EU Clinical Trials Register

Clinical trial results:
An open-label, single-arm Phase II study in patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) to evaluate efficacy and safety of treatment with single agent copanlisib and the impact of biomarkers thereupon.

Summary

EudraCT number	2014-004848-36
Trial protocol	BE DE GB IT ES DK
Global end of trial date	19 January 2018

Results information

Result version number	v1 (current)
This version publication date	23 December 2018
First version publication date	23 December 2018

Trial information

Trial identification

Sponsor protocol code	BAY80-6946/17119

Additional study identifiers

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

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	19 January 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	19 January 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to assess the potential efficacy (in terms of objective response) of single agent copanlisib in patients with relapsed or refractory DLBCL and assess the relationship between efficacy and a potentially predictive biomarker.

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 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	08 May 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 6
Country: Number of subjects enrolled	Belgium: 10
Country: Number of subjects enrolled	Denmark: 4
Country: Number of subjects enrolled	France: 15
Country: Number of subjects enrolled	Germany: 5
Country: Number of subjects enrolled	Italy: 1
Country: Number of subjects enrolled	Australia: 11
Country: Number of subjects enrolled	Canada: 4
Country: Number of subjects enrolled	Korea, Republic of: 6
Country: Number of subjects enrolled	Singapore: 5
Worldwide total number of subjects	67
EEA total number of subjects	41

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)	27
From 65 to 84 years	38
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 32 centers across 10 countries, between 08 MAY 2015 (first patient first visit) and 18 JAN 2018 (last patient last visit).

Pre-assignment

Screening details:

A total of 91 subjects were screened, of which 67 were assigned to study treatment and also started the treatment, and 24 were screened but never assigned to treatment. Altogether 27 subjects were excluded from the per protocol set, which comprised 40 subjects.

Period 1

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

Arms

Arm title	Copanlisib (BAY80-6946)

Arm description:

Subjects assigned to receive copanlisib intravenous (IV) infusion at a dose of 60 mg as single agent on Days 1, 8, and 15 of 28-day treatment cycle. Copanlisib treatment was to be continued until disease progression (PD), unacceptable toxicity, or until another criterion was met for withdrawal from the study treatment.

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

Dosage and administration details:

Starting dose 60mg for intravenous (IV) infusion as single agent on Days 1, 8, and 15 of 28-day treatment cycle; treatment was to be continued until disease progression (PD), unacceptable toxicity, or until another criterion was met for withdrawal from the study treatment.

Number of subjects in period 1	Copanlisib (BAY80-6946)
Started	67
Included in per protocol set	40 [1]
Entered Safety follow-up	56 [2]
Entered Active follow-up	9 [3]
Entered Survival follow-up	46 [4]
Completed	60
Not completed	7
Consent withdrawn by subject	6
Switching to Other Therapy	1

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Altogether 27 patients were excluded from the per protocol set, which comprised 40 subjects.

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: This period excludes 2 deaths on treatment and 9 subjects entering active follow-up.

[3] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: This period incorporates safety follow-up with radiological assessments.

[4] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: 21 subjects discontinued from treatment didn't enter due to withdrawal by subject(3) and death(18).

Baseline characteristics

Reporting groups

Reporting group title	Overall trial	
Reporting group description: -		

Reporting group values	Overall trial	Total	
Number of subjects	67	67	
Age categorical			
Units: Subjects			
In utero		0	
Preterm newborn infants (gestational age < 37 wks)		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)		0	
From 65-84 years		0	
85 years and over		0	
Age continuous			
Units: years			
arithmetic mean	65.3		
standard deviation	± 14.5	-	
Gender categorical			
Units: Subjects			
Female	28	28	
Male	39	39	
CD79b Status			
Units: Subjects			
CD79b Mutant	9	9	
CD79b Wild-type	45	45	
CD79b Status Missing	13	13	
DLBCL / Cell of Origin (COO) Subtype			
Units: Subjects			
Activated B-cell-like (ABC)	19	19	
Germinal center B-cell-like (GCB)	30	30	
Unclassifiable	3	3	
DLBCL/COO Subtype Missing	15	15	

Subject analysis sets

Subject analysis set title	Full analysis set (FAS)
Subject analysis set type	Full analysis

Subject analysis set description:

Included all subjects assigned to study treatment, i.e. subject´s eligibility criteria were confirmed and the investigator intended to treat the subject

Subject analysis set title	Per protocol set (PPS)
Subject analysis set type	Per protocol

Subject analysis set description:

Included all subjects with drug intake who were evaluable for the overall response assessment and without major protocol deviation effecting the primary efficacy evaluation

Subject analysis set title	CD79b Mutant
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Included all subjects with CD79b mutant classified at baseline depending on the biomarker value

Subject analysis set title	CD79b Wild-type
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Included all subjects with CD79b wild-type classified at baseline depending on biomarker value

Subject analysis set title	CD79b Status Missing
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Included all subjects with CD79b status missing at baseline

Subject analysis set title	Activated B-cell-like (ABC)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Included all subjects with activated B-cell-like (ABC) DLBCL classified at baseline depending on the biomarker value

Subject analysis set title	Germinal center B-cell-like (GCB)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Included all subjects with germinal center B-cell-like (GCB) DLBCL classified at baseline depending on the biomarker value

Subject analysis set title	DLBCL/COO Subtype Unclassifiable
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Included all subjects with unclassifiable DLBCL/COO subtype at baseline

Subject analysis set title	DLBCL/COO Subtype Missing
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Included all subjects with DLBCL/COO subtype missing at baseline

Subject analysis set title	Safety analysis set (SAF)
Subject analysis set type	Safety analysis

Subject analysis set description:

Included all subjects with at least one study drug application

Reporting group values	Full analysis set (FAS)	Per protocol set (PPS)	CD79b Mutant
Number of subjects	67	40	9
Age categorical			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			

Age continuous			
Units: years			
arithmetic mean	65.3	69.2	72.3
standard deviation	± 14.5	± 12.2	± 8.7
Gender categorical			
Units: Subjects			
Female	28	15	1
Male	39	25	8
CD79b Status			
Units: Subjects			
CD79b Mutant	9	8	
CD79b Wild-type	45	32	
CD79b Status Missing	13	0	
DLBCL / Cell of Origin (COO) Subtype			
Units: Subjects			
Activated B-cell-like (ABC)	19	16	
Germinal center B-cell-like (GCB)	30	22	
Unclassifiable	3	2	
DLBCL/COO Subtype Missing	15	0	

Reporting group values	CD79b Wild-type	CD79b Status Missing	Activated B-cell-like (ABC)
Number of subjects	45	13	19
Age categorical			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous			
Units: years			
arithmetic mean	65.6	59.5	70.6
standard deviation	± 13.7	± 18.6	± 11.2
Gender categorical			
Units: Subjects			
Female	22	5	8
Male	23	8	11
CD79b Status			
Units: Subjects			
CD79b Mutant			
CD79b Wild-type			
CD79b Status Missing			
DLBCL / Cell of Origin (COO) Subtype			
Units: Subjects			
Activated B-cell-like (ABC)			
Germinal center B-cell-like (GCB)			

Unclassifiable			
DLBCL/COO Subtype Missing			

Reporting group values	Germinal center B-cell-like (GCB)	DLBCL/COO Subtype Unclassifiable	DLBCL/COO Subtype Missing
Number of subjects	30	3	15
Age categorical			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous			
Units: years			
arithmetic mean	63.6	62.3	62.5
standard deviation	± 14.8	± 13.3	± 17.3
Gender categorical			
Units: Subjects			
Female	13	1	6
Male	17	2	9
CD79b Status			
Units: Subjects			
CD79b Mutant			
CD79b Wild-type			
CD79b Status Missing			
DLBCL / Cell of Origin (COO) Subtype			
Units: Subjects			
Activated B-cell-like (ABC)			
Germinal center B-cell-like (GCB)			
Unclassifiable			
DLBCL/COO Subtype Missing			

Reporting group values	Safety analysis set (SAF)		
Number of subjects	67		
Age categorical			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			

From 65-84 years			
85 years and over			

Age continuous Units: years			
arithmetic mean			
standard deviation	±		
Gender categorical Units: Subjects			
Female			
Male			
CD79b Status Units: Subjects			
CD79b Mutant			
CD79b Wild-type			
CD79b Status Missing			
DLBCL / Cell of Origin (COO) Subtype Units: Subjects			
Activated B-cell-like (ABC)			
Germinal center B-cell-like (GCB)			
Unclassifiable			
DLBCL/COO Subtype Missing			

End points

End points reporting groups

Reporting group title	Copanlisib (BAY80-6946)

Reporting group description:

Subjects assigned to receive copanlisib intravenous (IV) infusion at a dose of 60 mg as single agent on Days 1, 8, and 15 of 28-day treatment cycle. Copanlisib treatment was to be continued until disease progression (PD), unacceptable toxicity, or until another criterion was met for withdrawal from the study treatment.

Subject analysis set title	Full analysis set (FAS)
Subject analysis set type	Full analysis

Subject analysis set description:

Included all subjects assigned to study treatment, i.e. subject´s eligibility criteria were confirmed and the investigator intended to treat the subject

Subject analysis set title	Per protocol set (PPS)
Subject analysis set type	Per protocol

Subject analysis set description:

Included all subjects with drug intake who were evaluable for the overall response assessment and without major protocol deviation effecting the primary efficacy evaluation

Subject analysis set title	CD79b Mutant
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Included all subjects with CD79b mutant classified at baseline depending on the biomarker value

Subject analysis set title	CD79b Wild-type
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Included all subjects with CD79b wild-type classified at baseline depending on biomarker value

Subject analysis set title	CD79b Status Missing
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Included all subjects with CD79b status missing at baseline

Subject analysis set title	Activated B-cell-like (ABC)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Included all subjects with activated B-cell-like (ABC) DLBCL classified at baseline depending on the biomarker value

Subject analysis set title	Germinal center B-cell-like (GCB)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Included all subjects with germinal center B-cell-like (GCB) DLBCL classified at baseline depending on the biomarker value

Subject analysis set title	DLBCL/COO Subtype Unclassifiable
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Included all subjects with unclassifiable DLBCL/COO subtype at baseline

Subject analysis set title	DLBCL/COO Subtype Missing
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Included all subjects with DLBCL/COO subtype missing at baseline

Subject analysis set title	Safety analysis set (SAF)
Subject analysis set type	Safety analysis

Subject analysis set description:

Included all subjects with at least one study drug application

Primary: Objective response rate (ORR) in total population based on investigator assessment

End point title	Objective response rate (ORR) in total population based on investigator assessment[1]

End point description:

The objective response rate (ORR) was defined as the percentage of subjects who had at least one post-baseline overall response of complete response (CR) or partial response (PR) during study conduct according to the criteria defined by the Lugano Classification, 2014 and assessed by CT/MRI/PET-CT. The primary efficacy overall response assessment was based on investigator assessment of response.

End point type	Primary

End point timeframe:

From start of study treatment assessed up to 24 weeks after the last subject fully evaluable for the primary endpoint started treatment (about 12 months)

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: In this one-arm study the confidence interval can be considered to be the statistical analysis.

End point values	Full analysis set (FAS)	Per protocol set (PPS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	67	40		
Units: percentage of subjects				
number (confidence interval 90%)	19.4 (11.9 to 29.1)	25.0 (14.2 to 38.7)		

Statistical analyses

No statistical analyses for this end point

Primary: ORR by CD79b status based on investigator assessment

End point title	ORR by CD79b status based on investigator assessment

End point description:

The objective response rate (ORR) was defined as the percentage of subjects who had at least one post-baseline overall response of complete response (CR) or partial response (PR) during study conduct according to the criteria defined by the Lugano Classification, 2014 and assessed by CT/MRI/PET-CT. The primary efficacy overall response assessment was based on investigator assessment of response.

End point type	Primary

End point timeframe:

From start of study treatment assessed up to 24 weeks after the last subject fully evaluable for the primary endpoint started treatment (about 12 months)

End point values	CD79b Mutant	CD79b Wild-type	CD79b Status Missing	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	9[2]	45[3]	13[4]	
Units: percentage of subjects				
number (confidence interval 90%)				
Full analysis set (FAS)	22.2 (4.1 to 55.0)	20.0 (10.9 to 32.3)	15.4 (2.8 to 41.0)	

Per protocol set (PPS)	25.0 (4.6 to 60.0)	25.0 (13.1 to 40.6)	0 (0 to 0)	

Notes:

[2] - N=9 in full analysis set (FAS) and N=8 in per protocol set (PPS)

[3] - N=45 in full analysis set (FAS) and N=32 in per protocol set (PPS)

[4] - N=13 in full analysis set (FAS) and N=0 in per protocol set (PPS)

Statistical analyses

Statistical analysis title	ORR by CD79b Status assessed by Investigators

Statistical analysis description:

ORR difference in FAS (N=54): ORR in CD79b mutant subgroup minus ORR in CD79b wild-type subgroup

Comparison groups	CD79b Mutant v CD79b Wild-type
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	other
Method	Exact confidence intervals (CI)
Parameter estimate	ORR difference
Point estimate	2.2
Confidence interval	
level	90 %
sides	2-sided
lower limit	-28.7
upper limit	32.9

Statistical analysis title	ORR by CD79b Status assessed by Investigators

Statistical analysis description:

ORR difference in PPS (N=40): ORR in CD79b mutant subgroup minus ORR in CD79b wild-type subgroup

Comparison groups	CD79b Mutant v CD79b Wild-type
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	other
Method	Exact confidence intervals
Parameter estimate	ORR difference
Point estimate	0
Confidence interval	
level	90 %
sides	2-sided
lower limit	-33.5
upper limit	33.5

Primary: ORR by DLBCL/COO Subtype Based on Investigator Assessment

End point title	ORR by DLBCL/COO Subtype Based on Investigator Assessment

End point description:

The objective response rate (ORR) was defined as the percentage of subjects who had at least one post-

baseline overall response of complete response (CR) or partial response (PR) during study conduct according to the criteria defined by the Lugano Classification, 2014 and assessed by CT/MRI/PET-CT. The primary efficacy overall response assessment was based on investigator assessment of response.

End point type	Primary
End point timeframe:	

From start of study treatment assessed up to 24 weeks after the last subject fully evaluable for the primary endpoint started treatment (about 12 months)

End point values	Activated B-cell-like (ABC)	Germinal center B-cell-like (GCB)	DLBCL/COO Subtype Unclassifiable	DLBCL/COO Subtype Missing
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	19[5]	30[6]	3[7]	15[8]
Units: percentage of subjects				
number (confidence interval 90%)				
Full analysis set (FAS)	31.6 (14.7 to 53.0)	13.3 (4.7 to 28.0)	33.3 (1.7 to 86.5)	13.3 (2.4 to 36.3)
Per protocol set (PPS)	37.5 (17.8 to 60.9)	13.6 (3.8 to 31.6)	50.0 (2.5 to 97.5)	0 (0 to 0)

Notes:

[5] - N=19 in full analysis set (FAS) and N=16 in per protocol set (PPS)

[6] - N=30 in full analysis set (FAS) and N=22 in per protocol set (PPS)

[7] - N=3 in full analysis set (FAS) and N=2 in per protocol set (PPS)

[8] - N=15 in full analysis set (FAS) and N=0 in per protocol set (PPS)

Statistical analyses

Statistical analysis title	ORR by DLBCL/COO Subtype assessed by Investigators
Statistical analysis description:	

ORR difference in FAS (N=52): ORR in ABC subgroup minus ORR in non-ABC group (i.e. combined GCB subgroup and Unclassifiable subgroup)

Comparison groups	Activated B-cell-like (ABC) v Germinal center B-cell-like (GCB) v DLBCL/COO Subtype Unclassifiable
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	other
Method	Exact confidence intervals (CI)
Parameter estimate	ORR difference
Point estimate	16.4
Confidence interval	
level	90 %
sides	2-sided
lower limit	-7.2
upper limit	39.1

Statistical analysis title	ORR by DLBCL/COO Subtype assessed by Investigators
Statistical analysis description:	

ORR difference in PPS (N=40): ORR in ABC subgroup minus ORR in non-ABC group (i.e. combined GCB subgroup and Unclassifiable subgroup)

Comparison groups	Activated B-cell-like (ABC) v Germinal center B-cell-like (GCB)

	v DLBCL/COO Subtype Unclassifiable
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	other
Method	Exact confidence intervals (CI)
Parameter estimate	ORR difference
Point estimate	20.8
Confidence interval	
level	90 %
sides	2-sided
lower limit	-6.8
upper limit	46.2

Statistical analysis title	ORR by DLBCL/COO Subtype assessed by Investigators
Statistical analysis description:	
ORR difference in FAS (N=52): ORR in GCB subgroup minus ORR in non-GCB subgroup (i.e. combined ABC subgroup and Unclassifiable subgroup)	
Comparison groups	Activated B-cell-like (ABC) v Germinal center B-cell-like (GCB) v DLBCL/COO Subtype Unclassifiable
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	other
Method	Exact confidence intervals (CI)
Parameter estimate	ORR difference
Point estimate	-18.5
Confidence interval	
level	90 %
sides	2-sided
lower limit	-40.1
upper limit	4.6

Statistical analysis title	ORR by DLBCL/COO Subtype assessed by Investigators
Statistical analysis description:	
ORR difference in PPS (N=40): ORR in GCB subgroup minus ORR in non-GCB subgroup (i.e. combined ABC subgroup and Unclassifiable subgroup)	
Comparison groups	Activated B-cell-like (ABC) v Germinal center B-cell-like (GCB) v DLBCL/COO Subtype Unclassifiable
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	other
Method	Exact confidence intervals (CI)
Parameter estimate	ORR difference
Point estimate	-25.3
Confidence interval	
level	90 %
sides	2-sided
lower limit	-49.1
upper limit	1.1

Statistical analysis title	ORR by DLBCL/COO Subtype assessed by Investigators

Statistical analysis description:

ORR difference in FAS (N=52): ORR in Unclassifiable subgroup minus ORR in ABC / GCB subgroup (i.e. combined ABC subgroup and GCB subgroup)

Comparison groups	Activated B-cell-like (ABC) v Germinal center B-cell-like (GCB) v DLBCL/COO Subtype Unclassifiable
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	other
Method	Exact confidence intervals (CI)
Parameter estimate	ORR difference
Point estimate	12.9
Confidence interval	
level	90 %
sides	2-sided
lower limit	-42.4
upper limit	63.2

Statistical analysis title	ORR by DLBCL/COO Subtype assessed by Investigators

Statistical analysis description:

ORR difference in PPS (N=40): ORR in Unclassifiable subgroup minus ORR in ABC / GCB subgroup (i.e. combined ABC subgroup and GCB subgroup)

Comparison groups	Activated B-cell-like (ABC) v Germinal center B-cell-like (GCB) v DLBCL/COO Subtype Unclassifiable
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	other
Method	Exact confidence intervals (CI)
Parameter estimate	ORR difference
Point estimate	26.3
Confidence interval	
level	90 %
sides	2-sided
lower limit	-44.3
upper limit	77.6

Secondary: Duration of Response (DOR) in Total Population

End point title	Duration of Response (DOR) in Total Population

End point description:

The duration of response (DOR) was defined as the time from the date of first observed overall response (CR or PR) until radiological PD or death due to any cause, whichever was earlier. DOR was defined for responders only (i.e. subjects with a best response of CR or PR), based on the investigator assessment of tumor response according to the criteria defined by the Lugano Classification, 2014 and assessed by CT/MRI/PET-CT.

End point type	Secondary

End point timeframe:

From start of study treatment assessed up to 2 years after the last subject's first treatment or the last subject dies, whichever occurs first

End point values	Copanlisib (BAY80-6946)			
Subject group type	Reporting group			
Number of subjects analysed	13[9]			
Units: days				
median (confidence interval 95%)	132 (57 to 345)			

Notes:

[9] - Responders (i.e. subjects with a best response of CR or PR) in FAS assessed by the investigators

Statistical analyses

No statistical analyses for this end point

Secondary: DOR by CD79b Status

End point title	DOR by CD79b Status

End point description:

The duration of response (DOR) was defined as the time from the date of first observed overall response (CR or PR) until radiological PD or death due to any cause, whichever was earlier. DOR was defined for responders only (i.e. subjects with a best response of CR or PR), based on the investigator assessment of tumor response according to the criteria defined by the Lugano Classification, 2014 and assessed by CT/MRI/PET-CT.

End point type	Secondary

End point timeframe:

From start of study treatment assessed up to 2 years after the last subject's first treatment or the last subject dies, whichever occurs first

End point values	CD79b Mutant	CD79b Wild-type	CD79b Status Missing	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	2[10]	9[11]	2[12]	
Units: days				
median (confidence interval 95%)	516 (417 to 615)	113 (39 to 272)	113 (93 to 132)	

Notes:

[10] - Responders (i.e. subjects with a best response of CR or PR) in FAS assessed by the investigators

[11] - Responders (i.e. subjects with a best response of CR or PR) in FAS assessed by the investigators

[12] - Responders (i.e. subjects with a best response of CR or PR) in FAS assessed by the investigators

Statistical analyses

No statistical analyses for this end point

Secondary: DOR by DLBCL/COO Subtype

End point title	DOR by DLBCL/COO Subtype

End point description:

The duration of response (DOR) was defined as the time from the date of first observed overall response (CR or PR) until radiological PD or death due to any cause, whichever was earlier. DOR was defined for responders only (i.e. subjects with a best response of CR or PR), based on the investigator assessment of tumor response according to the criteria defined by the Lugano Classification, 2014 and assessed by CT/MRI/PET-CT. "-99999" and "99999" denote that value could not be estimated due to censored data or data not available.

End point type	Secondary

End point timeframe:

From start of study treatment assessed up to 2 years after the last subject's first treatment or the last subject dies, whichever occurs first

End point values	Activated B-cell-like (ABC)	Germinal center B-cell-like (GCB)	DLBCL/COO Subtype Unclassifiable	DLBCL/COO Subtype Missing
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	6[13]	4[14]	1[15]	2[16]
Units: days				
median (confidence interval 95%)	193 (39 to 417)	183 (63 to 615)	52 (-99999 to 99999)	113 (93 to 132)

Notes:

[13] - Responders (i.e. subjects with a best response of CR or PR) in FAS assessed by the investigators

[14] - Responders (i.e. subjects with a best response of CR or PR) in FAS assessed by the investigators

[15] - Responders (i.e. subjects with a best response of CR or PR) in FAS assessed by the investigators

[16] - Responders (i.e. subjects with a best response of CR or PR) in FAS assessed by the investigators

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free Survival (PFS) in Total Population

End point title	Progression-free Survival (PFS) in Total Population

End point description:

The progression-free survival (PFS) was defined as the time from date of start of study treatment to radiological PD or death due to any cause, whichever was earlier, based on the investigator assessment of tumor response according to the criteria defined by the Lugano Classification, 2014 and assessed by CT/MRI/PET-CT.

End point type	Secondary

End point timeframe:

From start of study treatment assessed up to 2 years after the last subject's first treatment or the last subject dies, whichever occurs first

End point values	Copanlisib (BAY80-6946)			
Subject group type	Reporting group			
Number of subjects analysed	67[17]			
Units: days				
median (confidence interval 95%)	54 (50 to 84)			

Notes:

[17] - Full analysis set (FAS)

Statistical analyses

No statistical analyses for this end point

Secondary: PFS by CD79b Status

End point title	PFS by CD79b Status

End point description:

The progression-free survival (PFS) was defined as the time from date of start of study treatment to radiological PD or death due to any cause, whichever was earlier, based on the investigator assessment of tumor response according to the criteria defined by the Lugano Classification, 2014 and assessed by CT/MRI/PET-CT.

End point type	Secondary

End point timeframe:

From start of study treatment assessed up to 2 years after the last subject's first treatment or the last subject dies, whichever occurs first

End point values	CD79b Mutant	CD79b Wild-type	CD79b Status Missing	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	9[18]	45[19]	13[20]	
Units: days				
median (confidence interval 95%)	73 (43 to 465)	52 (46 to 88)	56 (46 to 138)	

Notes:

[18] - Full analysis set (FAS)

[19] - Full analysis set (FAS)

[20] - Full analysis set (FAS)

Statistical analyses

No statistical analyses for this end point

Secondary: PFS by DLBCL/COO Subtype

End point title	PFS by DLBCL/COO Subtype

End point description:

The progression-free survival (PFS) was defined as the time from date of start of study treatment to radiological PD or death due to any cause, whichever was earlier, based on the investigator assessment of tumor response according to the criteria defined by the Lugano Classification, 2014 and assessed by CT/MRI/PET-CT.

End point type	Secondary

End point timeframe:

From start of study treatment assessed up to 2 years after the last subject's first treatment or the last subject dies, whichever occurs first

End point values	Activated B-cell-like (ABC)	Germinal center B-cell-like (GCB)	DLBCL/COO Subtype Unclassifiable	DLBCL/COO Subtype Missing
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	19[21]	30[22]	3[23]	15[24]
Units: days				
median (confidence interval 95%)	73 (44 to 101)	52 (46 to 116)	84 (26 to 164)	51 (33 to 58)

Notes:

[21] - Full analysis set (FAS)

[22] - Full analysis set (FAS)

[23] - Full analysis set (FAS)

[24] - Full analysis set (FAS)

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS) in Total Population

End point title	Overall Survival (OS) in Total Population

End point description:

The overall survival (OS) was defined as the time from date of start of study treatment until death from any cause.

End point type	Secondary

End point timeframe:

From start of study treatment assessed up to 2 years after the last subject's first treatment or the last subject dies, whichever occurs first

End point values	Copanlisib (BAY80-6946)			
Subject group type	Reporting group			
Number of subjects analysed	67[25]			
Units: days				
median (confidence interval 95%)	224 (104 to 327)			

Notes:

[25] - Full analysis set (FAS)

Statistical analyses

No statistical analyses for this end point

Secondary: OS by CD79b Status

End point title	OS by CD79b Status

End point description:

The overall survival (OS) was defined as the time from date of start of study treatment until death from any cause. "99999" denotes that value could not be estimated due to censored data.

End point type	Secondary

End point timeframe:

From start of study treatment assessed up to 2 years after the last subject's first treatment or the last subject dies, whichever occurs first

End point values	CD79b Mutant	CD79b Wild-type	CD79b Status Missing	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	9[26]	45[27]	13[28]	
Units: days				
median (confidence interval 95%)	178 (57 to 99999)	242 (73 to 385)	224 (56 to 388)	

Notes:

[26] - Full analysis set (FAS)

[27] - Full analysis set (FAS)

[28] - Full analysis set (FAS)

Statistical analyses

No statistical analyses for this end point

Secondary: OS by DLBCL/COO Subtype

End point title	OS by DLBCL/COO Subtype

End point description:

The overall survival (OS) was defined as the time from date of start of study treatment until death from any cause.

End point type	Secondary

End point timeframe:

From start of study treatment assessed up to 2 years after the last subject's first treatment or the last subject dies, whichever occurs first

End point values	Activated B-cell-like (ABC)	Germinal center B-cell-like (GCB)	DLBCL/COO Subtype Unclassifiable	DLBCL/COO Subtype Missing
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	19[29]	30[30]	3[31]	15[32]
Units: days				
median (confidence interval 95%)	210 (63 to 421)	287 (94 to 436)	164 (93 to 273)	160 (46 to 400)

Notes:

[29] - Full analysis set (FAS)

[30] - Full analysis set (FAS)

[31] - Full analysis set (FAS)

[32] - Full analysis set (FAS)

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Stable Disease (DOSD) in Total Population

End point title	Duration of Stable Disease (DOSD) in Total Population

End point description:

The duration of stable disease (DOSD) was defined as the time (in days) from date of start of study treatment to radiological PD or death due to any cause, whichever was earlier. The DOSD was only evaluated in subjects failing to achieve a best response of CR or PR, but who achieved SD (stable disease), based on the investigator assessment of tumor response according to the criteria defined by the Lugano Classification, 2014 and assessed by CT/MRI/PET-CT.

End point type	Secondary

End point timeframe:

From start of study treatment assessed up to 2 years after the last subject's first treatment or the last subject dies, whichever occurs first

End point values	Copanlisib (BAY80-6946)			
Subject group type	Reporting group			
Number of subjects analysed	14[33]			
Units: days				
median (confidence interval 95%)	106 (73 to 138)			

Notes:

[33] - Subjects who failed to achieve CR or PR but achieved SD in FAS assessed by the investigators

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Control Rate (DCR) in Total Population

End point title	Disease Control Rate (DCR) in Total Population

End point description:

The disease control rate (DCR) was defined as the percentage of subjects who had a best response rating of CR, PR, or SD that was achieved during treatment or within 30 days after termination of study drug. The tumor response was based on investigator assessment according to the criteria defined by the Lugano Classification, 2014 and assessed by CT/MRI/PET-CT.

End point type	Secondary

End point timeframe:

From start of study treatment assessed up to 2 years after the last subject's first treatment or the last subject dies, whichever occurs first

End point values	Copanlisib (BAY80-6946)			
Subject group type	Reporting group			
Number of subjects analysed	67[34]			
Units: percentage of subjects				
number (confidence interval 90%)	40.3 (30.2 to 51.1)			

Notes:

[34] - Full analysis set (FAS)

Statistical analyses

No statistical analyses for this end point

Secondary: DCR by CD79b Status

End point title	DCR by CD79b Status

End point description:

The disease control rate (DCR) was defined as the percentage of subjects who had a best response rating of CR, PR, or SD that was achieved during treatment or within 30 days after termination of study drug. The tumor response was based on investigator assessment according to the criteria defined by the Lugano Classification, 2014 and assessed by CT/MRI/PET-CT.

End point type	Secondary

End point timeframe:

From start of study treatment assessed up to 2 years after the last subject's first treatment or the last subject dies, whichever occurs first

End point values	CD79b Mutant	CD79b Wild-type	CD79b Status Missing	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	9[35]	45[36]	13[37]	
Units: percentage of subjects				
number (confidence interval 90%)	55.6 (25.1 to 83.1)	40.0 (27.7 to 53.3)	30.8 (11.3 to 57.3)	

Notes:

[35] - Full analysis set (FAS)

[36] - Full analysis set (FAS)

[37] - Full analysis set (FAS)

Statistical analyses

No statistical analyses for this end point

Secondary: DCR by DLBCL/COO Subtype

End point title	DCR by DLBCL/COO Subtype

End point description:

The disease control rate (DCR) was defined as the percentage of subjects who had a best response rating of CR, PR, or SD that was achieved during treatment or within 30 days after termination of study drug. The tumor response was based on investigator assessment according to the criteria defined by the Lugano Classification, 2014 and assessed by CT/MRI/PET-CT.

End point type	Secondary

End point timeframe:

From start of study treatment assessed up to 2 years after the last subject's first treatment or the last subject dies, whichever occurs first

End point values	Activated B-cell-like (ABC)	Germinal center B-cell-like (GCB)	DLBCL/COO Subtype Unclassifiable	DLBCL/COO Subtype Missing
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	19[38]	30[39]	3[40]	15[41]
Units: percentage of subjects				
number (confidence interval 90%)	52.6 (32.0 to 72.6)	40.0 (25.0 to 56.6)	33.3 (1.7 to 86.5)	26.7 (9.7 to 51.1)

Notes:

[38] - Full analysis set (FAS)

[39] - Full analysis set (FAS)

[40] - Full analysis set (FAS)

[41] - Full analysis set (FAS)

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Treatment-emergent Adverse Events (TEAEs) and Treatment-emergent Serious Adverse Events (TESAEs)

End point title	Number of Subjects With Treatment-emergent Adverse Events (TEAEs) and Treatment-emergent Serious Adverse Events (TESAEs)

End point description:

A treatment-emergent AE is defined as any event arising or worsening after start of test drug administration until 30 days (modified by amendment 4) after the last test drug intake (end of Safety follow-up).

End point type	Secondary

End point timeframe:

From start of test drug to 30 days after the last test drug intake, assessed up to 2 years after the last subject's first treatment or the last subject dies (whichever occurs first), with an average of 15 weeks for individual subject

End point values	Copanlisib (BAY80-6946)			
Subject group type	Reporting group			
Number of subjects analysed	67[42]			
Units: subjects				
Any TEAE	65			
Any TESAE	44			

Notes:

[42] - Safety analysis set (SAF)

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Time to Response (TTR) in Total Population

End point title	Time to Response (TTR) in Total Population

End point description:

The time to response (TTR) was defined as the time (days) from start of study treatment to the date of first observed response (first measured CR or PR). TTR was defined for responders only (i.e. patients

with CR or PR), based on the investigator assessment of tumor response according to the criteria defined by the Lugano Classification, 2014 and assessed by CT/MRI/PET-CT.

End point type	Other pre-specified

End point timeframe:

From start of study treatment assessed up to 2 years after the last subject's first treatment or the last subject dies, whichever occurs first

End point values	Copanlisib (BAY80-6946)			
Subject group type	Reporting group			
Number of subjects analysed	13[43]			
Units: days				
median (confidence interval 95%)	52 (49 to 56)			

Notes:

[43] - Responders (i.e. subjects with a best response of CR or PR) in FAS assessed by the investigators

Statistical analyses

No statistical analyses for this end point

Other pre-specified: ORR in Total Population Based on Central Imaging Review

End point title	ORR in Total Population Based on Central Imaging Review

End point description:

The objective response rate (ORR) was defined as the percentage of subjects who had at least one post-baseline overall response of complete response (CR) or partial response (PR) during study conduct according to the criteria defined by the Lugano Classification, 2014 and assessed by CT/MRI/PET-CT. The overall response assessment for this outcome measure was based on central imaging review.

End point type	Other pre-specified

End point timeframe:

From start of study treatment assessed up to 24 weeks after the last subject fully evaluable for the primary endpoint started treatment (about 12 months)

End point values	Copanlisib (BAY80-6946)			
Subject group type	Reporting group			
Number of subjects analysed	67[44]			
Units: percentage of subjects				
number (confidence interval 90%)	22.4 (14.3 to 32.4)			

Notes:

[44] - Full analysis set (FAS)

Statistical analyses

No statistical analyses for this end point

Other pre-specified: ORR by CD79b Status Based on Central Imaging Review

End point title	ORR by CD79b Status Based on Central Imaging Review

End point description:

The objective response rate (ORR) was defined as the percentage of subjects who had at least one post-baseline overall response of complete response (CR) or partial response (PR) during study conduct according to the criteria defined by the Lugano Classification, 2014 and assessed by CT/MRI/PET-CT. The overall response assessment for this outcome measure was based on central imaging review.

End point type	Other pre-specified

End point timeframe:

From start of study treatment assessed up to 24 weeks after the last subject fully evaluable for the primary endpoint started treatment (about 12 months)

End point values	CD79b Mutant	CD79b Wild-type	CD79b Status Missing	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	9[45]	45[46]	13[47]	
Units: percentage of subjects				
number (confidence interval 90%)	44.4 (16.9 to 74.9)	20.0 (10.9 to 32.3)	15.4 (2.8 to 41.0)	

Notes:

[45] - Full analysis set (FAS)

[46] - Full analysis set (FAS)

[47] - Full analysis set (FAS)

Statistical analyses

No statistical analyses for this end point

Other pre-specified: ORR by DLBCL/COO Subtype Based on Central Imaging Review

End point title	ORR by DLBCL/COO Subtype Based on Central Imaging Review

End point description:

The objective response rate (ORR) was defined as the percentage of subjects who had at least one post-baseline overall response of complete response (CR) or partial response (PR) during study conduct according to the criteria defined by the Lugano Classification, 2014 and assessed by CT/MRI/PET-CT. The overall response assessment for this outcome measure was based on central imaging review.

End point type	Other pre-specified

End point timeframe:

From start of study treatment assessed up to 24 weeks after the last subject fully evaluable for the primary endpoint started treatment (about 12 months)

End point values	Activated B-cell-like (ABC)	Germinal center B-cell-like (GCB)	DLBCL/COO Subtype Unclassifiable	DLBCL/COO Subtype Missing
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	19[48]	30[49]	3[50]	15[51]
Units: percentage of subjects				
number (confidence interval 90%)	47.4 (27.4 to 68.0)	13.3 (4.7 to 28.0)	0.0 (0.0 to 63.2)	13.3 (2.4 to 36.3)

Notes:

[48] - Full analysis set (FAS)

[49] - Full analysis set (FAS)

[50] - Full analysis set (FAS)

[51] - Full analysis set (FAS)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From start of test drug to 30 days after the last test drug intake, assessed up to 2 years after the last subject's first treatment or the last subject dies (whichever occurs first), with an average of 15 weeks for individual subject

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.1

Reporting groups

Reporting group title	Copanlisib (BAY80-6946)

Reporting group description:

Subjects assigned to receive copanlisib intravenous (IV) infusion at a dose of 60 mg as single agent on Days 1, 8, and 15 of 28-day treatment cycle. Copanlisib treatment was to be continued until disease progression (PD), unacceptable toxicity, or until another criterion was met for withdrawal from the study treatment

Serious adverse events	Copanlisib (BAY80-6946)		
Total subjects affected by serious adverse events			
subjects affected / exposed	44 / 67 (65.67%)		
number of deaths (all causes)	53		
number of deaths resulting from adverse events	14		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Inflammatory carcinoma of the breast			
subjects affected / exposed	1 / 67 (1.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Mycosis fungoides			
subjects affected / exposed	1 / 67 (1.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cancer pain			
subjects affected / exposed	1 / 67 (1.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			

Hypertension				
subjects affected / exposed	1 / 67 (1.49%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Deep vein thrombosis				
subjects affected / exposed	1 / 67 (1.49%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
Asthenia				
subjects affected / exposed	1 / 67 (1.49%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Death				
subjects affected / exposed	2 / 67 (2.99%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 2			
Fatigue				
subjects affected / exposed	1 / 67 (1.49%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Pyrexia				
subjects affected / exposed	4 / 67 (5.97%)			
occurrences causally related to treatment / all	1 / 4			
deaths causally related to treatment / all	0 / 0			
Sudden death				
subjects affected / exposed	1 / 67 (1.49%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
General physical health deterioration				
subjects affected / exposed	9 / 67 (13.43%)			
occurrences causally related to treatment / all	0 / 9			
deaths causally related to treatment / all	0 / 8			

Respiratory, thoracic and mediastinal disorders			
Acute pulmonary oedema			
subjects affected / exposed	1 / 67 (1.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cough			
subjects affected / exposed	1 / 67 (1.49%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Dyspnoea			
subjects affected / exposed	2 / 67 (2.99%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Pleural effusion			
subjects affected / exposed	2 / 67 (2.99%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Pneumonitis			
subjects affected / exposed	3 / 67 (4.48%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		
Investigations			
Amylase increased			
subjects affected / exposed	1 / 67 (1.49%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Blood creatinine increased			
subjects affected / exposed	1 / 67 (1.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lipase increased			
subjects affected / exposed	1 / 67 (1.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Neutrophil count decreased	
subjects affected / exposed	1 / 67 (1.49%)
occurrences causally related to treatment / all	0 / 1
deaths causally related to treatment / all	0 / 0
Nervous system disorders	
Neurological symptom	
subjects affected / exposed	1 / 67 (1.49%)
occurrences causally related to treatment / all	0 / 1
deaths causally related to treatment / all	0 / 0
Blood and lymphatic system disorders	
Febrile neutropenia	
subjects affected / exposed	1 / 67 (1.49%)
occurrences causally related to treatment / all	1 / 1
deaths causally related to treatment / all	0 / 0
Lymphadenopathy	
subjects affected / exposed	1 / 67 (1.49%)
occurrences causally related to treatment / all	0 / 1
deaths causally related to treatment / all	0 / 0
Thrombocytopenia	
subjects affected / exposed	1 / 67 (1.49%)
occurrences causally related to treatment / all	1 / 1
deaths causally related to treatment / all	0 / 0
Eye disorders	
Diplopia	
subjects affected / exposed	1 / 67 (1.49%)
occurrences causally related to treatment / all	0 / 1
deaths causally related to treatment / all	0 / 0
Gastrointestinal disorders	
Abdominal pain	
subjects affected / exposed	3 / 67 (4.48%)
occurrences causally related to treatment / all	0 / 3
deaths causally related to treatment / all	0 / 0
Colitis	

subjects affected / exposed	1 / 67 (1.49%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 67 (1.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Nausea			
subjects affected / exposed	1 / 67 (1.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	1 / 67 (1.49%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Stevens-Johnson syndrome			
subjects affected / exposed	1 / 67 (1.49%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	1 / 67 (1.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal failure			
subjects affected / exposed	1 / 67 (1.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary retention			
subjects affected / exposed	1 / 67 (1.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Acute kidney injury			

subjects affected / exposed	1 / 67 (1.49%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Musculoskeletal and connective tissue disorders

Back pain

subjects affected / exposed	2 / 67 (2.99%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			

Infections and infestations

Cystitis

subjects affected / exposed	1 / 67 (1.49%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Herpes zoster

subjects affected / exposed	1 / 67 (1.49%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			

Lower respiratory tract infection

subjects affected / exposed	1 / 67 (1.49%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Pneumonia pneumococcal

subjects affected / exposed	1 / 67 (1.49%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			

Thrombophlebitis septic

subjects affected / exposed	1 / 67 (1.49%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Urosepsis

subjects affected / exposed	1 / 67 (1.49%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Escherichia urinary tract infection				
subjects affected / exposed	1 / 67 (1.49%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Lung infection				
subjects affected / exposed	2 / 67 (2.99%)			
occurrences causally related to treatment / all	1 / 3			
deaths causally related to treatment / all	0 / 0			
Respiratory tract infection viral				
subjects affected / exposed	1 / 67 (1.49%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Splenic infection fungal				
subjects affected / exposed	1 / 67 (1.49%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatic infection fungal				
subjects affected / exposed	1 / 67 (1.49%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumocystis jirovecii pneumonia				
subjects affected / exposed	1 / 67 (1.49%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
Cachexia				
subjects affected / exposed	1 / 67 (1.49%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Dehydration				
subjects affected / exposed	1 / 67 (1.49%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hypercalcaemia				

subjects affected / exposed	1 / 67 (1.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hyperglycaemia			
subjects affected / exposed	5 / 67 (7.46%)		
occurrences causally related to treatment / all	5 / 5		
deaths causally related to treatment / all	0 / 0		
Hyponatraemia			
subjects affected / exposed	1 / 67 (1.49%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 4 %

Non-serious adverse events	Copanlisib (BAY80-6946)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	64 / 67 (95.52%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour pain			
subjects affected / exposed	4 / 67 (5.97%)		
occurrences (all)	4		
Vascular disorders			
Haematoma			
subjects affected / exposed	3 / 67 (4.48%)		
occurrences (all)	3		
Hypertension			
subjects affected / exposed	27 / 67 (40.30%)		
occurrences (all)	42		
Hypotension			
subjects affected / exposed	3 / 67 (4.48%)		
occurrences (all)	3		
General disorders and administration site conditions			
Asthenia			

subjects affected / exposed	3 / 67 (4.48%)		
occurrences (all)	3		
Chest pain			
subjects affected / exposed	3 / 67 (4.48%)		
occurrences (all)	3		
Chills			
subjects affected / exposed	3 / 67 (4.48%)		
occurrences (all)	3		
Fatigue			
subjects affected / exposed	18 / 67 (26.87%)		
occurrences (all)	19		
Mucosal inflammation			
subjects affected / exposed	4 / 67 (5.97%)		
occurrences (all)	4		
Oedema peripheral			
subjects affected / exposed	7 / 67 (10.45%)		
occurrences (all)	7		
Pyrexia			
subjects affected / exposed	12 / 67 (17.91%)		
occurrences (all)	12		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	12 / 67 (17.91%)		
occurrences (all)	12		
Dyspnoea			
subjects affected / exposed	5 / 67 (7.46%)		
occurrences (all)	5		
Productive cough			
subjects affected / exposed	4 / 67 (5.97%)		
occurrences (all)	4		
Oropharyngeal pain			
subjects affected / exposed	3 / 67 (4.48%)		
occurrences (all)	3		
Psychiatric disorders			

Insomnia			
subjects affected / exposed	3 / 67 (4.48%)		
occurrences (all)	3		
Investigations			
Lipase increased			
subjects affected / exposed	3 / 67 (4.48%)		
occurrences (all)	3		
Lymphocyte count decreased			
subjects affected / exposed	3 / 67 (4.48%)		
occurrences (all)	4		
Platelet count decreased			
subjects affected / exposed	5 / 67 (7.46%)		
occurrences (all)	5		
Weight decreased			
subjects affected / exposed	3 / 67 (4.48%)		
occurrences (all)	3		
White blood cell count decreased			
subjects affected / exposed	3 / 67 (4.48%)		
occurrences (all)	3		
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	3 / 67 (4.48%)		
occurrences (all)	4		
Cardiac disorders			
Tachycardia			
subjects affected / exposed	3 / 67 (4.48%)		
occurrences (all)	3		
Nervous system disorders			
Dizziness			
subjects affected / exposed	4 / 67 (5.97%)		
occurrences (all)	6		
Headache			
subjects affected / exposed	9 / 67 (13.43%)		
occurrences (all)	9		
Paraesthesia			

subjects affected / exposed	4 / 67 (5.97%)		
occurrences (all)	6		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	6 / 67 (8.96%)		
occurrences (all)	6		
Neutropenia			
subjects affected / exposed	9 / 67 (13.43%)		
occurrences (all)	9		
Thrombocytopenia			
subjects affected / exposed	6 / 67 (8.96%)		
occurrences (all)	6		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	5 / 67 (7.46%)		
occurrences (all)	5		
Constipation			
subjects affected / exposed	11 / 67 (16.42%)		
occurrences (all)	11		
Diarrhoea			
subjects affected / exposed	25 / 67 (37.31%)		
occurrences (all)	38		
Mouth ulceration			
subjects affected / exposed	8 / 67 (11.94%)		
occurrences (all)	8		
Nausea			
subjects affected / exposed	20 / 67 (29.85%)		
occurrences (all)	23		
Stomatitis			
subjects affected / exposed	5 / 67 (7.46%)		
occurrences (all)	5		
Vomiting			
subjects affected / exposed	12 / 67 (17.91%)		
occurrences (all)	13		
Paraesthesia oral			

subjects affected / exposed	3 / 67 (4.48%)		
occurrences (all)	5		
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	6 / 67 (8.96%)		
occurrences (all)	7		
Rash			
subjects affected / exposed	9 / 67 (13.43%)		
occurrences (all)	10		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	4 / 67 (5.97%)		
occurrences (all)	4		
Muscle spasms			
subjects affected / exposed	6 / 67 (8.96%)		
occurrences (all)	7		
Pain in extremity			
subjects affected / exposed	3 / 67 (4.48%)		
occurrences (all)	5		
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	4 / 67 (5.97%)		
occurrences (all)	4		
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	21 / 67 (31.34%)		
occurrences (all)	27		
Hypoglycaemia			
subjects affected / exposed	3 / 67 (4.48%)		
occurrences (all)	3		
Hypokalaemia			
subjects affected / exposed	8 / 67 (11.94%)		
occurrences (all)	15		
Hyponatraemia			
subjects affected / exposed	4 / 67 (5.97%)		
occurrences (all)	6		

Hypophosphataemia				
subjects affected / exposed	3 / 67 (4.48%)			
occurrences (all)	4			
Decreased appetite				
subjects affected / exposed	10 / 67 (14.93%)			
occurrences (all)	14			

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 January 2016	•Removal of a response requirement to first-line therapy for NHL transformed from follicular lymphoma •Removal of the exclusion of patients with fasting plasma glucose > 160 mg/dL at screening •Removal of the conservative requirement for blood pressure levels during eligibility evaluation •Updates to the management and monitoring of transient glucose increases •Modification of guidelines on dose modification of study treatment for non-hematological toxicity •Guidance on the differentiation of non-infectious pneumonitis (NIP) and other pneumonitis included, and alterations to the dose-modification of study treatment in the event of NIP •Revision of laboratory evaluations and clarification that laboratory tests considered clinically significant should have been reported as an AE •Update copanlisib safety information pertaining to potential drug-related transient blood pressure increase •Fasting for lipid panels was revised to reflect local standards rather than a centrally defined period.
21 July 2016	•Implementation of ongoing central review rather than retrospective central image review •Clarification that primary analysis of efficacy was based upon the investigator's assessment. •Clarification that AEs were collected until 30 days after last treatment with study drug. •Addition of guidance on the monitoring and prophylaxis of opportunistic infections in patients at risk for such whilst on study treatment, including additional CD4, CD8, cytomegalovirus (CMV) and blood culture laboratory tests and lung examinations, following Health Authority alerts, and allowance of a delay in study drug administration of up to 2 cycles due to reactivation of CMV.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

 None reported