subjects affected / exposed	1 / 146 (0.68%)	0 / 307 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal fracture			
subjects affected / exposed	0 / 146 (0.00%)	2 / 307 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infusion related reaction			
subjects affected / exposed	1 / 146 (0.68%)	0 / 307 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transfusion-related acute lung injury			
subjects affected / exposed	0 / 146 (0.00%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stoma site haemorrhage			
subjects affected / exposed	0 / 146 (0.00%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			

Eustachian valve hypertrophy			
subjects affected / exposed	0 / 146 (0.00%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	0 / 146 (0.00%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular arrhythmia			
subjects affected / exposed	1 / 146 (0.68%)	0 / 307 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular extrasystoles			
subjects affected / exposed	0 / 146 (0.00%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	0 / 146 (0.00%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Nervous system disorders			
Cerebral infarction			
subjects affected / exposed	1 / 146 (0.68%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haemorrhage			
subjects affected / exposed	0 / 146 (0.00%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	0 / 146 (0.00%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
IIIrd nerve paralysis			

subjects affected / exposed	1 / 146 (0.68%)	0 / 307 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	0 / 146 (0.00%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tension headache			
subjects affected / exposed	0 / 146 (0.00%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	1 / 146 (0.68%)	0 / 307 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure like phenomena			
subjects affected / exposed	0 / 146 (0.00%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuralgia			
subjects affected / exposed	0 / 146 (0.00%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 146 (0.00%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 146 (0.68%)	3 / 307 (0.98%)	
occurrences causally related to treatment / all	0 / 2	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune thrombocytopenia			

subjects affected / exposed	0 / 146 (0.00%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	0 / 146 (0.00%)	2 / 307 (0.65%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myelosuppression			
subjects affected / exposed	0 / 146 (0.00%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	3 / 146 (2.05%)	4 / 307 (1.30%)	
occurrences causally related to treatment / all	2 / 3	6 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Haemorrhoids			
subjects affected / exposed	0 / 146 (0.00%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis			
subjects affected / exposed	0 / 146 (0.00%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Enteritis			
subjects affected / exposed	0 / 146 (0.00%)	2 / 307 (0.65%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	0 / 146 (0.00%)	2 / 307 (0.65%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			

subjects affected / exposed	0 / 146 (0.00%)	2 / 307 (0.65%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal fissure			
subjects affected / exposed	0 / 146 (0.00%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incarcerated inguinal hernia			
subjects affected / exposed	0 / 146 (0.00%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	0 / 146 (0.00%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 146 (0.00%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal incarcerated hernia			
subjects affected / exposed	1 / 146 (0.68%)	0 / 307 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal toxicity			
subjects affected / exposed	0 / 146 (0.00%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis microscopic			
subjects affected / exposed	0 / 146 (0.00%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			

subjects affected / exposed	0 / 146 (0.00%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biliary colic			
subjects affected / exposed	0 / 146 (0.00%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bile duct stone			
subjects affected / exposed	1 / 146 (0.68%)	0 / 307 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis acute			
subjects affected / exposed	0 / 146 (0.00%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Panniculitis			
subjects affected / exposed	0 / 146 (0.00%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dermatitis exfoliative generalised			
subjects affected / exposed	0 / 146 (0.00%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 146 (0.00%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydronephrosis			
subjects affected / exposed	0 / 146 (0.00%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Calculus urinary			

subjects affected / exposed	1 / 146 (0.68%)	0 / 307 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	0 / 146 (0.00%)	4 / 307 (1.30%)	
occurrences causally related to treatment / all	0 / 0	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterococcal bacteraemia			
subjects affected / exposed	0 / 146 (0.00%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocarditis bacterial			
subjects affected / exposed	0 / 146 (0.00%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	0 / 146 (0.00%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	1 / 146 (0.68%)	3 / 307 (0.98%)	
occurrences causally related to treatment / all	0 / 1	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchiolitis			
subjects affected / exposed	0 / 146 (0.00%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atypical pneumonia			
subjects affected / exposed	0 / 146 (0.00%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			

subjects affected / exposed	0 / 146 (0.00%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia viral			
subjects affected / exposed	0 / 146 (0.00%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia mycoplasmal			
subjects affected / exposed	0 / 146 (0.00%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia cytomegaloviral			
subjects affected / exposed	1 / 146 (0.68%)	0 / 307 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	5 / 146 (3.42%)	22 / 307 (7.17%)	
occurrences causally related to treatment / all	4 / 5	15 / 25	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pulmonary tuberculosis			
subjects affected / exposed	0 / 146 (0.00%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oral candidiasis			
subjects affected / exposed	0 / 146 (0.00%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	1 / 146 (0.68%)	3 / 307 (0.98%)	
occurrences causally related to treatment / all	1 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			

subjects affected / exposed	0 / 146 (0.00%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parvovirus B19 infection			
subjects affected / exposed	0 / 146 (0.00%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 146 (0.00%)	2 / 307 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinusitis			
subjects affected / exposed	1 / 146 (0.68%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic sepsis			
subjects affected / exposed	0 / 146 (0.00%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal abscess			
subjects affected / exposed	0 / 146 (0.00%)	2 / 307 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	1 / 146 (0.68%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			
subjects affected / exposed	0 / 146 (0.00%)	2 / 307 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			

subjects affected / exposed	2 / 146 (1.37%)	4 / 307 (1.30%)	
occurrences causally related to treatment / all	0 / 2	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	0 / 146 (0.00%)	2 / 307 (0.65%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subcutaneous abscess			
subjects affected / exposed	0 / 146 (0.00%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscle abscess			
subjects affected / exposed	1 / 146 (0.68%)	0 / 307 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Penile infection			
subjects affected / exposed	0 / 146 (0.00%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atypical mycobacterial infection			
subjects affected / exposed	1 / 146 (0.68%)	0 / 307 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia bacterial			
subjects affected / exposed	2 / 146 (1.37%)	4 / 307 (1.30%)	
occurrences causally related to treatment / all	2 / 3	3 / 5	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cytomegalovirus infection reactivation			
subjects affected / exposed	0 / 146 (0.00%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia urinary tract infection			

subjects affected / exposed	1 / 146 (0.68%)	0 / 307 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection viral			
subjects affected / exposed	1 / 146 (0.68%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	0 / 146 (0.00%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	0 / 146 (0.00%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumocystis jirovecii pneumonia			
subjects affected / exposed	0 / 146 (0.00%)	8 / 307 (2.61%)	
occurrences causally related to treatment / all	0 / 0	7 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19			
subjects affected / exposed	3 / 146 (2.05%)	8 / 307 (2.61%)	
occurrences causally related to treatment / all	0 / 3	0 / 9	
deaths causally related to treatment / all	0 / 0	0 / 3	
COVID-19 pneumonia			
subjects affected / exposed	0 / 146 (0.00%)	2 / 307 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Diabetes mellitus			
subjects affected / exposed	0 / 146 (0.00%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia			

subjects affected / exposed	1 / 146 (0.68%)	0 / 307 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	0 / 146 (0.00%)	21 / 307 (6.84%)	
occurrences causally related to treatment / all	0 / 0	27 / 27	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	0 / 146 (0.00%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour lysis syndrome			
subjects affected / exposed	0 / 146 (0.00%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo + Rituximab	Copanlisib + Rituximab	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	127 / 146 (86.99%)	298 / 307 (97.07%)	
Investigations			
Blood cholesterol increased			
subjects affected / exposed	8 / 146 (5.48%)	13 / 307 (4.23%)	
occurrences (all)	15	14	
Blood bilirubin increased			
subjects affected / exposed	2 / 146 (1.37%)	16 / 307 (5.21%)	
occurrences (all)	4	31	
Aspartate aminotransferase increased			
subjects affected / exposed	12 / 146 (8.22%)	28 / 307 (9.12%)	
occurrences (all)	22	37	
Amylase increased			
subjects affected / exposed	4 / 146 (2.74%)	16 / 307 (5.21%)	
occurrences (all)	13	20	

Alanine aminotransferase increased			
subjects affected / exposed	11 / 146 (7.53%)	30 / 307 (9.77%)	
occurrences (all)	20	46	
Blood creatine phosphokinase increased			
subjects affected / exposed	7 / 146 (4.79%)	25 / 307 (8.14%)	
occurrences (all)	11	41	
Neutrophil count decreased			
subjects affected / exposed	34 / 146 (23.29%)	102 / 307 (33.22%)	
occurrences (all)	74	434	
Lymphocyte count decreased			
subjects affected / exposed	9 / 146 (6.16%)	42 / 307 (13.68%)	
occurrences (all)	38	122	
Lipase increased			
subjects affected / exposed	4 / 146 (2.74%)	18 / 307 (5.86%)	
occurrences (all)	16	39	
Blood creatinine increased			
subjects affected / exposed	6 / 146 (4.11%)	16 / 307 (5.21%)	
occurrences (all)	7	26	
Platelet count decreased			
subjects affected / exposed	12 / 146 (8.22%)	42 / 307 (13.68%)	
occurrences (all)	23	121	
Weight decreased			
subjects affected / exposed	4 / 146 (2.74%)	47 / 307 (15.31%)	
occurrences (all)	5	67	
White blood cell count decreased			
subjects affected / exposed	17 / 146 (11.64%)	61 / 307 (19.87%)	
occurrences (all)	53	315	
Vascular disorders			
Hypertension			
subjects affected / exposed	31 / 146 (21.23%)	157 / 307 (51.14%)	
occurrences (all)	119	779	
Nervous system disorders			
Dysgeusia			
subjects affected / exposed	2 / 146 (1.37%)	21 / 307 (6.84%)	
occurrences (all)	2	28	
Dizziness			

subjects affected / exposed	6 / 146 (4.11%)	16 / 307 (5.21%)	
occurrences (all)	6	19	
Headache			
subjects affected / exposed	10 / 146 (6.85%)	43 / 307 (14.01%)	
occurrences (all)	20	73	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	16 / 146 (10.96%)	60 / 307 (19.54%)	
occurrences (all)	62	139	
Neutropenia			
subjects affected / exposed	24 / 146 (16.44%)	64 / 307 (20.85%)	
occurrences (all)	57	249	
Thrombocytopenia			
subjects affected / exposed	8 / 146 (5.48%)	13 / 307 (4.23%)	
occurrences (all)	14	32	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	14 / 146 (9.59%)	61 / 307 (19.87%)	
occurrences (all)	21	93	
Mucosal inflammation			
subjects affected / exposed	2 / 146 (1.37%)	18 / 307 (5.86%)	
occurrences (all)	2	23	
Influenza like illness			
subjects affected / exposed	7 / 146 (4.79%)	17 / 307 (5.54%)	
occurrences (all)	10	19	
Fatigue			
subjects affected / exposed	11 / 146 (7.53%)	44 / 307 (14.33%)	
occurrences (all)	16	51	
Chills			
subjects affected / exposed	7 / 146 (4.79%)	22 / 307 (7.17%)	
occurrences (all)	10	33	
Asthenia			
subjects affected / exposed	5 / 146 (3.42%)	21 / 307 (6.84%)	
occurrences (all)	7	27	
Gastrointestinal disorders			

Constipation			
subjects affected / exposed	12 / 146 (8.22%)	31 / 307 (10.10%)	
occurrences (all)	14	37	
Diarrhoea			
subjects affected / exposed	15 / 146 (10.27%)	106 / 307 (34.53%)	
occurrences (all)	19	245	
Mouth ulceration			
subjects affected / exposed	4 / 146 (2.74%)	21 / 307 (6.84%)	
occurrences (all)	6	31	
Nausea			
subjects affected / exposed	17 / 146 (11.64%)	70 / 307 (22.80%)	
occurrences (all)	25	116	
Abdominal pain			
subjects affected / exposed	6 / 146 (4.11%)	17 / 307 (5.54%)	
occurrences (all)	7	23	
Vomiting			
subjects affected / exposed	5 / 146 (3.42%)	45 / 307 (14.66%)	
occurrences (all)	5	62	
Stomatitis			
subjects affected / exposed	4 / 146 (2.74%)	41 / 307 (13.36%)	
occurrences (all)	9	59	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	19 / 146 (13.01%)	47 / 307 (15.31%)	
occurrences (all)	30	69	
Dyspnoea			
subjects affected / exposed	14 / 146 (9.59%)	17 / 307 (5.54%)	
occurrences (all)	18	17	
Oropharyngeal pain			
subjects affected / exposed	6 / 146 (4.11%)	18 / 307 (5.86%)	
occurrences (all)	7	21	
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	2 / 146 (1.37%)	20 / 307 (6.51%)	
occurrences (all)	2	22	
Rash maculo-papular			

subjects affected / exposed	4 / 146 (2.74%)	21 / 307 (6.84%)	
occurrences (all)	5	33	
Rash			
subjects affected / exposed	10 / 146 (6.85%)	35 / 307 (11.40%)	
occurrences (all)	13	51	
Pruritus			
subjects affected / exposed	9 / 146 (6.16%)	30 / 307 (9.77%)	
occurrences (all)	12	39	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	5 / 146 (3.42%)	18 / 307 (5.86%)	
occurrences (all)	5	19	
Musculoskeletal and connective tissue disorders			
Muscle spasms			
subjects affected / exposed	2 / 146 (1.37%)	19 / 307 (6.19%)	
occurrences (all)	2	26	
Back pain			
subjects affected / exposed	13 / 146 (8.90%)	19 / 307 (6.19%)	
occurrences (all)	17	21	
Arthralgia			
subjects affected / exposed	9 / 146 (6.16%)	21 / 307 (6.84%)	
occurrences (all)	15	24	
Myalgia			
subjects affected / exposed	11 / 146 (7.53%)	8 / 307 (2.61%)	
occurrences (all)	12	10	
Pain in extremity			
subjects affected / exposed	5 / 146 (3.42%)	19 / 307 (6.19%)	
occurrences (all)	6	27	
Infections and infestations			
Bronchitis			
subjects affected / exposed	8 / 146 (5.48%)	18 / 307 (5.86%)	
occurrences (all)	9	30	
Influenza			
subjects affected / exposed	12 / 146 (8.22%)	8 / 307 (2.61%)	
occurrences (all)	14	9	
Nasopharyngitis			

subjects affected / exposed	7 / 146 (4.79%)	28 / 307 (9.12%)	
occurrences (all)	12	41	
Pneumonia			
subjects affected / exposed	12 / 146 (8.22%)	36 / 307 (11.73%)	
occurrences (all)	15	54	
Upper respiratory tract infection			
subjects affected / exposed	28 / 146 (19.18%)	62 / 307 (20.20%)	
occurrences (all)	37	124	
COVID-19			
subjects affected / exposed	6 / 146 (4.11%)	21 / 307 (6.84%)	
occurrences (all)	6	28	
Oral herpes			
subjects affected / exposed	4 / 146 (2.74%)	19 / 307 (6.19%)	
occurrences (all)	5	29	
Urinary tract infection			
subjects affected / exposed	13 / 146 (8.90%)	38 / 307 (12.38%)	
occurrences (all)	20	67	
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	35 / 146 (23.97%)	210 / 307 (68.40%)	
occurrences (all)	93	940	
Hyperuricaemia			
subjects affected / exposed	8 / 146 (5.48%)	20 / 307 (6.51%)	
occurrences (all)	18	33	
Hypokalaemia			
subjects affected / exposed	1 / 146 (0.68%)	25 / 307 (8.14%)	
occurrences (all)	2	38	
Decreased appetite			
subjects affected / exposed	4 / 146 (2.74%)	23 / 307 (7.49%)	
occurrences (all)	4	28	
Hypertriglyceridaemia			
subjects affected / exposed	7 / 146 (4.79%)	21 / 307 (6.84%)	
occurrences (all)	23	35	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 January 2015	- The study target population for the efficacy analysis was changed from iNHL patients to FL patients. - The randomization ratio was changed from 1:1 to 2:1 and the stratification factors were changed. - Time to improvement in DRS-P was added as a secondary efficacy variable.
18 February 2016	- The conservative requirement for blood pressure levels during the evaluation of patient's eligibility was removed due to feedback from the investigators and lymphoma specialists. - A requirement for prophylactic antiviral therapy to be given to patients who are positive for HBsAg or HBcAb at screening was added. - Copanlisib was added to the list of prohibited previous therapies and medications.
28 July 2016	- Guidance on dose modification of copanlisib or placebo for hematological toxicity was updated. - Following Health Authority alerts related to safety issues with Zydelig (idelalisib, a PI3K inhibitor) treatment in clinical trials, text was added to provide guidance for monitoring and prophylaxis of opportunistic infections in patients who are at risk for opportunistic infection development while on study treatment.
02 February 2018	- The total sample size was reduced from 567 patients to 450 patients and the primary efficacy analysis was revised to be performed in the FAS instead of both the FAS and FL subpopulation. - Patients considered unwilling/unfit to receive chemotherapy were bundled to differentiate them in a subgroup different from the long-term responders (i.e., progression-free and treatment-free interval of ≥12 months after completion of the last rituximab-containing treatment).
08 October 2019	- The statistical assumptions for the primary efficacy analysis of PFS were modified. The required number of PFS events was changed from 288 to 190. - The confirmatory testing strategy was modified.
22 May 2020	- Number of events necessary for primary completion analyses was changed to "at least 190 PFS events" to remain flexible. - Removed potential pooling of strata. In order to avoid a too low number of events, only stratification factors "iNHL histology" and "entry criterion" will be adjusted simultaneously in the statistical analyses. - Confirmatory statistical testing strategy for the US was revised and an additional confirmatory statistical testing strategy for the EU was added.
09 February 2023	- Survival follow-up period extended up to 7 years after the last patient started study treatment. - Reduced efficacy and safety assessments, and other minor changes.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

The Overall Survival analysis is very immature due to the low number of events. In Subject disposition section, the number of subjects for Completed were ongoing with treatment.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/33848462

http://www.ncbi.nlm.nih.gov/pubmed/39984775