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	

Results information

Result version number	v1
This version publication date	12 September 2021
First version publication date	12 September 2021

Trial information

Trial identification

Sponsor protocol code	BAY806946/17067

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, 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	Interim
Date of interim/final analysis	31 August 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 August 2020
Global end of trial reached?	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 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	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	Vietnam: 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 31 August 2020 (primary completion date).

Pre-assignment

Screening details:

Overall, 652 were screened and total of 458 participants were randomized in a 2:1 ratio to study treatment: 307 participants to copanlisib /rituximab and 151 participants 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	Investigator, Carer, Assessor, Subject

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	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/m2 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 is 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.

Investigational medicinal product name	Copanlisib
Investigational medicinal product code	BAY 80-6946
Other name	
Pharmaceutical forms	Concentrate for emulsion for infusion
Routes of administration	Intravenous use

Dosage and administration details:

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

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

Number of subjects in period 1	Copanlisib + Rituximab	Placebo + Rituximab
Started	307	151
Received treatment	304	149
Completed	70	29
Not completed	237	122
Progressive disease – radiological progression	39	67
AE associated with clinical disease progression	1	3
Physician decision	2	8
Drug not administered	3	2
Randomized by mistake with study treatment	1	-
AE not associated clinical disease progression	104	9
Failure to meet continuation criteria	1	-
Progressive disease – clinical progression	2	6
Consent withdrawn by subject	41	14
Patient decision	35	11
Non-compliance with study drug	1	-
Switching to other therapy	2	-
Lost to follow-up	1	1
Patient decision: COVID-19 pandemic related	1	-
Required procedure failed	1	-
Lack of efficacy	1	-
Protocol deviation	1	-
Additional primary malignancy	-	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
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
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

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.	

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 (in days) from randomization to progressive disease (PD) or death from any cause (if no progression was documented), whichever occurred earlier. PFS for patients without progression or death at the time of analysis was censored at the last actual date of tumor assessment or last biochemical assessment for patients with Waldenstrom macroglobulinemia (WM) without lesions evaluable by imaging.	
End point type	Primary
End point timeframe:	
From randomization to 31-Aug-2020	

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%)	21.5 (17.8 to 33.0)	13.8 (10.2 to 17.5)		

Statistical analyses

Statistical analysis title	Progression free survival (PFS)
Comparison groups	Copanlisib + Rituximab v Placebo + Rituximab
Number of subjects included in analysis	458
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.000002 [2]
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:

[1] - PFS was evaluated with the stratified log-rank test. HR and 95% CI were based on Cox Regression Model.
[2] - 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 patients who had 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 Cheson 2014 criteria 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 randomization to 31-Aug-2020

End point values	Copanlisib + Rituximab	Placebo + Rituximab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	307	151		
Units: Percentage of participants				
number (not applicable)	80.8	47.7		

Statistical analyses

Statistical analysis title	Objective response rate (ORR)
Comparison groups	Copanlisib + Rituximab v Placebo + Rituximab
Number of subjects included in analysis	458
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	< 0.000001 [4]
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:

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

[4] - 1-sided p-value

Secondary: Complete response rate (CRR)

End point title	Complete response rate (CRR)

End point description:

Complete response rate (CRR) was assessed in all patients up to the time of analysis of PFS. CRR was defined as the proportion of patients who had a best response rating over the whole duration of the study (i.e., until the time of analysis of PFS) of CR according to the Cheson 2014 criteria and for patients with Waldenstrom macroglobulinemia (WM) a response rating of CR according to the Owen criteria.

End point type	Secondary

End point timeframe:

From randomization to 31-Aug-2020

End point values	Copanlisib + Rituximab	Placebo + Rituximab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	307	151		
Units: Percentage of participants				
number (not applicable)	33.9	14.6		

Statistical analyses

Statistical analysis title	Complete response rate (CRR)
Comparison groups	Copanlisib + Rituximab v Placebo + Rituximab
Number of subjects included in analysis	458
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	< 0.000001 [6]
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:

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

[6] - 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. DOR was only

patients with at least one CR, VGPR, PR, or MR.

End point type	Secondary

End point timeframe:

From randomization to to 31-Aug-2020

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%)	20.4 (17.0 to 30.8)	17.3 (11.8 to 25.3)		

Statistical analyses

Statistical analysis title	Duration of response (DOR)
Comparison groups	Copanlisib + Rituximab v Placebo + Rituximab
Number of subjects included in analysis	458
Analysis specification	Pre-specified
Analysis type	superiority[7]
P-value	= 0.058262 [8]
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:

[7] - DOR was evaluated with the stratified log-rank test. HR and 95% CI were based on Cox Regression Model.
[8] - 1-sided p-value

Secondary: Disease control rate (DCR)

End point title	Disease control rate (DCR)

End point description:

Disease control rate (DCR) was defined as the proportion of patients who had a best response rating of complete response (CR), very good partial response (VGPR), partial response (PR) according or minor response (MR) or stable disease (SD) (excluding unconfirmed early SD [uSD]) that was achieved during treatment or within 35 days after termination of study treatment. The uSD was defined as SD on or before Study Day 48.

End point type	Secondary

End point timeframe:

From randomization to to 31-Aug-2020

End point values	Copanlisib + Rituximab	Placebo + Rituximab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	307	151		
Units: Percentage of participants				
number (not applicable)	89.3	84.8		

Statistical analyses

Statistical analysis title	Disease control rate (DCR)
Comparison groups	Copanlisib + Rituximab v Placebo + Rituximab
Number of subjects included in analysis	458
Analysis specification	Pre-specified
Analysis type	superiority[9]
P-value	= 0.097339 [10]
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:

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

[10] - 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 (in days) from randomization to progression or death related to progression, whichever occurred earlier.

End point type	Secondary

End point timeframe:

From randomization to 31-Aug-2020

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%)	22.3 (19.4 to 33.2)	13.8 (10.8 to 18.7)		

Statistical analyses

Statistical analysis title	Time to progression (TTP)
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	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:

[11] - TTP was evaluated with the stratified log-rank test. HR and 95% CI were based on Cox Regression Model.
[12] - 1-sided p-value

Secondary: Overall survival (OS) till Primary Completion date.

End point title	Overall survival (OS) till Primary Completion date.

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 to 31-Aug-2020.

End point values	Copanlisib + Rituximab	Placebo + Rituximab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	307[13]	151[14]		
Units: Months				
median (confidence interval 95%)	57.4 (-99999 to 99999)	99999 (-99999 to 99999)		

Notes:

[13] - 99999 - value cannot be estimated due to censored data (insufficient number of events).

[14] - 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[15]
P-value	= 0.597747 [16]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.07

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.628
upper limit	1.821

Notes:

[15] - OS was evaluated with the stratified log-rank test. HR and 95% CI were based on Cox Regression Model.
[16] - 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.

End point type	Secondary

End point timeframe:

From randomization to 31-Aug-2020

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%)	5.5 (4.2 to 5.9)	5.5 (4.0 to 7.4)		

Statistical analyses

Statistical analysis title	Time to deterioration in DRS-P
Comparison groups	Copanlisib + Rituximab v Placebo + Rituximab
Number of subjects included in analysis	458
Analysis specification	Pre-specified
Analysis type	superiority[17]
P-value	= 0.69261 [18]
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:

[17] - Time to deterioration in DRS-P was evaluated with the stratified log-rank test. HR and 95% CI were based on Cox Regression Model.
[18] - 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.

End point type	Secondary

End point timeframe:

From randomization to 31-Aug-2020

End point values	Copanlisib + Rituximab	Placebo + Rituximab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	307[19]	151[20]		
Units: Months				
median (confidence interval 95%)	99999 (8.3 to 99999)	99999 (6.0 to 99999)		

Notes:

[19] - 99999 - value cannot be estimated due to censored data (insufficient number of events).

[20] - 99999 - value cannot be estimated due to censored data (insufficient number of events).

Statistical analyses

Statistical analysis title	Time to improvement in DRS-P
Comparison groups	Copanlisib + Rituximab v Placebo + Rituximab
Number of subjects included in analysis	458
Analysis specification	Pre-specified
Analysis type	superiority[21]
P-value	= 0.510038 [22]
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:

[21] - Time to improvement in DRS-P was evaluated with the stratified log-rank test. HR and 95% CI were based on Cox Regression Model.
[22] - 1-sided p-value

Secondary: Number of participants with treatment-emergent adverse events (TEAEs).

End point title	Number of participants with treatment-emergent adverse events (TEAEs).

End point description:

Adverse events are 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

End point values	Copanlisib + Rituximab	Placebo + Rituximab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	307	146		
Units: Participants				
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

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first administration of study drug until 30 days after the last study drug intake.

Adverse event reporting additional description:

Three patients were randomized to the placebo/rituximab arm but received at least one dose of copanlisib by mistake. These patients were included in the copanlisib/rituximab arm in the analysis of safety variables.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.0

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	27 / 146 (18.49%)	145 / 307 (47.23%)	
number of deaths (all causes)	20	43	
number of deaths resulting from adverse events	1	6	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal 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	
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	
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	
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%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
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	
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	
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			
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	
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	
General disorders and administration site conditions			
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	
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	
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	
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	
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	
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	
Immune system disorders			
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	
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	
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			
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	
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	
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	
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	
Interstitial lung disease			
subjects affected / exposed	0 / 146 (0.00%)	5 / 307 (1.63%)	
occurrences causally related to treatment / all	0 / 0	5 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
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	
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	
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	
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	
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	
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	0 / 146 (0.00%)	5 / 307 (1.63%)	
occurrences causally related to treatment / all	0 / 0	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			
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	
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	
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	
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	
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	
Cardiac disorders			
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	
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	
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	
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	
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	
Nervous system disorders			
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	
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	
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	
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	
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	
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	
Blood and lymphatic system disorders			
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	
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	
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	
Bone marrow failure			
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	
Gastrointestinal disorders			
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	
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	
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	
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	
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	
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	
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	
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	
Hepatobiliary disorders			
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	
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	
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	
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			
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			
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	
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	
Infections and infestations			
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	
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	
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	
Bronchitis			
subjects affected / exposed	1 / 146 (0.68%)	2 / 307 (0.65%)	
occurrences causally related to treatment / all	0 / 1	2 / 2	
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	
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	
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	
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	
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	
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	
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	
Pneumonia			

subjects affected / exposed	5 / 146 (3.42%)	17 / 307 (5.54%)	
occurrences causally related to treatment / all	4 / 5	10 / 18	
deaths causally related to treatment / all	0 / 0	0 / 1	
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 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 influenzal			
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	
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	
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	
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	
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	
Viral 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	
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	
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	
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	
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	
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	
Pneumonia bacterial			
subjects affected / exposed	1 / 146 (0.68%)	4 / 307 (1.30%)	
occurrences causally related to treatment / all	0 / 1	3 / 4	
deaths causally related to treatment / all	0 / 1	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	
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	
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	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	
COVID-19 pneumonia			
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	
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	
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	
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	

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	122 / 146 (83.56%)	296 / 307 (96.42%)	
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	10 / 146 (6.85%)	25 / 307 (8.14%)	
occurrences (all)	19	30	
Alanine aminotransferase increased			
subjects affected / exposed	9 / 146 (6.16%)	25 / 307 (8.14%)	
occurrences (all)	15	37	
Blood creatine phosphokinase increased			
subjects affected / exposed	7 / 146 (4.79%)	23 / 307 (7.49%)	
occurrences (all)	9	36	
Lipase increased			
subjects affected / exposed	4 / 146 (2.74%)	17 / 307 (5.54%)	
occurrences (all)	11	26	
Lymphocyte count decreased			
subjects affected / exposed	9 / 146 (6.16%)	38 / 307 (12.38%)	
occurrences (all)	37	107	
Weight decreased			
subjects affected / exposed	4 / 146 (2.74%)	45 / 307 (14.66%)	
occurrences (all)	5	63	
Platelet count decreased			
subjects affected / exposed	12 / 146 (8.22%)	40 / 307 (13.03%)	
occurrences (all)	22	107	
Neutrophil count decreased			
subjects affected / exposed	34 / 146 (23.29%)	101 / 307 (32.90%)	
occurrences (all)	73	410	
White blood cell count decreased			
subjects affected / exposed	16 / 146 (10.96%)	61 / 307 (19.87%)	
occurrences (all)	51	293	
Vascular disorders			
Hypertension			
subjects affected / exposed	28 / 146 (19.18%)	151 / 307 (49.19%)	
occurrences (all)	94	710	
Nervous system disorders			

Headache			
subjects affected / exposed	9 / 146 (6.16%)	42 / 307 (13.68%)	
occurrences (all)	19	67	
Dysgeusia			
subjects affected / exposed	1 / 146 (0.68%)	20 / 307 (6.51%)	
occurrences (all)	1	27	
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	24 / 146 (16.44%)	63 / 307 (20.52%)	
occurrences (all)	57	202	
Anaemia			
subjects affected / exposed	15 / 146 (10.27%)	57 / 307 (18.57%)	
occurrences (all)	53	127	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	4 / 146 (2.74%)	21 / 307 (6.84%)	
occurrences (all)	6	27	
Chills			
subjects affected / exposed	7 / 146 (4.79%)	20 / 307 (6.51%)	
occurrences (all)	10	29	
Fatigue			
subjects affected / exposed	10 / 146 (6.85%)	42 / 307 (13.68%)	
occurrences (all)	15	48	
Mucosal inflammation			
subjects affected / exposed	2 / 146 (1.37%)	18 / 307 (5.86%)	
occurrences (all)	2	23	
Pyrexia			
subjects affected / exposed	11 / 146 (7.53%)	59 / 307 (19.22%)	
occurrences (all)	18	88	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	12 / 146 (8.22%)	30 / 307 (9.77%)	
occurrences (all)	14	33	
Mouth ulceration			
subjects affected / exposed	4 / 146 (2.74%)	19 / 307 (6.19%)	
occurrences (all)	6	27	

Diarrhoea			
subjects affected / exposed	14 / 146 (9.59%)	103 / 307 (33.55%)	
occurrences (all)	18	229	
Nausea			
subjects affected / exposed	17 / 146 (11.64%)	69 / 307 (22.48%)	
occurrences (all)	25	114	
Stomatitis			
subjects affected / exposed	4 / 146 (2.74%)	39 / 307 (12.70%)	
occurrences (all)	9	53	
Vomiting			
subjects affected / exposed	5 / 146 (3.42%)	44 / 307 (14.33%)	
occurrences (all)	5	61	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	17 / 146 (11.64%)	45 / 307 (14.66%)	
occurrences (all)	28	63	
Dyspnoea			
subjects affected / exposed	11 / 146 (7.53%)	17 / 307 (5.54%)	
occurrences (all)	15	17	
Oropharyngeal pain			
subjects affected / exposed	6 / 146 (4.11%)	17 / 307 (5.54%)	
occurrences (all)	7	19	
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	1 / 146 (0.68%)	17 / 307 (5.54%)	
occurrences (all)	1	18	
Rash maculo-papular			
subjects affected / exposed	3 / 146 (2.05%)	19 / 307 (6.19%)	
occurrences (all)	4	30	
Pruritus			
subjects affected / exposed	9 / 146 (6.16%)	30 / 307 (9.77%)	
occurrences (all)	11	36	
Rash			
subjects affected / exposed	10 / 146 (6.85%)	35 / 307 (11.40%)	
occurrences (all)	13	49	
Psychiatric disorders			

Insomnia			
subjects affected / exposed	4 / 146 (2.74%)	17 / 307 (5.54%)	
occurrences (all)	4	18	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	7 / 146 (4.79%)	19 / 307 (6.19%)	
occurrences (all)	10	20	
Back pain			
subjects affected / exposed	13 / 146 (8.90%)	17 / 307 (5.54%)	
occurrences (all)	16	19	
Myalgia			
subjects affected / exposed	9 / 146 (6.16%)	8 / 307 (2.61%)	
occurrences (all)	10	10	
Muscle spasms			
subjects affected / exposed	2 / 146 (1.37%)	18 / 307 (5.86%)	
occurrences (all)	2	25	
Pain in extremity			
subjects affected / exposed	4 / 146 (2.74%)	17 / 307 (5.54%)	
occurrences (all)	5	24	
Infections and infestations			
Influenza			
subjects affected / exposed	9 / 146 (6.16%)	8 / 307 (2.61%)	
occurrences (all)	10	8	
Bronchitis			
subjects affected / exposed	7 / 146 (4.79%)	17 / 307 (5.54%)	
occurrences (all)	7	23	
Nasopharyngitis			
subjects affected / exposed	7 / 146 (4.79%)	27 / 307 (8.79%)	
occurrences (all)	12	36	
Pneumonia			
subjects affected / exposed	12 / 146 (8.22%)	32 / 307 (10.42%)	
occurrences (all)	14	45	
Upper respiratory tract infection			
subjects affected / exposed	24 / 146 (16.44%)	55 / 307 (17.92%)	
occurrences (all)	30	98	
Urinary tract infection			

subjects affected / exposed	10 / 146 (6.85%)	33 / 307 (10.75%)	
occurrences (all)	16	58	
Oral herpes			
subjects affected / exposed	4 / 146 (2.74%)	17 / 307 (5.54%)	
occurrences (all)	5	25	
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	34 / 146 (23.29%)	210 / 307 (68.40%)	
occurrences (all)	87	912	
Hypertriglyceridaemia			
subjects affected / exposed	6 / 146 (4.11%)	18 / 307 (5.86%)	
occurrences (all)	20	26	
Hyperuricaemia			
subjects affected / exposed	8 / 146 (5.48%)	18 / 307 (5.86%)	
occurrences (all)	17	29	
Hypokalaemia			
subjects affected / exposed	1 / 146 (0.68%)	20 / 307 (6.51%)	
occurrences (all)	2	33	
Decreased appetite			
subjects affected / exposed	4 / 146 (2.74%)	23 / 307 (7.49%)	
occurrences (all)	4	28	

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.

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.

Notes:

Online references

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