Clinical trial results:
A Phase Ib/II Study Evaluating the Safety and Efficacy of Obinutuzumab in Combination with Atezolizumab Plus Polatuzumab Vedotin in Patients with Relapsed or Refractory Follicular Lymphoma and Rituximab in Combination with Atezolizumab Plus Polatuzumab Vedotin in Patients with Relapsed or Refractory Diffuse Large B-Cell Lymphoma

Summary

EudraCT number	2015-004845-25
Trial protocol	DE PL
Global end of trial date	07 October 2019

Results information

Result version number	v3
This version publication date	04 November 2020
First version publication date	21 September 2019
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	BO29561

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02729896
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	F. Hoffmann-La Roche AG
Sponsor organisation address	Grenzacherstrasse 124, Basel, Switzerland, CH-4070
Public contact	F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, 41 616878333, global.trial_information@roche.com
Scientific contact	F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, 41 616878333, globa.trial_information@roche.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	07 October 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	07 October 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To Evaluate the Safety and Efficacy of Obinutuzumab in Combination with Atezolizumab plus Polatuzumab Vedotin in Patients with Relapsed or Refractory Follicular Lymphoma and Rituximab in Combination with Atezolizumab plus Polatuzumab Vedotin in Patients with Relapsed or Refractory Diffuse Large B Cell Lymphoma.

Protection of trial subjects:

All study subjects were required to read and sign an Informed Consent Form.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	09 November 2016
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	Germany: 11
Country: Number of subjects enrolled	Poland: 14
Country: Number of subjects enrolled	United States: 11
Worldwide total number of subjects	36
EEA total number of subjects	25

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)	20
From 65 to 84 years	15

85 years and over	1

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

56 patients were screened and 36 patients enrolled and dosed in the study.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Dose-Escalation FL Cohort

Arm description:

During the induction treatment Cycle 1 (21-day cycles): participants received obinutuzumab on Days 1, 8, and 15 and Pola on Day 1; Cycles 2-6: participants received 1000 mg of obinutuzumab on Day 1, 1200 mg of Atezo on Day 1, and either 1.4 mg/kilogram (kg) or 1.8 mg/kg of Pola on Day 1. The 1.4 mg/kg dose was cleared and escalated to 1.8 mg/kg which was declared the recommended Phase 2 dose (RP2D). This was followed by obinutuzumab on Day 1 of every other month starting with Month 1 for 24 months, during maintenance treatment for FL participants. Due to unexpected toxicity, recruitment was stopped, and atezolizumab discontinued in all treated patients. This combination will not be further developed.

Arm type	Experimental
Investigational medicinal product name	Atezolizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

1200 mg

Investigational medicinal product name	Obinutuzumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

1000 mg

Investigational medicinal product name	Polatuzumab Vedotin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

1.4 mg

Arm title	Expansion FL Cohort

Arm description:

During the induction treatment Cycle 1 (21-day cycles): participants received obinutuzumab on Days 1, 8, and 15 and Pola on Day 1; Cycles 2-6: participants received 1000 mg of obinutuzumab on Day 1, 1200 mg of Atezo on Day 1, and 1.8 mg/kg of Pola (RP2D) on Day 1. This was followed by

obinutuzumab on Day 1 of every other month starting with Month 1 for 24 months, during maintenance treatment for FL participants. Due to unexpected toxicity, recruitment was stopped, and atezolizumab discontinued in all treated patients. This combination will not be further developed.

Arm type	Experimental
Investigational medicinal product name	Atezolizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

1200 mg

Investigational medicinal product name	Obinutuzumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

1000 mg

Investigational medicinal product name	Polatuzumab Vedotin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

1.8 mg

Arm title	Safety Run-in and Expansion DLBCL Cohort

Arm description:

For DLBCL, during the induction treatment Cycles 1-6 (21-day cycles): participants received a 375 mg/m^2 IV of rituximab on Day 1 and on Day 1 of every other month during consolidation. Participants also received a 1.8 mg/kg IV of Pola on Day 1. Cycles 2-6: participants received 1200 mg of Atezo on Day 1. Due to unexpected toxicity, recruitment was stopped, and atezolizumab discontinued in all treated patients. This combination will not be further developed.

Arm type	Experimental
Investigational medicinal product name	Atezolizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

1200 mg

Investigational medicinal product name	Rituximab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

375 mg/m2

Investigational medicinal product name	Polatuzumab Vedotin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:
1.4 mg or 1.8 mg

Number of subjects in period 1	Dose-Escalation FL Cohort	Expansion FL Cohort	Safety Run-in and Expansion DLBCL Cohort
Started	3	10	23
Completed	1	1	1
Not completed	2	9	22
Physician decision	1	2	3
Withdrawal By Subject	1	-	3
Death	-	2	13
Progressive Disease	-	1	-
Not Specified	-	2	-
Lost to follow-up	-	2	3

Baseline characteristics

Reporting groups	
Reporting group title	Dose-Escalation FL Cohort
Reporting group description:	
During the induction treatment Cycle 1 (21-day cycles): participants received obinutuzumab on Days 1, 8, and 15 and Pola on Day 1; Cycles 2-6: participants received 1000 mg of obinutuzumab on Day 1, 1200 mg of Atezo on Day 1, and either 1.4 mg/kilogram (kg) or 1.8 mg/kg of Pola on Day 1. The 1.4 mg/kg dose was cleared and escalated to 1.8 mg/kg which was declared the recommended Phase 2 dose (RP2D). This was followed by obinutuzumab on Day 1 of every other month starting with Month 1 for 24 months, during maintenance treatment for FL participants. Due to unexpected toxicity, recruitment was stopped, and atezolizumab discontinued in all treated patients. This combination will not be further developed.	
Reporting group title	Expansion FL Cohort
Reporting group description:	
During the induction treatment Cycle 1 (21-day cycles): participants received obinutuzumab on Days 1, 8, and 15 and Pola on Day 1; Cycles 2-6: participants received 1000 mg of obinutuzumab on Day 1, 1200 mg of Atezo on Day 1, and 1.8 mg/kg of Pola (RP2D) on Day 1. This was followed by obinutuzumab on Day 1 of every other month starting with Month 1 for 24 months, during maintenance treatment for FL participants. Due to unexpected toxicity, recruitment was stopped, and atezolizumab discontinued in all treated patients. This combination will not be further developed.	
Reporting group title	Safety Run-in and Expansion DLBCL Cohort
Reporting group description:	
For DLBCL, during the induction treatment Cycles 1-6 (21-day cycles): participants received a 375 mg/m^2 IV of rituximab on Day 1 and on Day 1 of every other month during consolidation. Participants also received a 1.8 mg/kg IV of Pola on Day 1. Cycles 2-6: participants received 1200 mg of Atezo on Day 1. Due to unexpected toxicity, recruitment was stopped, and atezolizumab discontinued in all treated patients. This combination will not be further developed.	

Reporting group values	Dose-Escalation FL Cohort	Expansion FL Cohort	Safety Run-in and Expansion DLBCL Cohort
Number of subjects	3	10	23
Age Categorical Units: Subjects			
<=18 years	0	0	0
Between 18 and 65 years	2	6	12
>=65 years	1	4	11
Age Continuous Units: Years			
arithmetic mean	52.3	57.7	64.3
standard deviation	± 13.6	± 11.7	± 15.3
Sex: Female, Male Units: Subjects			
Female	0	4	9
Male	3	6	14
Race/Ethnicity, Customized Units: Subjects			
Hispanic or Latino	0	1	3
Not Hispanic or Latino	3	9	18
Unknown	0	0	2
Race/Ethnicity, Customized Units: Subjects			
Other	0	1	2

White	3	9	21

Reporting group values	Total		
Number of subjects	36		
Age Categorical Units: Subjects			
<=18 years	0		
Between 18 and 65 years	20		
>=65 years	16		
Age Continuous Units: Years arithmetic mean standard deviation	 -		
Sex: Female, Male Units: Subjects			
Female	13		
Male	23		
Race/Ethnicity, Customized Units: Subjects			
Hispanic or Latino	4		
Not Hispanic or Latino	30		
Unknown	2		
Race/Ethnicity, Customized Units: Subjects			
Other	3		
White	33		

End points

End points reporting groups

Reporting group title	Dose-Escalation FL Cohort

Reporting group description:

During the induction treatment Cycle 1 (21-day cycles): participants received obinutuzumab on Days 1, 8, and 15 and Pola on Day 1; Cycles 2-6: participants received 1000 mg of obinutuzumab on Day 1, 1200 mg of Atezo on Day 1, and either 1.4 mg/kilogram (kg) or 1.8 mg/kg of Pola on Day 1. The 1.4 mg/kg dose was cleared and escalated to 1.8 mg/kg which was declared the recommended Phase 2 dose (RP2D). This was followed by obinutuzumab on Day 1 of every other month starting with Month 1 for 24 months, during maintenance treatment for FL participants. Due to unexpected toxicity, recruitment was stopped, and atezolizumab discontinued in all treated patients. This combination will not be further developed.

Reporting group title	Expansion FL Cohort

Reporting group description:

During the induction treatment Cycle 1 (21-day cycles): participants received obinutuzumab on Days 1, 8, and 15 and Pola on Day 1; Cycles 2-6: participants received 1000 mg of obinutuzumab on Day 1, 1200 mg of Atezo on Day 1, and 1.8 mg/kg of Pola (RP2D) on Day 1. This was followed by obinutuzumab on Day 1 of every other month starting with Month 1 for 24 months, during maintenance treatment for FL participants. Due to unexpected toxicity, recruitment was stopped, and atezolizumab discontinued in all treated patients. This combination will not be further developed.

Reporting group title	Safety Run-in and Expansion DLBCL Cohort

Reporting group description:

For DLBCL, during the induction treatment Cycles 1-6 (21-day cycles): participants received a 375 mg/m^2 IV of rituximab on Day 1 and on Day 1 of every other month during consolidation. Participants also received a 1.8 mg/kg IV of Pola on Day 1. Cycles 2-6: participants received 1200 mg of Atezo on Day 1. Due to unexpected toxicity, recruitment was stopped, and atezolizumab discontinued in all treated patients. This combination will not be further developed.

Primary: Percentage of Participants with CR at EOI, as Determined by the investigator on the Basis of Positron Emission Tomography and Computed Tomography (PET-CT) Scan

End point title	Percentage of Participants with CR at EOI, as Determined by the investigator on the Basis of Positron Emission Tomography and Computed Tomography (PET-CT) Scan[1]

End point description:

Tumor response assessment was performed by the investigator according to modified Lugano classification using PET/CT scan. CR was defined as a score of 1 (no uptake above background), 2 (uptake </=mediastinum), or 3 (uptake <mediastinum but </=liver) with or without a residual mass on PET 5-PS, for lymph nodes and extralymphatic sites; no new lesions; no evidence of FDG-avid disease in bone marrow; and normal/IHC-negative bone marrow morphology. 90% confidence interval (CI) for percentage of responders was calculated using Clopper-Pearson method. All PET evaluable 1L FL and 1L DLBCL patients with at least one dose of atezolizumab were included in efficacy population.

End point type	Primary

End point timeframe:

Within 6 to 8 weeks after Day 1 of Cycle 6 (up to approximately 6 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: This endpoint is only reporting the percentage of participants

End point values	Dose-Escalation FL Cohort	Expansion FL Cohort	Safety Run-in and Expansion DLBCL Cohort	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	3	7	16	
Units: Percentage of participants				
number (not applicable)	33.33	14.30	12.5	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with CR at EOI, as Determined by Investigator on the Basis of CT Scans Alone

End point title	Percentage of Participants with CR at EOI, as Determined by Investigator on the Basis of CT Scans Alone

End point description:

Tumor response assessment was performed by investigator according to modified Lugano classification using computed tomography (CT) scan. OR: a response of CR or PR. CR: Target nodes/nodal masses regressed to <= 1.5 cm in LDi; no extralymphatic sites of disease; organ enlargement regressed to normal; no new lesions; normal/IHC-negative bone marrow morphology. All CT evaluable 1L FL and 1L DLBCL patients with at least one dose of atezolizumab were included in efficacy population.

End point type	Secondary

End point timeframe:

Within 6 to 8 weeks after Day 1 of Cycle 6 (up to approximately 6 months)

End point values	Dose-Escalation FL Cohort	Expansion FL Cohort	Safety Run-in and Expansion DLBCL Cohort	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	3	7	16	
Units: Percentage of participants				
number (not applicable)	0.00	57.14	12.50	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Objective Response (CR + PR) at EOI, as Determined by the Investigator on the Basis of PET-CT Scans

End point title	Percentage of Participants with Objective Response (CR + PR) at EOI, as Determined by the Investigator on the Basis of PET-CT Scans

End point description:

Tumor response assessment was performed by investigator according to modified Lugano classification using PET/CT scan. OR: a response of CR or PR. CR: a score of 1 (no uptake above background), 2 (uptake </=mediastinum), or 3 (uptake <mediastinum but </=liver) with or without a residual mass on PET 5-PS, for lymph nodes & extralymphatic sites; no new lesions; no evidence of FDG-avid disease in

bone marrow; and normal/IHC-negative bone marrow morphology. PR with a score 4 (uptake moderately greater than [>] liver) or 5 (uptake markedly >liver and/or new lesions) with reduced uptake compared with baseline and residual mass(es) of any size on PET 5-PS for lymph nodes and extralymphatic sites; no new lesions; and reduced residual uptake in bone marrow compared with baseline. All PET evaluable 1L FL and 1L DLBCL patients with at least one dose of atezolizumab were included in efficacy population

End point type	Secondary

End point timeframe:

Within 6 to 8 weeks after Day 1 of Cycle 6 (up to approximately 6 months)

End point values	Dose-Escalation FL Cohort	Expansion FL Cohort	Safety Run-in and Expansion DLBCL Cohort	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	3	7	16	
Units: Percentage of participants				
number (not applicable)	33.33	57.14	25.00	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Objective Response (CR + PR) at EOI, as Determined by the Investigator on the Basis of CT Scans Alone

End point title	Percentage of Participants with Objective Response (CR + PR) at EOI, as Determined by the Investigator on the Basis of CT Scans Alone

End point description:

Tumor response assessment was performed by investigator according to modified Lugano classification using CT scan. OR: a response of CR or PR. CR: Target nodes/nodal masses regressed to <= 1.5 cm in LDi; no extralymphatic sites of disease; organ enlargement regressed to normal; no new lesions; normal/IHC-negative bone marrow morphology. PR with >= 50 percet decrease in SPD of up to six target measurable nodes and extranodal sites, a 5 mm x 5 mm default value when lesions were too small, 0 x0 mm value when lesions were no longer visible, actual measurements were used for nodes greater than 5 mm x 5 mm for lymph nodes & extralymphatic sites; absent/normal, regression for non-measured lesion; spleen enlargement regression by > 50 percent; no new lesions; reduced residual uptake in bone marrow compared to baseline. All CT evaluable 1L FL and 1L DLBCL patients with at least one dose of atezolizumab were included in efficacy population.

End point type	Secondary

End point timeframe:

Within 6 to 8 weeks after Day 1 of Cycle 6 (up to approximately 6 months)

End point values	Dose-Escalation FL Cohort	Expansion FL Cohort	Safety Run-in and Expansion DLBCL Cohort	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	3	7	16	
Units: Percentage of participants				
number (not applicable)	33.33	57.14	25.00	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Best Response of CR or PR during the Study, as Determined by the Investigator on the Basis of CT Scans Alone

End point title	Percentage of Participants with Best Response of CR or PR during the Study, as Determined by the Investigator on the Basis of CT Scans Alone

End point description:

Tumor response assessment was performed by investigator according to modified Lugano classification using CT scan. OR: a response of CR or PR. CR: Target nodes/nodal masses regressed to <= 1.5 cm in LDi; no extralymphatic sites of disease; organ enlargement regressed to normal; no new lesions; normal/IHC-negative bone marrow morphology. PR with >= 50 percet decrease in SPD of up to six target measurable nodes and extranodal sites, a 5 mm x 5 mm default value when lesions were too small, 0 x0 mm value when lesions were no longer visible, actual measurements were used for nodes greater than 5 mm x 5 mm for lymph nodes & extralymphatic sites; absent/normal, regression for non-measured lesion; spleen enlargement regression by > 50 percent; no new lesions; reduced residual uptake in bone marrow compared to baseline. All CT evaluable 1L FL and 1L DLBCL patients with at least one dose of atezolizumab were included in efficacy population.

End point type	Secondary

End point timeframe:

Baseline up to 35 months

End point values	Dose-Escalation FL Cohort	Expansion FL Cohort	Safety Run-in and Expansion DLBCL Cohort	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	3	7	16	
Units: Percentage of participants				
number (not applicable)				
Complete response	33.3	14.3	12.5	
Partial response	0	42.9	12.5	
Stable disease	33.3	14.3	6.3	
Progressive disease	33.3	14.3	31.3	
Not available	0	14.3	37.5	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Adverse Events and Serious Adverse Events

End point title	Percentage of Participants with Adverse Events and Serious

	Adverse Events

End point description:

An AE was any untoward medical occurrence in a participant administered a pharmaceutical product and which did not necessarily have to have a causal relationship with the treatment. An adverse event was therefore any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a pharmaceutical product, whether or not considered related to the pharmaceutical product. Grading was completed according to the CTCAE, version 4.0 for severity and tumor flare reactions were graded according to NCI CTCAE v3.0.

End point type	Secondary

End point timeframe:

Baseline up to 35 months

End point values	Dose-Escalation FL Cohort	Expansion FL Cohort	Safety Run-in and Expansion DLBCL Cohort	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	3	10	21	
Units: Participants				
number (not applicable)	100.00	100.00	81.00	

Statistical analyses

No statistical analyses for this end point

Secondary: Serum Obinutuzumab Concentration

End point title	Serum Obinutuzumab Concentration[2]

End point description:

pre-dose (0 hr), 30 min after EOI on Day 1 Cycle 1; pre-dose (within 5 hr), 30 min after EOI on Day 1 of Cycles 2, 4, 6; maintenance phase: pre-dose (within 5 hr) on Day 1 of Months 1, 7, 13, 19; anytime during treatment discontinuation visit, 120 days after the last dose, and 1 year after the last dose up to approximately 4 years (1 cycle=21 days; infusion rate: starts with 50 mg/hr and decreases every 30 min to maximum of 400 mg/hr). 99999 represents the upper limit of confidence interval was not estimable due to the low number of subjects within events.

End point type	Secondary

End point timeframe:

Pre-dose (0 hr) up to 35 months

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only arms treated with Obinutuzumab were included in this endpoint

End point values	Dose-Escalation FL Cohort	Expansion FL Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	10		
Units: mcg/mL				
arithmetic mean (standard deviation)				
Induction cycle 1 Day 1 Pre-dose (N=3, 10)	99999 (± 99999)	99999 (± 99999)		

Induction cycle 1 Day 1 Post-dose (N=3, 10)	308 (± 41.6)	295 (± 171)		
Induction cycle 2 Day 1 Pre-dose (N=3, 10)	351 (± 81.3)	403 (± 143)		
Induction cycle 2 Day 1 Post-dose (N=3, 10)	616 (± 115)	672 (± 130)		
Induction cycle 4 Day 1 Pre-dose (N=3, 10)	433 (± 322)	311 (± 177)		
Induction cycle 4 Day 1 Post-dose (N=3, 18)	583 (± 189)	619 (± 160)		
Induction cycle 6 Day 1 Pre-dose (N=3, 9)	288 (± 123)	308 (± 194)		
Induction cycle 6 Day 1 Post-dose (N=3, 8)	514 (± 121)	605 (± 161)		
Maintenance Month 1 Day 1 Pre-dose (N=1, 6)	221 (± 99999)	171 (± 131)		
Maintenance Month 7 Pre-dose (N=2, 6)	90.4 (± 58.8)	83.8 (± 59.6)		
Maintenance Month 13 Pre-dose (N=2, 2)	78.8 (± 42.8)	158 (± 1.41)		
Drug completion or early discontinuation (N=0, 1)	0 (± 0)	37.2 (± 99999)		
PK and Immunogenicity follow up (N=2, 3)	110 (± 120)	15.4 (± 3.20)		

Statistical analyses

No statistical analyses for this end point

Secondary: Serum Rituximab Concentration

End point title	Serum Rituximab Concentration[3]

End point description:

pre-dose (0 hr), 30 min after EOI on Day 1 Cycle 1; pre-dose (within 5 hr) on Day 1 of Cycles 2, 4; pre-dose (within 5 hr), 30 min after EOI on Day 1 of Cycle 6; anytime during treatment discontinuation visit, 120 days after the last dose, and 1 year after the last dose up to approximately 4 years (1 cycle=21 days; infusion rate: starts with 50 mg/hr and increases every 30 min to maximum of 400 mg/hr)

End point type	Secondary

End point timeframe:

Pre-dose (0 hr) up to 35 months

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only arms treated with Rituximab were included in this endpoint

End point values	Safety Run-in and Expansion DLBCL Cohort			
Subject group type	Reporting group			
Number of subjects analysed	21			
Units: mcg/mL				
arithmetic mean (standard deviation)				
Induction Cycle 1 Day 1 Pre-dose (N=9)	30.4 (± 28.8)			
Induction Cycle 1 Day 1 Post-dose (N=19)	197 (± 56.9)			
Induction Cycle 2 Day 1 Pre-dose (N=17)	43.5 (± 28.7)			

Induction Cycle 4 Day 1 Pre-dose (N=10)	84.8 (± 35.7)			
Induction Cycle 6 Day 1 Pre-dose (N=13)	101 (± 45.5)			
Induction Cycle 6 Day 1 Post-dose (N=12)	239 (± 42.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Serum Atezo Concentration

End point title	Serum Atezo Concentration

End point description:

pre-dose (within 5 hr), 30 min after EOI on Day 1 of Cycles 2, 3, 4; pre-dose (within 5 hr) on Day 1 of Cycle 6; maintenance phase: pre-dose (within 5 hr) on Day 1 of Month 1; 30 min after EOI on Day 2 of Month 1; pre-dose (within 5 hr) on Day 1 of Month 4, 7, 13, 19; anytime during treatment discontinuation visit, 120 days after the last dose, and 1-2 years after the last dose up to approximately 4 years (1 cycle=21 days; infusion rate: starts with 60 min and decreases to 30 min). 99999 represents the upper limit of confidence interval was not estimable due to the low number of subjects within events.

End point type	Secondary

End point timeframe:

Pre-dose (0 hr) up to 35 months

End point values	Dose-Escalation FL Cohort	Expansion FL Cohort	Safety Run-in and Expansion DLBCL Cohort	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	3	10	21	
Units: mcg/mL				
arithmetic mean (standard deviation)				
Induction Cycle 2 Day 1 Pre-dose (N=3, 10, 18)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	
Induction Cycle 2 Day 1 Post-dose (N=3, 10, 18)	332 (± 56.7)	365 (± 80.7)	355 (± 78.8)	
Induction Cycle 3 Day 1 Pre-dose (N=3, 9, 14)	86.9 (± 28.8)	78.7 (± 18.4)	79.7 (± 30.6)	
Induction Cycle 4 Day 1 Pre-dose (N=3, 7, 9)	139 (± 33.1)	125 (± 47.3)	139 (± 56.4)	
Induction Cycle 4 Day 1 Post-dose (N=3, 6, 8)	462 (± 82.0)	450 (± 136)	489 (± 131)	
Induction Cycle 6 Day 1 Pre-dose (N=3, 6, 8)	194 (± 67.7)	181 (± 112)	180 (± 90.6)	
Maintenance Month 1 Day 1 Pre-dose (N=2, 4, 0)	100 (± 66.0)	70.7 (± 55.5)	0 (± 0)	
Maintenance Month 1 Day 2 Post-dose (N=3, 4, 0)	577 (± 144)	473 (± 177)	0 (± 0)	
Maintenance Month 4 Pre-dose (N=3, 3, 0)	240 (± 101)	140 (± 141)	0 (± 0)	
Maintenance Month 7 Pre-dose (N=2, 2, 0)	226 (± 134)	221 (± 90.5)	0 (± 0)	

Maintenance Month 13 Pre-dose (N=2, 0, 0)	106 (± 83.0)	0 (± 0)	0 (± 0)	
Drug completion or early discontinuation (N=0,1,2)	0 (± 0)	127 (± 99999)	93.0 (± 14.2)	
Consolidation Month 1 Day 1 Pre-dose (N=0, 0, 4)	0 (± 0)	0 (± 0)	132 (± 43.3)	
Consolidation Month 1 Day 2 Post-dose (N=0, 0, 3)	0 (± 0)	0 (± 0)	503 (± 214)	
PK and Immunogenicity followup 120D (N=2, 3, 2)	61.4 (± 60.3)	16.8 (± 26.8)	19.9 (± 0.778)	
PK and Immunogenicity followup 1 Year (N=0, 2, 0)	0 (± 0)	0 (± 0)	0 (± 0)	

Statistical analyses

No statistical analyses for this end point

Secondary: Serum Pola Concentration

End point title	Serum Pola Concentration

End point description:

pre-dose (0 hr) on Day 1 Cycle 1; pre-dose (within 5 hr) on Day 1 of Cycles 2, 4; maintenance phase: pre-dose (within 5 hr) on Day 1 of Months 1; anytime during treatment discontinuation visit, 120 days after the last dose, and 1 year after the last dose up to approximately 4 years (1 cycle=21 days; infusion rate: starts with 90 min and decreases to 30 min). 99999 represents the upper limit of confidence interval was not estimable due to the low number of subjects within events.

End point type	Secondary

End point timeframe:

Pre-dose (0 hr) up to 35 months

End point values	Dose-Escalation FL Cohort	Expansion FL Cohort	Safety Run-in and Expansion DLBCL Cohort	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	3	10	21	
Units: mcg/mL				
arithmetic mean (standard deviation)				
Pre Day 120 Follow-up (N=0, 1, 1)	0 (± 0)	0.136 (± 99999)	2.91 (± 99999)	
Induction Cycle 1 Day 1 Pre-dose (N=0, 1, 1)	0 (± 0)	0.847 (± 99999)	35.9 (± 99999)	
Induction Cycle 2 Day 1 Pre-dose (N=3, 8, 17)	2.54 (± 0.918)	2.62 (± 1.22)	3.37 (± 3.60)	
Induction Cycle 4 Day 1 Pre-dose (N=3, 9, 12)	4.73 (± 2.10)	4.27 (± 1.63)	4.92 (± 2.65)	
Maintenance Month 1 Day 1 Pre-dose (N=2, 3, 0)	1.30 (± 0.696)	1.63 (± 1.75)	0 (± 0)	
Drug completion or early discontinuation (N=0,0,2)	0 (± 0)	0 (± 0)	0.716 (± 0.200)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Human Anti-Human Antibodies (HAHAs) to Obinutuzumab

End point title	Percentage of Participants with Human Anti-Human Antibodies (HAHAs) to Obinutuzumab[4]

End point description:

Pre-dose (0 hr) on Day 1 of Cycle 1, 6, anytime during treatment discontinuation visit, 120 days after the last dose, and 1 year after the last dose up to approximately 4 years (1 cycle=21 days; infusion rate: starts with 50 mg/hr and increased every 30 min to maximum of 400 mg/hr)

End point type	Secondary

End point timeframe:

Baseline up to 35 months

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only arms treated with Obinutuzumab were included in this endpoint

End point values	Dose-Escalation FL Cohort	Expansion FL Cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	10		
Units: Percentage of participants	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Human Anti-Chimeric Antibodies (HACAs) to Rituximab

End point title	Percentage of Participants with Human Anti-Chimeric Antibodies (HACAs) to Rituximab[5]

End point description:

Pre-dose (0 hr) on Day 1 of Cycle 1, 2, 4, 6, anytime during treatment discontinuation visit, 120 days after the last dose, and 1 year after the last dose up to approximately 4 years (1 cycle=21 days; infusion rate: starts with 50 mg/hr and increased every 30 min to maximum of 400 mg/hr)

End point type	Secondary

End point timeframe:

Baseline to 35 months

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only arms treated with Rituximab were included in this endpoint

End point values	Safety Run-in and Expansion DLBCL Cohort			
Subject group type	Reporting group			
Number of subjects analysed	21			
Units: Percentage of participants				
number (not applicable)				
Baseline, positive (N=18)	5.6			
Baseline, negative (N=18)	94.4			
Induction Cycle 2 Day 1, positive (N=18)	5.6			
Induction Cycle 2 Day 1, negative (N=18)	94.4			
Induction Cycle 4 Day 1 (N=12)	100			
Induction Cycle 6 Day 1 (N=13)	100			
Study drug completion (N=1)	100			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Anti-Therapeutic Antibodies (ATAs) to Atezo

End point title	Percentage of Participants with Anti-Therapeutic Antibodies (ATAs) to Atezo

End point description:

Pre-dose (0 hr) on Day 1 of Cycle 2, 3, 4, 6, Month 1, 4, 7, 13 and 19, anytime during treatment discontinuation visit, 120 days after the last dose, and 1 year after the last dose up to approximately 4 years (1 cycle=21 days; infusion rate: starts with 60 min and decreases to 30 min)

End point type	Secondary

End point timeframe:

Baseline to 35 months

End point values	Dose-Escalation FL Cohort	Expansion FL Cohort	Safety Run-in and Expansion DLBCL Cohort	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	3	10	21	
Units: Percentage of participants				
number (not applicable)				
Induction, Cycle 2 Day 1, positive (N=3, 10, 1)	0	0	5.3	
Induction, Cycle 2 Day 1, negative (N=3, 10, 18)	0	0	94.7	
Induction, Cycle 3 Day 1, positive (N=3, 10, 1)	0	0	7.1	
Induction, Cycle 3 Day 1, negative (N=3, 10, 13)	0	0	92.9	
Induction, Cycle 4 Day 1, negative (N=3, 10, 9)	0	0	100.0	

Induction, Cycle 6 Day 1, negative (N=3, 10, 7)	0	0	100.0	
Consolidation Month 1 Day 1, negative (N=3, 10, 4)	0	0	100.0	
Study drug completion, negative (N=3, 10, 2)	0	0	100.0	
PK Immuno. Follow up (120D), negative (N=3, 10, 2)	0	0	100.0	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with ATAs to Pola

End point title	Percentage of Participants with ATAs to Pola

End point description:

Pre-dose (0 hr) on Day 1 of Cycle 1, 2, 4, anytime during treatment discontinuation visit, 120 days after the last dose, and 1 year after the last dose up to approximately 4 years (1 cycle=21 days; infusion rate: starts with 90 min and decreases to 30 min)

End point type	Secondary

End point timeframe:

Baseline to 35 months

End point values	Dose-Escalation FL Cohort	Expansion FL Cohort	Safety Run-in and Expansion DLBCL Cohort	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	3	10	21	
Units: Percentage of participants	0	0	0	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From randomization up to 35 months

Adverse event reporting additional description:

All adverse events that occurred on or after the first dose of study treatment are summarized by mapped term, appropriate thesaurus levels, and National Cancer Institute Common Terminology Criteria (NCI CTCAE) v4.0 grade. All-Cause Mortality is reported for the ITT population.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.1

Reporting groups

Reporting group title	Dose-Escalation FL Cohort

Reporting group description:

During the induction treatment Cycle 1 (21-day cycles): participants received obinutuzumab on Days 1, 8, and 15 and Pola on Day 1; Cycles 2-6: participants received 1000 mg of obinutuzumab on Day 1, 1200 mg of Atezo on Day 1, and either 1.4 mg/kilogram (kg) or 1.8 mg/kg of Pola on Day 1. The 1.4 mg/kg dose was cleared and escalated to 1.8 mg/kg which was declared the recommended Phase 2 dose (RP2D). This was followed by obinutuzumab on Day 1 of every other month starting with Month 1 for 24 months, during maintenance treatment for FL participants. Due to unexpected toxicity, recruitment was stopped, and atezolizumab discontinued in all treated patients. This combination will not be further developed.

Reporting group title	Safety Run-in and Expansion DLBCL Cohort

Reporting group description:

For DLBCL, during the induction treatment Cycles 1-6 (21-day cycles): participants received a 375 mg/m^2 IV of rituximab on Day 1 and on Day 1 of every other month during consolidation. Participants also received a 1.8 mg/kg IV of Pola on Day 1. Cycles 2-6: participants received 1200 mg of Atezo on Day 1. Due to unexpected toxicity, recruitment was stopped, and atezolizumab discontinued in all treated patients. This combination will not be further developed.

Reporting group title	Expansion FL Cohort

Reporting group description:

During the induction treatment Cycle 1 (21-day cycles): participants received obinutuzumab on Days 1, 8, and 15 and Pola on Day 1; Cycles 2-6: participants received 1000 mg of obinutuzumab on Day 1, 1200 mg of Atezo on Day 1, and 1.8 mg/kg of Pola (RP2D) on Day 1. This was followed by obinutuzumab on Day 1 of every other month starting with Month 1 for 24 months, during maintenance treatment for FL participants. Due to unexpected toxicity, recruitment was stopped, and atezolizumab discontinued in all treated patients. This combination will not be further developed.

Serious adverse events	Dose-Escalation FL Cohort	Safety Run-in and Expansion DLBCL Cohort	Expansion FL Cohort
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 3 (0.00%)	2 / 23 (8.70%)	4 / 10 (40.00%)
number of deaths (all causes)	0	13	2
number of deaths resulting from adverse events			
Investigations			
C-REACTIVE PROTEIN INCREASED			

subjects affected / exposed[1]	0 / 3 (0.00%)	0 / 21 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
GUILLAIN-BARRE SYNDROME			
subjects affected / exposed[2]	0 / 3 (0.00%)	0 / 21 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
LETHARGY			
subjects affected / exposed[3]	0 / 3 (0.00%)	1 / 21 (4.76%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed[4]	0 / 3 (0.00%)	0 / 21 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
FEBRILE NEUTROPENIA			
subjects affected / exposed[5]	0 / 3 (0.00%)	0 / 21 (0.00%)	2 / 10 (20.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
DEATH			
subjects affected / exposed[6]	0 / 3 (0.00%)	0 / 21 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
PYREXIA			
subjects affected / exposed[7]	0 / 3 (0.00%)	0 / 21 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
ABDOMINAL PAIN			

subjects affected / exposed[8]	0 / 3 (0.00%)	1 / 21 (4.76%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
STOMATITIS			
subjects affected / exposed[9]	0 / 3 (0.00%)	0 / 21 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
PLEURAL EFFUSION			
subjects affected / exposed[10]	0 / 3 (0.00%)	1 / 21 (4.76%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
PNEUMONITIS			
subjects affected / exposed[11]	0 / 3 (0.00%)	0 / 21 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
DERMATITIS			
subjects affected / exposed[12]	0 / 3 (0.00%)	0 / 21 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ERYTHEMA			
subjects affected / exposed[13]	0 / 3 (0.00%)	0 / 21 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
BRONCHOPULMONARY ASPERGILLOSIS			
subjects affected / exposed[14]	0 / 3 (0.00%)	0 / 21 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
ERYSIPELAS			

subjects affected / exposed[15]	0 / 3 (0.00%)	0 / 21 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SEPSIS			
subjects affected / exposed[16]	0 / 3 (0.00%)	1 / 21 (4.76%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Notes:

[1] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: In the DLBCL Safety Run in phase 23 subjects enrolled in study. However two patients did not receive any study treatment and therefore were not included in the Safety Evaluable population (n=21).

[2] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: In the DLBCL Safety Run in phase 23 subjects enrolled in study. However two patients did not receive any study treatment and therefore were not included in the Safety Evaluable population (n=21).

[3] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: In the DLBCL Safety Run in phase 23 subjects enrolled in study. However two patients did not receive any study treatment and therefore were not included in the Safety Evaluable population (n=21).

[4] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: In the DLBCL Safety Run in phase 23 subjects enrolled in study. However two patients did not receive any study treatment and therefore were not included in the Safety Evaluable population (n=21).

[5] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: In the DLBCL Safety Run in phase 23 subjects enrolled in study. However two patients did not receive any study treatment and therefore were not included in the Safety Evaluable population (n=21).

[6] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: In the DLBCL Safety Run in phase 23 subjects enrolled in study. However two patients did not receive any study treatment and therefore were not included in the Safety Evaluable population (n=21).

[7] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: In the DLBCL Safety Run in phase 23 subjects enrolled in study. However two patients did not receive any study treatment and therefore were not included in the Safety Evaluable population (n=21).

[8] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: In the DLBCL Safety Run in phase 23 subjects enrolled in study. However two patients did not receive any study treatment and therefore were not included in the Safety Evaluable population (n=21).

[9] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: In the DLBCL Safety Run in phase 23 subjects enrolled in study. However two patients did not receive any study treatment and therefore were not included in the Safety Evaluable population (n=21).

[10] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: In the DLBCL Safety Run in phase 23 subjects enrolled in study. However two patients did not receive any study treatment and therefore were not included in the Safety Evaluable population (n=21).

[11] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: In the DLBCL Safety Run in phase 23 subjects enrolled in study. However two patients did not receive any study treatment and therefore were not included in the Safety Evaluable population (n=21).
[12] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: In the DLBCL Safety Run in phase 23 subjects enrolled in study. However two patients did not receive any study treatment and therefore were not included in the Safety Evaluable population (n=21).
[13] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: In the DLBCL Safety Run in phase 23 subjects enrolled in study. However two patients did not receive any study treatment and therefore were not included in the Safety Evaluable population (n=21).
[14] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: In the DLBCL Safety Run in phase 23 subjects enrolled in study. However two patients did not receive any study treatment and therefore were not included in the Safety Evaluable population (n=21).
[15] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: In the DLBCL Safety Run in phase 23 subjects enrolled in study. However two patients did not receive any study treatment and therefore were not included in the Safety Evaluable population (n=21).
[16] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: In the DLBCL Safety Run in phase 23 subjects enrolled in study. However two patients did not receive any study treatment and therefore were not included in the Safety Evaluable population (n=21).

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

Non-serious adverse events	Dose-Escalation FL Cohort	Safety Run-in and Expansion DLBCL Cohort	Expansion FL Cohort
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 3 (100.00%)	15 / 23 (65.22%)	10 / 10 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
BASAL CELL CARCINOMA			
subjects affected / exposed[17]	1 / 3 (33.33%)	0 / 21 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Vascular disorders			
HYPERTENSION			
subjects affected / exposed[18]	0 / 3 (0.00%)	0 / 21 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
THROMBOSIS			
subjects affected / exposed[19]	0 / 3 (0.00%)	0 / 21 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
CHEST PAIN			
subjects affected / exposed[20]	0 / 3 (0.00%)	0 / 21 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
FACE OEDEMA			

subjects affected / exposed[21]	0 / 3 (0.00%)	0 / 21 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
FATIGUE			
subjects affected / exposed[22]	2 / 3 (66.67%)	1 / 21 (4.76%)	3 / 10 (30.00%)
occurrences (all)	2	1	3
INFLUENZA LIKE ILLNESS			
subjects affected / exposed[23]	1 / 3 (33.33%)	0 / 21 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
INFUSION SITE EXTRAVASATION			
subjects affected / exposed[24]	1 / 3 (33.33%)	0 / 21 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
OEDEMA			
subjects affected / exposed[25]	0 / 3 (0.00%)	0 / 21 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
OEDEMA PERIPHERAL			
subjects affected / exposed[26]	0 / 3 (0.00%)	5 / 21 (23.81%)	3 / 10 (30.00%)
occurrences (all)	0	5	3
PERIPHERAL SWELLING			
subjects affected / exposed[27]	0 / 3 (0.00%)	1 / 21 (4.76%)	1 / 10 (10.00%)
occurrences (all)	0	1	3
PYREXIA			
subjects affected / exposed[28]	0 / 3 (0.00%)	0 / 21 (0.00%)	4 / 10 (40.00%)
occurrences (all)	0	0	6
Respiratory, thoracic and mediastinal disorders			
COUGH			
subjects affected / exposed[29]	0 / 3 (0.00%)	2 / 21 (9.52%)	2 / 10 (20.00%)
occurrences (all)	0	3	3
DYSPNOEA			
subjects affected / exposed[30]	0 / 3 (0.00%)	2 / 21 (9.52%)	0 / 10 (0.00%)
occurrences (all)	0	2	0
DYSPNOEA EXERTIONAL			
subjects affected / exposed[31]	0 / 3 (0.00%)	2 / 21 (9.52%)	0 / 10 (0.00%)
occurrences (all)	0	2	0
HICCUPS			

subjects affected / exposed[32]	0 / 3 (0.00%)	0 / 21 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
LARYNGEAL OEDEMA			
subjects affected / exposed[33]	0 / 3 (0.00%)	0 / 21 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
PULMONARY EMBOLISM			
subjects affected / exposed[34]	0 / 3 (0.00%)	0 / 21 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	2
PULMONARY THROMBOSIS			
subjects affected / exposed[35]	0 / 3 (0.00%)	0 / 21 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Psychiatric disorders			
DEPRESSION			
subjects affected / exposed[36]	1 / 3 (33.33%)	1 / 21 (4.76%)	0 / 10 (0.00%)
occurrences (all)	1	1	0
INSOMNIA			
subjects affected / exposed[37]	1 / 3 (33.33%)	0 / 21 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
ANXIETY			
subjects affected / exposed[38]	0 / 3 (0.00%)	1 / 21 (4.76%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Investigations			
ALANINE AMINOTRANSFERASE INCREASED			
subjects affected / exposed[39]	1 / 3 (33.33%)	0 / 21 (0.00%)	2 / 10 (20.00%)
occurrences (all)	1	0	2
BLOOD CREATININE INCREASED			
subjects affected / exposed[40]	0 / 3 (0.00%)	0 / 21 (0.00%)	2 / 10 (20.00%)
occurrences (all)	0	0	2
BLOOD LACTATE DEHYDROGENASE INCREASED			
subjects affected / exposed[41]	0 / 3 (0.00%)	1 / 21 (4.76%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
C-REACTIVE PROTEIN INCREASED			
subjects affected / exposed[42]	0 / 3 (0.00%)	0 / 21 (0.00%)	2 / 10 (20.00%)
occurrences (all)	0	0	5
GAMMA-GLUTAMYLTRANSFERASE INCREASED			

subjects affected / exposed[43]	0 / 3 (0.00%)	0 / 21 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
LIPASE INCREASED			
subjects affected / exposed[44]	0 / 3 (0.00%)	1 / 21 (4.76%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
NEUTROPHIL COUNT DECREASED			
subjects affected / exposed[45]	0 / 3 (0.00%)	0 / 21 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	2
PROCALCITONIN INCREASED			
subjects affected / exposed[46]	0 / 3 (0.00%)	0 / 21 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
THYROXINE DECREASED			
subjects affected / exposed[47]	0 / 3 (0.00%)	0 / 21 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
TRI-IODOTHYRONINE DECREASED			
subjects affected / exposed[48]	0 / 3 (0.00%)	0 / 21 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
WEIGHT DECREASED			
subjects affected / exposed[49]	0 / 3 (0.00%)	0 / 21 (0.00%)	4 / 10 (40.00%)
occurrences (all)	0	0	4
WHITE BLOOD CELL COUNT DECREASED			
subjects affected / exposed[50]	0 / 3 (0.00%)	0 / 21 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Injury, poisoning and procedural complications			
INFUSION RELATED REACTION			
subjects affected / exposed[51]	1 / 3 (33.33%)	0 / 21 (0.00%)	1 / 10 (10.00%)
occurrences (all)	1	0	1
Cardiac disorders			
SINUS TACHYCARDIA			
subjects affected / exposed[52]	0 / 3 (0.00%)	0 / 21 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Nervous system disorders			
DIZZINESS			
subjects affected / exposed[53]	0 / 3 (0.00%)	2 / 21 (9.52%)	1 / 10 (10.00%)
occurrences (all)	0	2	1
FACIAL PARALYSIS			

subjects affected / exposed[54]	0 / 3 (0.00%)	0 / 21 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
HEADACHE			
subjects affected / exposed[55]	0 / 3 (0.00%)	1 / 21 (4.76%)	1 / 10 (10.00%)
occurrences (all)	0	1	2
HYPOAESTHESIA			
subjects affected / exposed[56]	0 / 3 (0.00%)	1 / 21 (4.76%)	1 / 10 (10.00%)
occurrences (all)	0	1	2
NEUROPATHY PERIPHERAL			
subjects affected / exposed[57]	0 / 3 (0.00%)	0 / 21 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	2
PARAESTHESIA			
subjects affected / exposed[58]	0 / 3 (0.00%)	0 / 21 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	2
POLYNEUROPATHY			
subjects affected / exposed[59]	0 / 3 (0.00%)	0 / 21 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed[60]	0 / 3 (0.00%)	2 / 21 (9.52%)	1 / 10 (10.00%)
occurrences (all)	0	2	1
ANAEMIA FOLATE DEFICIENCY			
subjects affected / exposed[61]	0 / 3 (0.00%)	0 / 21 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
LEUKOPENIA			
subjects affected / exposed[62]	0 / 3 (0.00%)	1 / 21 (4.76%)	2 / 10 (20.00%)
occurrences (all)	0	1	5
NEUTROPENIA			
subjects affected / exposed[63]	1 / 3 (33.33%)	3 / 21 (14.29%)	4 / 10 (40.00%)
occurrences (all)	1	4	7
THROMBOCYTOPENIA			
subjects affected / exposed[64]	0 / 3 (0.00%)	0 / 21 (0.00%)	4 / 10 (40.00%)
occurrences (all)	0	0	5
Eye disorders			
DRY EYE			

subjects affected / exposed[65]	0 / 3 (0.00%)	1 / 21 (4.76%)	2 / 10 (20.00%)
occurrences (all)	0	1	2
GLAUCOMA			
subjects affected / exposed[66]	0 / 3 (0.00%)	0 / 21 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
SCLERITIS			
subjects affected / exposed[67]	0 / 3 (0.00%)	0 / 21 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
CATARACT NUCLEAR			
subjects affected / exposed[68]	0 / 3 (0.00%)	0 / 21 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
VITREOUS DEGENERATION			
subjects affected / exposed[69]	0 / 3 (0.00%)	0 / 21 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
ABDOMINAL PAIN			
subjects affected / exposed[70]	0 / 3 (0.00%)	1 / 21 (4.76%)	1 / 10 (10.00%)
occurrences (all)	0	1	2
CONSTIPATION			
subjects affected / exposed[71]	0 / 3 (0.00%)	0 / 21 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
DIARRHOEA			
subjects affected / exposed[72]	0 / 3 (0.00%)	0 / 21 (0.00%)	3 / 10 (30.00%)
occurrences (all)	0	0	3
DRY MOUTH			
subjects affected / exposed[73]	0 / 3 (0.00%)	1 / 21 (4.76%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
DYSPEPSIA			
subjects affected / exposed[74]	0 / 3 (0.00%)	0 / 21 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
GASTROOESOPHAGEAL REFLUX DISEASE			
subjects affected / exposed[75]	0 / 3 (0.00%)	0 / 21 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
STOMATITIS			

subjects affected / exposed[76]	0 / 3 (0.00%)	0 / 21 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
VOMITING			
subjects affected / exposed[77]	0 / 3 (0.00%)	0 / 21 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Skin and subcutaneous tissue disorders			
NIGHT SWEATS			
subjects affected / exposed[78]	0 / 3 (0.00%)	0 / 21 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
RASH			
subjects affected / exposed[79]	0 / 3 (0.00%)	0 / 21 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	4
Renal and urinary disorders			
ACUTE KIDNEY INJURY			
subjects affected / exposed[80]	0 / 3 (0.00%)	2 / 21 (9.52%)	0 / 10 (0.00%)
occurrences (all)	0	3	0
Endocrine disorders			
AUTOIMMUNE THYROIDITIS			
subjects affected / exposed[81]	0 / 3 (0.00%)	0 / 21 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
HYPOTHYROIDISM			
subjects affected / exposed[82]	0 / 3 (0.00%)	0 / 21 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
subjects affected / exposed[83]	0 / 3 (0.00%)	2 / 21 (9.52%)	0 / 10 (0.00%)
occurrences (all)	0	2	0
BACK PAIN			
subjects affected / exposed[84]	0 / 3 (0.00%)	0 / 21 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
BONE PAIN			
subjects affected / exposed[85]	1 / 3 (33.33%)	0 / 21 (0.00%)	1 / 10 (10.00%)
occurrences (all)	1	0	1
MUSCULOSKELETAL PAIN			
subjects affected / exposed[86]	0 / 3 (0.00%)	0 / 21 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1

SACROILIITIS			
subjects affected / exposed[87]	1 / 3 (33.33%)	0 / 21 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
TENDONITIS			
subjects affected / exposed[88]	0 / 3 (0.00%)	0 / 21 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Infections and infestations			
BACTERAEMIA			
subjects affected / exposed[89]	0 / 3 (0.00%)	0 / 21 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	2
BACTERIAL INFECTION			
subjects affected / exposed[90]	0 / 3 (0.00%)	0 / 21 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
BRONCHOPULMONARY ASPERGILLOSIS			
subjects affected / exposed[91]	0 / 3 (0.00%)	0 / 21 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
CONJUNCTIVITIS			
subjects affected / exposed[92]	0 / 3 (0.00%)	1 / 21 (4.76%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
CYTOMEGALOVIRUS INFECTION			
subjects affected / exposed[93]	0 / 3 (0.00%)	0 / 21 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
LARYNGITIS			
subjects affected / exposed[94]	0 / 3 (0.00%)	0 / 21 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
NASOPHARYNGITIS			
subjects affected / exposed[95]	1 / 3 (33.33%)	0 / 21 (0.00%)	2 / 10 (20.00%)
occurrences (all)	2	0	2
ORAL FUNGAL INFECTION			
subjects affected / exposed[96]	0 / 3 (0.00%)	0 / 21 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	2
PELVIC ABSCESS			
subjects affected / exposed[97]	1 / 3 (33.33%)	0 / 21 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
PNEUMONIA			

subjects affected / exposed[98]	0 / 3 (0.00%)	1 / 21 (4.76%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
RHINITIS			
subjects affected / exposed[99]	1 / 3 (33.33%)	0 / 21 (0.00%)	1 / 10 (10.00%)
occurrences (all)	4	0	1
SINUSITIS			
subjects affected / exposed[100]	2 / 3 (66.67%)	0 / 21 (0.00%)	1 / 10 (10.00%)
occurrences (all)	2	0	1
UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed[101]	0 / 3 (0.00%)	3 / 21 (14.29%)	1 / 10 (10.00%)
occurrences (all)	0	3	2
URINARY TRACT INFECTION			
subjects affected / exposed[102]	0 / 3 (0.00%)	0 / 21 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	2
VIRAL INFECTION			
subjects affected / exposed[103]	0 / 3 (0.00%)	0 / 21 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
VIRAL UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed[104]	0 / 3 (0.00%)	0 / 21 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
ACUTE SINUSITIS			
subjects affected / exposed[105]	0 / 3 (0.00%)	0 / 21 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
CONJUNCTIVITIS VIRAL			
subjects affected / exposed[106]	0 / 3 (0.00%)	0 / 21 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Metabolism and nutrition disorders			
DECREASED APPETITE			
subjects affected / exposed[107]	0 / 3 (0.00%)	1 / 21 (4.76%)	3 / 10 (30.00%)
occurrences (all)	0	1	3
FLUID RETENTION			
subjects affected / exposed[108]	0 / 3 (0.00%)	0 / 21 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
HYPERGLYCAEMIA			

subjects affected / exposed[109]	0 / 3 (0.00%)	0 / 21 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
HYPOALBUMINAEMIA			
subjects affected / exposed[110]	0 / 3 (0.00%)	1 / 21 (4.76%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
HYPOKALAEMIA			
subjects affected / exposed[111]	0 / 3 (0.00%)	1 / 21 (4.76%)	3 / 10 (30.00%)
occurrences (all)	0	1	3

Notes:

[17] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: In the DLBCL Safety Run in phase 23 subjects enrolled in study. However two patients did not receive any study treatment and therefore were not included in the Safety Evaluable population (n=21).

[18] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: In the DLBCL Safety Run in phase 23 subjects enrolled in study. However two patients did not receive any study treatment and therefore were not included in the Safety Evaluable population (n=21).

[19] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: In the DLBCL Safety Run in phase 23 subjects enrolled in study. However two patients did not receive any study treatment and therefore were not included in the Safety Evaluable population (n=21).

[20] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: In the DLBCL Safety Run in phase 23 subjects enrolled in study. However two patients did not receive any study treatment and therefore were not included in the Safety Evaluable population (n=21).

[21] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: In the DLBCL Safety Run in phase 23 subjects enrolled in study. However two patients did not receive any study treatment and therefore were not included in the Safety Evaluable population (n=21).

[22] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: In the DLBCL Safety Run in phase 23 subjects enrolled in study. However two patients did not receive any study treatment and therefore were not included in the Safety Evaluable population (n=21).

[23] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: In the DLBCL Safety Run in phase 23 subjects enrolled in study. However two patients did not receive any study treatment and therefore were not included in the Safety Evaluable population (n=21).

[24] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: In the DLBCL Safety Run in phase 23 subjects enrolled in study. However two patients did not receive any study treatment and therefore were not included in the Safety Evaluable population (n=21).

[25] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: In the DLBCL Safety Run in phase 23 subjects enrolled in study. However two patients did not receive any study treatment and therefore were not included in the Safety Evaluable population (n=21).

[26] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: In the DLBCL Safety Run in phase 23 subjects enrolled in study. However two patients did not receive any study treatment and therefore were not included in the Safety Evaluable population (n=21).

[27] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: In the DLBCL Safety Run in phase 23 subjects enrolled in study. However two patients did not receive any study treatment and therefore were not included in the Safety Evaluable population (n=21).
[28] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: In the DLBCL Safety Run in phase 23 subjects enrolled in study. However two patients did not receive any study treatment and therefore were not included in the Safety Evaluable population (n=21).
[29] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: In the DLBCL Safety Run in phase 23 subjects enrolled in study. However two patients did not receive any study treatment and therefore were not included in the Safety Evaluable population (n=21).
[30] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: In the DLBCL Safety Run in phase 23 subjects enrolled in study. However two patients did not receive any study treatment and therefore were not included in the Safety Evaluable population (n=21).
[31] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: In the DLBCL Safety Run in phase 23 subjects enrolled in study. However two patients did not receive any study treatment and therefore were not included in the Safety Evaluable population (n=21).
[32] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: In the DLBCL Safety Run in phase 23 subjects enrolled in study. However two patients did not receive any study treatment and therefore were not included in the Safety Evaluable population (n=21).
[33] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: In the DLBCL Safety Run in phase 23 subjects enrolled in study. However two patients did not receive any study treatment and therefore were not included in the Safety Evaluable population (n=21).
[34] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: In the DLBCL Safety Run in phase 23 subjects enrolled in study. However two patients did not receive any study treatment and therefore were not included in the Safety Evaluable population (n=21).
[35] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: In the DLBCL Safety Run in phase 23 subjects enrolled in study. However two patients did not receive any study treatment and therefore were not included in the Safety Evaluable population (n=21).
[36] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: In the DLBCL Safety Run in phase 23 subjects enrolled in study. However two patients did not receive any study treatment and therefore were not included in the Safety Evaluable population (n=21).
[37] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: In the DLBCL Safety Run in phase 23 subjects enrolled in study. However two patients did not receive any study treatment and therefore were not included in the Safety Evaluable population (n=21).
[38] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: In the DLBCL Safety Run in phase 23 subjects enrolled in study. However two patients did not receive any study treatment and therefore were not included in the Safety Evaluable population (n=21).
[39] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
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[40] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: In the DLBCL Safety Run in phase 23 subjects enrolled in study. However two patients did

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[41] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
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[42] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: In the DLBCL Safety Run in phase 23 subjects enrolled in study. However two patients did not receive any study treatment and therefore were not included in the Safety Evaluable population (n=21).
[43] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: In the DLBCL Safety Run in phase 23 subjects enrolled in study. However two patients did not receive any study treatment and therefore were not included in the Safety Evaluable population (n=21).
[44] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: In the DLBCL Safety Run in phase 23 subjects enrolled in study. However two patients did not receive any study treatment and therefore were not included in the Safety Evaluable population (n=21).
[45] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: In the DLBCL Safety Run in phase 23 subjects enrolled in study. However two patients did not receive any study treatment and therefore were not included in the Safety Evaluable population (n=21).
[46] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: In the DLBCL Safety Run in phase 23 subjects enrolled in study. However two patients did not receive any study treatment and therefore were not included in the Safety Evaluable population (n=21).
[47] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
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[48] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: In the DLBCL Safety Run in phase 23 subjects enrolled in study. However two patients did not receive any study treatment and therefore were not included in the Safety Evaluable population (n=21).
[49] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: In the DLBCL Safety Run in phase 23 subjects enrolled in study. However two patients did not receive any study treatment and therefore were not included in the Safety Evaluable population (n=21).
[50] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
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[51] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: In the DLBCL Safety Run in phase 23 subjects enrolled in study. However two patients did not receive any study treatment and therefore were not included in the Safety Evaluable population (n=21).
[52] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
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[53] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
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[56] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
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[57] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
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[59] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
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[60] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
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[61] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: In the DLBCL Safety Run in phase 23 subjects enrolled in study. However two patients did not receive any study treatment and therefore were not included in the Safety Evaluable population (n=21).
[62] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: In the DLBCL Safety Run in phase 23 subjects enrolled in study. However two patients did not receive any study treatment and therefore were not included in the Safety Evaluable population (n=21).
[63] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
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[64] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
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Justification: In the DLBCL Safety Run in phase 23 subjects enrolled in study. However two patients did not receive any study treatment and therefore were not included in the Safety Evaluable population (n=21).
[67] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: In the DLBCL Safety Run in phase 23 subjects enrolled in study. However two patients did

not receive any study treatment and therefore were not included in the Safety Evaluable population (n=21).
[68] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: In the DLBCL Safety Run in phase 23 subjects enrolled in study. However two patients did not receive any study treatment and therefore were not included in the Safety Evaluable population (n=21).
[69] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: In the DLBCL Safety Run in phase 23 subjects enrolled in study. However two patients did not receive any study treatment and therefore were not included in the Safety Evaluable population (n=21).
[70] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: In the DLBCL Safety Run in phase 23 subjects enrolled in study. However two patients did not receive any study treatment and therefore were not included in the Safety Evaluable population (n=21).
[71] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: In the DLBCL Safety Run in phase 23 subjects enrolled in study. However two patients did not receive any study treatment and therefore were not included in the Safety Evaluable population (n=21).
[72] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
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More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 January 2016	Version 2: The protocol has been revised to update the DLT window and to clarify inclusion/exclusion and stopping criteria. Additional minor changes have been made to improve clarity and consistency.
28 June 2016	Version 3: The inclusion criterion on contraception requirements for women of childbearing potential has been revised to include the duration of contraception for atezolizumab and polatuzumab vedotin. Enrollment rules into the dose escalation phase have been updated, for patients' safety considerations. A sequential enrollment instead of a parallel enrollment will be used for each of the two dosing groups,
17 November 2016	Version 4: "Immune-mediated" was revised to "immune-related" when referring to adverse events. Cut-off date for Atezolizumab was changed to 15 December 2016. The title has been revised. Study treatment has been modified to include Rituximab (RO0452294) in combination with atezolizumab plus polatuzumab vedotin in patients with relapsed or refractory diffuse large B-cell lymphoma.
04 May 2017	Version 5: The protocol has been modified to prohibit use of the term "sudden death" on the Adverse Event eCRF, unless it is combined with the presumed cause of death. Language has been added to clarify that the Sponsor will review all protocol deviations, and clarification has been added that prospective requests to deviate from the protocol are not allowed.
21 December 2017	Version 6: Clinical Data) has been updated with the most recent efficacy and safety results from Study GO29383. Aligned the protocol with the current atezolizumab Investigator's Brochure, Version 10. A few exclusion criteria updated.
01 May 2018	Version 7: The study design and treatment schedule has been revised to reflect discontinuation of atezolizumab in patients still receiving study treatment. In addition, the post-induction (rituximab + atezolizumab consolidation) treatment phase has been removed from the treatment schedule (rituximab + atezolizumab + polatuzumab vedotin [R+Atezo+Pola] treatment group) of patients with RR DLBCL.
07 November 2018	Version 8: Lists of risks for atezolizumab-associated adverse events were revised to include nephritis. Regular Internal Monitoring Committee assessments stopped taking place as no new safety signals identified. Language was changed allowing patients still under treatment to enter the extension study. Medical Moniter information was updated. Survival follow-up period for assessment of new anti-lymphoma treatment re-added. PK sampling one year after last dose for polatuzumab vedotin was removed.

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.

A safety signal was observed during the study in two patients in the R/R FL cohort. As a result, enrollment was permanently discontinued and atezolizumab was discontinued for all patients still receiving study treatment.

Notes: