Clinical trial results:
Ofatumumab versus Rituximab Salvage Chemoimmunotherapy followed by ASCT in Relapsed or Refractory DLBCL

Summary

EudraCT number	2009-009256-20
Trial protocol	NL BE SE IE GB ES CZ FI DK HU PL DE AT EE GR
Global end of trial date	21 November 2014

Results information

Result version number	v1 (current)
This version publication date	27 April 2016
First version publication date	24 July 2015

Trial information

Trial identification

Sponsor protocol code	OMB110928

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	GlaxoSmithKline
Sponsor organisation address	980 Great West Road, Brentford, Middlesex, United Kingdom,
Public contact	GSK Response Center, GlaxoSmithKline, 1 866-435-7343,
Scientific contact	GSK Response Center, GlaxoSmithKline, 1 866-435-7343,

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	17 April 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	21 November 2014
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To evaluate the progression-free survival (PFS) in subjects receiving ofatumumab in addition to salvage chemotherapy (O-chemo) compared to subjects receiving rituximab in addition to salvage chemotherapy (R-chemo).

Protection of trial subjects:

Not applicable

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	25 March 2010
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	Netherlands: 42
Country: Number of subjects enrolled	Norway: 5
Country: Number of subjects enrolled	Poland: 21
Country: Number of subjects enrolled	Spain: 17
Country: Number of subjects enrolled	Sweden: 11
Country: Number of subjects enrolled	United Kingdom: 94
Country: Number of subjects enrolled	Austria: 7
Country: Number of subjects enrolled	Belgium: 11
Country: Number of subjects enrolled	Czech Republic: 7
Country: Number of subjects enrolled	Denmark: 19
Country: Number of subjects enrolled	Estonia: 3
Country: Number of subjects enrolled	Finland: 8
Country: Number of subjects enrolled	Germany: 6
Country: Number of subjects enrolled	Greece: 4
Country: Number of subjects enrolled	Hungary: 15
Country: Number of subjects enrolled	Ireland: 6
Country: Number of subjects enrolled	Argentina: 2
Country: Number of subjects enrolled	China: 38
Country: Number of subjects enrolled	Israel: 5
Country: Number of subjects enrolled	Japan: 41
Country: Number of subjects enrolled	Russian Federation: 7

Country: Number of subjects enrolled	Korea, Republic of: 18
Country: Number of subjects enrolled	Thailand: 5
Country: Number of subjects enrolled	United States: 55
Worldwide total number of subjects	447
EEA total number of subjects	276

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)	370
From 65 to 84 years	77
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants who were refractory to, or had relapsed following, first-line treatment with rituximab in combination with an anthracycline- or anthracenedione-containing chemotherapy regimen, and who were eligible for autologous stem cell transplant (ASCT), were eligible for enrollment.

Pre-assignment

Screening details:

Eligible participants were randomized to receive either rituximab or ofatumumab in addition to salvage chemotherapy.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Rituximab + Chemotherapy

Arm description:

Participants received 3 cycles (21 days per cycle) of rituximab combined with salvage chemotherapy (SC): either the DHAP regimen (3 cycles of dexamethasone, cytarabine, cisplatin [DHAP]) or the DVD regimen (DHAP-VIM [etoposide, ifosfamide, mesna, methotrexate]-DHAP). Rituximab (375 milligrams per meters squared [mg/m^2]) was infused intravenously (IV) on Day (D) 1 (or up to 3 days prior to D1) and D8 (+/-2 days) of Cycle 1 of the SC, and then on D1 only of Cycles 2 and 3. The DHAP regimen (SC) contained: dexamethasone (40 mg/day) administered orally or IV on Days 1, 2, 3, or 4 of each cycle; cisplatin (100 mg/m^2/day) as an IV continuous infusion on D1 of each cycle; and cytarabine 2 grams (g)/m^2 over 3 hours every 12 hours (2 doses) for each infusion on D2 of each cycle. VIM: etoposide (90 mg/m^2 IV on Days 1, 3, and 5), ifosfamide (1200 mg/m^2 IV on Days 1, 2, 3, 4, and 5), mesna (10 or 20 mg/kilogram [kg] IV on Days 1, 2, 3, 4, and 5), methotrexate (30 mg/m^2 IV on Days 1 and 5).

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

Dosage and administration details:

375mg/m2 on Day 1 and Day 8 of cycle 1 of the chemotherapy, and then on Day 1 of cycles 2 and 3 of a 21 day cycle.

Arm title	Ofatumumab + Chemotherapy

Arm description:

Participants received 3 cycles (21 days per cycle) of ofatumumab combined with SC: either the DHAP regimen (three cycles of DHAP) or the DVD regimen (DHAP-VIM-DHAP). Ofatumumab (1000 mg/1000 milliliter [mL]) was infused IV on Day 1 (or up to 3 days prior to Day 1) and Day 8 (+/-2 days) of Cycle 1 of the SC, and then on Day 1 only of Cycles 2 and 3. The DHAP regimen (SC) contained: dexamethasone (40 mg/day) administered orally or IV on Days 1, 2, 3, or 4 of each cycle; cisplatin (100 mg/[m^2]/day) as an IV continuous infusion on Day 1 of each cycle; and cytarabine 2 g/m^2 over 3 hours every 12 hours (2 doses) for each infusion on Day 2 of each cycle. VIM: etoposide (90 mg/m^2 IV on Days 1, 3, and 5), ifosfamide (1200 mg/m^2 IV on Days 1, 2, 3, 4, and 5), mesna (10 or 20 mg/kg IV on Days 1, 2, 3, 4, and 5), methotrexate (30 mg/m^2 IV on Days 1 and 5).

Arm type	Experimental

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

Dosage and administration details:

1000mg on Day 1 and Day 8 of cycle 1 of the chemotherapy cycle, and then on Day 1 of cycles 2 and 3 of a 21 day cycle.

Number of subjects in period 1[1]	Rituximab + Chemotherapy	Ofatumumab + Chemotherapy
Started	223	222
Completed	131	122
Not completed	92	100
Consent withdrawn by subject	12	12
'Study Closed/terminated '	78	83
Lost to follow-up	2	5

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: A total of 447 participants were randomized and 445 participants entered the treatment period.

Baseline characteristics

Reporting groups	
Reporting group title	Rituximab + Chemotherapy

Reporting group description:

Participants received 3 cycles (21 days per cycle) of rituximab combined with salvage chemotherapy (SC): either the DHAP regimen (3 cycles of dexamethasone, cytarabine, cisplatin [DHAP]) or the DVD regimen (DHAP-VIM [etoposide, ifosfamide, mesna, methotrexate]-DHAP). Rituximab (375 milligrams per meters squared [mg/m^2]) was infused intravenously (IV) on Day (D) 1 (or up to 3 days prior to D1) and D8 (+/-2 days) of Cycle 1 of the SC, and then on D1 only of Cycles 2 and 3. The DHAP regimen (SC) contained: dexamethasone (40 mg/day) administered orally or IV on Days 1, 2, 3, or 4 of each cycle; cisplatin (100 mg/m^2/day) as an IV continuous infusion on D1 of each cycle; and cytarabine 2 grams (g)/m^2 over 3 hours every 12 hours (2 doses) for each infusion on D2 of each cycle. VIM: etoposide (90 mg/m^2 IV on Days 1, 3, and 5), ifosfamide (1200 mg/m^2 IV on Days 1, 2, 3, 4, and 5), mesna (10 or 20 mg/kilogram [kg] IV on Days 1, 2, 3, 4, and 5), methotrexate (30 mg/m^2 IV on Days 1 and 5).

Reporting group title	Ofatumumab + Chemotherapy

Reporting group description:

Participants received 3 cycles (21 days per cycle) of ofatumumab combined with SC: either the DHAP regimen (three cycles of DHAP) or the DVD regimen (DHAP-VIM-DHAP). Ofatumumab (1000 mg/1000 milliliter [mL]) was infused IV on Day 1 (or up to 3 days prior to Day 1) and Day 8 (+/-2 days) of Cycle 1 of the SC, and then on Day 1 only of Cycles 2 and 3. The DHAP regimen (SC) contained: dexamethasone (40 mg/day) administered orally or IV on Days 1, 2, 3, or 4 of each cycle; cisplatin (100 mg/[m^2]/day) as an IV continuous infusion on Day 1 of each cycle; and cytarabine 2 g/m^2 over 3 hours every 12 hours (2 doses) for each infusion on Day 2 of each cycle. VIM: etoposide (90 mg/m^2 IV on Days 1, 3, and 5), ifosfamide (1200 mg/m^2 IV on Days 1, 2, 3, 4, and 5), mesna (10 or 20 mg/kg IV on Days 1, 2, 3, 4, and 5), methotrexate (30 mg/m^2 IV on Days 1 and 5).

Reporting group values	Rituximab + Chemotherapy	Ofatumumab + Chemotherapy	Total
Number of subjects	223	222	445
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	53.4	55.2	
standard deviation	± 12.22	± 10.8	-
Gender categorical Units: Subjects			
Female	88	85	173
Male	135	137	272
Race Units: Subjects			
African American/African Heritage	4	4	8
American Indian or Alaska Native	0	1	1
Asian - Central/South Asian Heritage	3	4	7
Asian - East Asian Heritage	24	31	55
Asian - Japanese Heritage	19	22	41
Asian - South East Asian Heritage	4	4	8
Asian - Mixed Race	0	1	1
White - Arabic/North African Heritage	1	1	2

White - White/Caucasian/European Heritage	168	151	319
Missing	0	3	3
Number of participants with the indicated SaaIPI scores			
The secondary age adjusted international prognostic index (SaaIPI) is assessed according to the absence or presence of 3 risk factors (RFs) at the start of Screening: Eastern Cooperative Oncology Group performance status greater than 1, lactate dehydrogenase level greater than the upper level of normal, and Ann Arbor stage II or IV disease. The presence of 0, 1, or more than 1 RFs corresponds to a SaaIPI score reflecting low, intermediate, and high risk of disease progression.			
Units: Subjects			
0 or 1	136	133	269
2 or 3	87	89	176
Number of participants in the indicated categories per best response to first-line treatment			
Late relapsers are those participants with a complete response (CR: complete disappearance of all detectable clinical evidence of disease/disease-related symptoms) following first line treatment which lasts >12 months from diagnosis. Early relapsers/refractory are those participants with a CR <= 12 months, PR (>=50% decrease from Baseline in the sum of the product of the diameters of target lesions), SD (failure to attain CR or PR; no fulfillment of PD), or PD (disease that has grown or spread) after first-line treatment.			
Units: Subjects			
Late relapsers	66	63	129
Early relapsers/Refractory	157	159	316

End points

End points reporting groups

Reporting group title	Rituximab + Chemotherapy

Reporting group description:

Participants received 3 cycles (21 days per cycle) of rituximab combined with salvage chemotherapy (SC): either the DHAP regimen (3 cycles of dexamethasone, cytarabine, cisplatin [DHAP]) or the DVD regimen (DHAP-VIM [etoposide, ifosfamide, mesna, methotrexate]-DHAP). Rituximab (375 milligrams per meters squared [mg/m^2]) was infused intravenously (IV) on Day (D) 1 (or up to 3 days prior to D1) and D8 (+/-2 days) of Cycle 1 of the SC, and then on D1 only of Cycles 2 and 3. The DHAP regimen (SC) contained: dexamethasone (40 mg/day) administered orally or IV on Days 1, 2, 3, or 4 of each cycle; cisplatin (100 mg/m^2/day) as an IV continuous infusion on D1 of each cycle; and cytarabine 2 grams (g)/m^2 over 3 hours every 12 hours (2 doses) for each infusion on D2 of each cycle. VIM: etoposide (90 mg/m^2 IV on Days 1, 3, and 5), ifosfamide (1200 mg/m^2 IV on Days 1, 2, 3, 4, and 5), mesna (10 or 20 mg/kilogram [kg] IV on Days 1, 2, 3, 4, and 5), methotrexate (30 mg/m^2 IV on Days 1 and 5).

Reporting group title	Ofatumumab + Chemotherapy

Reporting group description:

Participants received 3 cycles (21 days per cycle) of ofatumumab combined with SC: either the DHAP regimen (three cycles of DHAP) or the DVD regimen (DHAP-VIM-DHAP). Ofatumumab (1000 mg/1000 milliliter [mL]) was infused IV on Day 1 (or up to 3 days prior to Day 1) and Day 8 (+/-2 days) of Cycle 1 of the SC, and then on Day 1 only of Cycles 2 and 3. The DHAP regimen (SC) contained: dexamethasone (40 mg/day) administered orally or IV on Days 1, 2, 3, or 4 of each cycle; cisplatin (100 mg/[m^2]/day) as an IV continuous infusion on Day 1 of each cycle; and cytarabine 2 g/m^2 over 3 hours every 12 hours (2 doses) for each infusion on Day 2 of each cycle. VIM: etoposide (90 mg/m^2 IV on Days 1, 3, and 5), ifosfamide (1200 mg/m^2 IV on Days 1, 2, 3, 4, and 5), mesna (10 or 20 mg/kg IV on Days 1, 2, 3, 4, and 5), methotrexate (30 mg/m^2 IV on Days 1 and 5).

Primary: Progression-free survival as assessed by independent reviewers

End point title	Progression-free survival as assessed by independent reviewers

End point description:

Progression-free survival is defined as the interval of time from the randomization date until the date of stable disease (SD; failure to attain the criteria needed for a CR or PR and no fulfillment of the criteria for progressive disease [PD]) after two cycles of salvage chemotherapy, progression, or death, whichever occurs first. Disease progression was based on the assessments of independent reviewers for the disease under study. Disease progression was based on imaging data via the Revised Response Criteria for Malignant Lymphoma (RRCML). Intent-to-Treat (ITT) Population: all participants who were randomized and commenced study therapy (at least one dose of a study drug).

End point type	Primary

End point timeframe:

From randomization until the date of stable disease after two cycles of salvage chemotherapy, progression, or death (assessed for up to 5 years)

End point values	Rituximab + Chemotherapy	Ofatumumab + Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	223[1]	222[2]		
Units: Months				
median (confidence interval 95%)	2.14 (1.64 to 4.37)	1.81 (1.54 to 2.53)		

Notes:

[1] - ITT Population

[2] - ITT Population

Statistical analyses

Statistical analysis title	Analysis 1
Comparison groups	Rituximab + Chemotherapy v Ofatumumab + Chemotherapy
Number of subjects included in analysis	445
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.333 [4]
Method	Stratified Log-rank test
Parameter estimate	Hazard ratio (HR)
Point estimate	1.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.89
upper limit	1.42

Notes:

[3] - The Pike estimator was the statistical method used to estimate the hazard ratio.

[4] - p-value from stratified log-rank test are adjusted for stratification factors.

Secondary: Number of participants with overall response (OR) and complete response (CR) after salvage chemoimmunotherapy

End point title	Number of participants with overall response (OR) and complete response (CR) after salvage chemoimmunotherapy

End point description:

OR is defined as the number of participants achieving either a complete response (CR) or a partial response (PR). CR is defined as the complete disappearance of all detectable clinical evidence of disease and disease-related symptoms. PR is defined as at least a 50% decrease from Baseline in the sum of the product of the diameters of target lesions. RRCML was used to assess CR and PR.

End point type	Secondary

End point timeframe:

At completion of up to 3 cycles of salvage chemoimmunotherapy (assessed up to 9 weeks)

End point values	Rituximab + Chemotherapy	Ofatumumab + Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	223[5]	222[6]		
Units: Participants				
Independent reviewer-assessed OR	94	84		
Independent reviewer-assessed CR	48	34		

Notes:

[5] - ITT Population

[6] - ITT Population

Statistical analyses

Statistical analysis title	Analysis 1
Comparison groups	Rituximab + Chemotherapy v Ofatumumab + Chemotherapy
Number of subjects included in analysis	445
Analysis specification	Pre-specified
Analysis type	superiority[7]
P-value	= 0.4053 [8]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	0.84
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.56
upper limit	1.24

Notes:

[7] - For Category title- Independent reviewer-assessed OR

[8] - p-value for the test of Odds Ratio being 1.

Statistical analysis title	Analysis 2
Comparison groups	Rituximab + Chemotherapy v Ofatumumab + Chemotherapy
Number of subjects included in analysis	445
Analysis specification	Pre-specified
Analysis type	superiority[9]
P-value	= 0.1167 [10]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	0.66
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.39
upper limit	1.1

Notes:

[9] - For Category title- Independent reviewer-assessed CR

[10] - p-value for the test of Odds Ratio being 1.

Secondary: Number of participants with overall response (OR) and complete response (CR) three months after autologous stem cell transplant

End point title	Number of participants with overall response (OR) and complete response (CR) three months after autologous stem cell transplant

End point description:

OR is defined as the number of participants achieving either a complete response (CR) or a partial response (PR). CR is defined as the complete disappearance of all detectable clinical evidence of disease and disease-related symptoms. PR is defined as at least a 50% decrease from Baseline in the sum of the product of the diameters of target lesions. RRCML was used to assess CR and PR.

End point type	Secondary

End point timeframe:

At 3 months after completion of autologous stem cell transplantation (ASCT) (assessed up to 6 months)

End point values	Rituximab + Chemotherapy	Ofatumumab + Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	83[11]	74[12]		
Units: Participants				
Independent reviewer-assessed OR	57	53		
Independent reviewer-assessed CR	44	43		

Notes:

[11] - ITT Population. Only participants completing HDT/ASCT are included.

[12] - ITT Population. Only participants completing HDT/ASCT are included.

Statistical analyses

Statistical analysis title	Analysis 1
Comparison groups	Rituximab + Chemotherapy v Ofatumumab + Chemotherapy
Number of subjects included in analysis	157
Analysis specification	Pre-specified
Analysis type	superiority[13]
P-value	= 0.8209 [14]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	1.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.55
upper limit	2.43

Notes:

[13] - For Category title- Independent reviewer-assessed OR

[14] - p-value for the test of Odds Ratio being 1.

Statistical analysis title	Analysis 2
Comparison groups	Rituximab + Chemotherapy v Ofatumumab + Chemotherapy
Number of subjects included in analysis	157
Analysis specification	Pre-specified
Analysis type	superiority[15]
P-value	= 0.6313 [16]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	1.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.62
upper limit	2.43

Notes:

[15] - For Category title- Independent reviewer-assessed CR

[16] - p-value for the test of Odds Ratio being 1.

Secondary: Event-free survival

End point title	Event-free survival

End point description:

Event-free survival is defined as the time from randomization to progressive disease (PD; disease whose course is growth, or spread of the disease), stable disease (SD; failure to attain the criteria needed for a CR or PR and no fulfillment of the criteria for PD) after completion of 2 cycles of therapy, commencement of a new treatment for diffuse large B cell lymphoma (DLBCL) (e.g., radiotherapy), or death from any cause, whichever occurs first. Disease progression was based on the assessments of independent reviewers for the disease under study. Disease progression was based on imaging data via the Revised Response Criteria for Malignant Lymphoma (RRCML).

End point type	Secondary

End point timeframe:

From randomization to progressive disease, stable disease after completion of 2 cycles of therapy, commencement of a new treatment for DLBCL, or death due to any cause (assessed for up to 5 years)

End point values	Rituximab + Chemotherapy	Ofatumumab + Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	223[17]	222[18]		
Units: Months				
median (confidence interval 95%)	1.84 (1.61 to 2.5)	1.74 (1.54 to 2.23)		

Notes:

[17] - ITT Population

[18] - ITT Population

Statistical analyses

Statistical analysis title	Analysis 1
Comparison groups	Rituximab + Chemotherapy v Ofatumumab + Chemotherapy
Number of subjects included in analysis	445
Analysis specification	Pre-specified
Analysis type	superiority[19]
P-value	= 0.346 [20]
Method	Stratified log-rank test
Parameter estimate	Hazard ratio (HR)
Point estimate	1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.9
upper limit	1.36

Notes:

[19] - Confidence Interval estimated using the Brookmeyer-Crowley method. HR are estimated using the Pike estimator. A hazard ratio <1 indicates a lower probability of recovery with Ofatumumab compared to Rituximab. HR was adjusted for stratification factors.

[20] - p-value from stratified log-rank test are adjusted for stratification factors.

Secondary: Overall survival (OS)

End point title	Overall survival (OS)

End point description:

OS is defined as the time from randomization to death due to any cause. Participants who were still alive by the end of the study were censored.

End point type	Secondary

End point timeframe:

From randomization to death due to any cause (assessed for up to 5 years)

End point values	Rituximab + Chemotherapy	Ofatumumab + Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	223[21]	222[22]		
Units: Months				
median (confidence interval 95%)	13.17 (10.02 to 14.98)	13.86 (10.91 to 22.41)		

Notes:

[21] - ITT Population

[22] - ITT Population

Statistical analyses

Statistical analysis title	Analysis 1
Comparison groups	Rituximab + Chemotherapy v Ofatumumab + Chemotherapy
Number of subjects included in analysis	445
Analysis specification	Pre-specified
Analysis type	superiority[23]
P-value	= 0.377 [24]
Method	Stratified log-rank test
Parameter estimate	Hazard ratio (HR)
Point estimate	0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.7
upper limit	1.15

Notes:

[23] - Confidence Interval estimated using the Brookmeyer-Crowley method. HR are estimated using the Pike estimator. A hazard ratio <1 indicates a lower probability of recovery with Ofatumumab compared to Rituximab. HR was adjusted for stratification factors.

[24] - p-value from stratified log-rank test are adjusted for stratification factors.

Secondary: Number of participants with the ability to mobilize at least 2 million cluster of differentiation (CD)34+ cells per kilogram from peripheral blood

End point title	Number of participants with the ability to mobilize at least 2 million cluster of differentiation (CD)34+ cells per kilogram from peripheral blood

End point description:

Stem cell mobilization is the process of stimulating the hematopoietic stem cells (CD34+) to move out of the bone marrow and into the bloodstream, where they can be collected via a process called apheresis. Successful mobilization is defined as the collection of >2*10^6 CD34+ cells/kg. Only those participants, who commenced harvest, following the administration of rituximab or ofatumumab in combination with DHAP combination chemotherapy, were assessed. The number of participants with adequate harvest of CD34+ stem cells (at least 2*10^6 CD34+ cells/kg) after dosing of salvage therapy in Cycle 2 and Cycle 3 was analyzed.

End point type	Secondary

End point timeframe:

During Cycles 2 and/or 3 (Weeks 4-9)

End point values	Rituximab + Chemotherapy	Ofatumumab + Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	134[25]	125[26]		
Units: Participants	121	120		

Notes:

[25] - ITT Population. Only participants commencing leukapheresis are included.

[26] - ITT Population. Only participants commencing leukapheresis are included.

Statistical analyses

Statistical analysis title	Analysis 1
Comparison groups	Rituximab + Chemotherapy v Ofatumumab + Chemotherapy
Number of subjects included in analysis	259
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1161 [27]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	2.57
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.83
upper limit	9.5

Notes:

[27] - p-value for the test of Odds Ratio being 1.

Secondary: Number of participants completing autologous stem cell transplant (ASCT)

End point title	Number of participants completing autologous stem cell transplant (ASCT)
End point description:	
The number of participants who completed ASCT is reported.	
End point type	Secondary
End point timeframe:	
Approximately 4 to 6 weeks following Cycle 3 (assessed up to 3 months)	

End point values	Rituximab + Chemotherapy	Ofatumumab + Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	223[28]	222[29]		
Units: Participants	83	74		

Notes:

[28] - ITT Population

[29] - ITT Population

Statistical analyses

Statistical analysis title	Analysis 1
Comparison groups	Rituximab + Chemotherapy v Ofatumumab + Chemotherapy
Number of subjects included in analysis	445
Analysis specification	Pre-specified
Analysis type	superiority[30]
P-value	= 0.4481 [31]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	0.84
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.56
upper limit	1.27

Notes:

[30] - Statistics are presented for Completion rate

[31] - p-value for the test of Odds Ratio being 1.

Secondary: Change from Baseline in Functional Assessment of Cancer Therapy-General (FACT-G) during treatment

End point title	Change from Baseline in Functional Assessment of Cancer Therapy-General (FACT-G) during treatment

End point description:

The FACT-G was developed by the Functional Assessment of Chronic Illness Therapy (FACIT) group for use in adults in a wide range of oncology clinical trial populations. The 27 items of the FACT-G are scored in the following domains: Physical Well-being (7 items), Social/Family Wellbeing (7 items), Emotional Well-being (6 items), and Functional Well-being (7 items). Participants responded to the items on a five-point Likert scale ranging from 0, "Not at all" to 4, "Very much." The total score ranges from 0 to 108; higher scores indicate a better patient-reported outcome/quality of life. Participants were asked to think back over the past week when responding to the items.

End point type	Secondary

End point timeframe:

Baseline and the end of the treatment period (until approximately 4 to 6 weeks following Cycle 3 [assessed up to 3 months])

End point values	Rituximab + Chemotherapy	Ofatumumab + Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	172[32]	175[33]		
Units: scores on a scale				
arithmetic mean (standard error)	-2.561 (± 0.7671)	-2.591 (± 0.7696)		

Notes:

[32] - ITT Population. Only those participants who provided data were assessed.

[33] - ITT Population. Only those participants who provided data were assessed.

Statistical analyses

Statistical analysis title	Analysis 1
Comparison groups	Rituximab + Chemotherapy v Ofatumumab + Chemotherapy
Number of subjects included in analysis	347
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.978
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.11
upper limit	2.17

Secondary: Change from Baseline in the Functional Assessment of Cancer Therapy Lymphoma Trial Outcome Index (FACT-Lym TOI) total score during treatment

End point title	Change from Baseline in the Functional Assessment of Cancer Therapy Lymphoma Trial Outcome Index (FACT-Lym TOI) total score during treatment

End point description:

The FACT-Lym TOI is a measure that combines the FACT-Lym subscale (15 items; responses to each item range from 0, "Not at all" to 4, "Very much") with two domains taken from the FACT-G (responses to each item range from "Not at all " to "Very much"): Physical Well-being (7 items: lack of energy, nausea, meeting family needs, pain, side effects, feels ill, spends time in bed) and Functional Well-being (7 items: ability to work, work fulfilment, ability to enjoy life, illness acceptance, ability to sleep well, enjoying things done for fun, satisfaction with quality of life). This index is designed to be sensitive to changes in treatment regimens. The total FACT-Lym TOI score ranges from 0 to 116; higher scores indicate a better patient-reported outcome/quality of life. Participants were asked to think back over the past week when responding to the items.

End point type	Secondary

End point timeframe:

Baseline and the end of the treatment period (until approximately 4 to 6 weeks following Cycle 3 [assessed up to 3 months])

End point values	Rituximab + Chemotherapy	Ofatumumab + Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	172[34]	174[35]		
Units: scores on a scale				
arithmetic mean (standard error)	-2.028 (± 0.9196)	-3.156 (± 0.9204)		

Notes:

[34] - ITT Population. Only those participants who provided data were assessed.

[35] - ITT Population. Only those participants who provided data were assessed.

Statistical analyses

Statistical analysis title	Analysis 1
Comparison groups	Rituximab + Chemotherapy v Ofatumumab + Chemotherapy
Number of subjects included in analysis	346
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.387
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	1.129
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.434
upper limit	3.691

Secondary: Time to neutrophil and platelet recovery after each cycle of salvage chemotherapy

End point title	Time to neutrophil and platelet recovery after each cycle of salvage chemotherapy

End point description:

Neutrophil (absolute neutrophil count [ANC]) recovery is defined as ANC >=0.5*10^9/Liter and increasing, and platelet (PLT) recovery is defined as PLT >=10*10^9/Liter and increasing. For each cycle, time to ANC recovery is defined as the time from the first dose to the first ANC >=0.5*10^9/Liter and increasing after the nadir in the cycle. For each cycle, time to PLT recovery is defined as the time from the first dose to the first PLT >=10*10^9/L and increasing after the nadir in the cycle.

End point type	Secondary

End point timeframe:

From the start of each cycle for a maximum of 5 weeks per cycle (assessed during treatment period of Baseline up to approximately 3 months)

End point values	Rituximab + Chemotherapy	Ofatumumab + Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	223[36]	222[37]		
Units: days				
median (confidence interval 95%)				
Neutrophils, Cycle 1, n=223, 222	8 (6 to 13)	11 (8 to 13)		
Neutrophils, Cycle 2, n=196, 199	8 (6 to 10)	11 (9 to 13)		
Neutrophils, Cycle 3, n=137, 129	10 (6 to 12)	7 (5 to 10)		
Platelets, Cycle 1, n=223, 222	13 (12 to 13)	12 (12 to 13)		
Platelets, Cycle 2, n=196, 199	13 (12 to 13)	13 (12 to 13)		
Platelets, Cycle 3, n=137, 129	13 (12 to 14)	13 (12 to 14)		

Notes:

[36] - Safety Population. Only those participants available for analysis in the given cycle were assessed.

[37] - Safety Population. Only those participants available for analysis in the given cycle were assessed.

Statistical analyses

Statistical analysis title	Analysis 1
Comparison groups	Rituximab + Chemotherapy v Ofatumumab + Chemotherapy
Number of subjects included in analysis	445
Analysis specification	Pre-specified
Analysis type	superiority[38]
P-value	= 0.479 [39]
Method	Stratified Log-Rank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.93
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.74
upper limit	1.16

Notes:

[38] - Statistics are presented for Category-Neutrophils, Cycle 1. Confidence Interval (CI) estimated using the Brookmeyer-Crowley method. HR are estimated using the Pike estimator. A hazard ratio <1 indicates a lower probability of recovery with Ofatumumab compared to Rituximab. HR was adjusted for stratification factors.

[39] - p-value from stratified log-rank test are adjusted for stratification factors.

Statistical analysis title	Analysis 2

Statistical analysis description:

The number of participants included in the analysis is as stated in the End Point Values table and not 445 which is automatically calculated by the system.

Comparison groups	Rituximab + Chemotherapy v Ofatumumab + Chemotherapy
Number of subjects included in analysis	445
Analysis specification	Pre-specified
Analysis type	superiority[40]
P-value	= 0.059 [41]
Method	Stratified Log-Rank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.81

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.64
upper limit	1.02

Notes:

[40] - Statistics are presented for Category-Neutrophils, Cycle 2. Confidence Interval (CI) estimated using the Brookmeyer-Crowley method. HR are estimated using the Pike estimator. A hazard ratio <1 indicates a lower probability of recovery with Ofatumumab compared to Rituximab. HR was adjusted for stratification factors.

[41] - p-value from stratified log-rank test are adjusted for stratification factors.

Statistical analysis title	Analysis 3

Statistical analysis description:

The number of participants included in the analysis is as stated in the End Point Values table and not 445 which is automatically calculated by the system.

Comparison groups	Rituximab + Chemotherapy v Ofatumumab + Chemotherapy
Number of subjects included in analysis	445
Analysis specification	Pre-specified
Analysis type	superiority[42]
P-value	= 0.451 [43]
Method	Stratified Log-Rank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.83
upper limit	1.48

Notes:

[42] - Statistics are presented for Category-Neutrophils, Cycle 3. Confidence Interval (CI) estimated using the Brookmeyer-Crowley method. HR are estimated using the Pike estimator. A hazard ratio <1 indicates a lower probability of recovery with Ofatumumab compared to Rituximab. HR was adjusted for stratification factors.

[43] - p-value from stratified log-rank test are adjusted for stratification factors.

Statistical analysis title	Analysis 4
Comparison groups	Rituximab + Chemotherapy v Ofatumumab + Chemotherapy
Number of subjects included in analysis	445
Analysis specification	Pre-specified
Analysis type	superiority[44]
P-value	= 0.597 [45]
Method	Stratified Log-Rank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.86
upper limit	1.29

Notes:

[44] - Statistics are presented for Category-Platelets, Cycle 1. Confidence Interval (CI) estimated using the Brookmeyer-Crowley method. HR are estimated using the Pike estimator. A hazard ratio <1 indicates a lower probability of recovery with Ofatumumab compared to Rituximab. HR was adjusted for stratification factors.

[45] - p-value from stratified log-rank test are adjusted for stratification factors.

Statistical analysis title	Analysis 5

Statistical analysis description:

The number of participants included in the analysis is as stated in the End Point Values table and not 445 which is automatically calculated by the system.

Comparison groups	Rituximab + Chemotherapy v Ofatumumab + Chemotherapy
Number of subjects included in analysis	445
Analysis specification	Pre-specified
Analysis type	superiority[46]
P-value	= 0.199 [47]
Method	Stratified Log-Rank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.88
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.7
upper limit	1.1

Notes:

[46] - Statistics are presented for Category-Platelets, Cycle 2. Confidence Interval (CI) estimated using the Brookmeyer-Crowley method. HR are estimated using the Pike estimator. A hazard ratio <1 indicates a lower probability of recovery with Ofatumumab compared to Rituximab. HR was adjusted for stratification factors.
[47] - p-value from stratified log-rank test are adjusted for stratification factors.

Statistical analysis title	Analysis 6

Statistical analysis description:

The number of participants included in the analysis is as stated in the End Point Values table and not 445 which is automatically calculated by the system.

Comparison groups	Rituximab + Chemotherapy v Ofatumumab + Chemotherapy
Number of subjects included in analysis	445
Analysis specification	Pre-specified
Analysis type	superiority[48]
P-value	= 0.102 [49]
Method	Stratified Log-Rank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.93
upper limit	1.59

Notes:

[48] - Statistics are presented for Category-Platelets, Cycle 3. Confidence Interval (CI) estimated using the Brookmeyer-Crowley method. HR are estimated using the Pike estimator. A hazard ratio <1 indicates a lower probability of recovery with Ofatumumab compared to Rituximab. HR was adjusted for stratification factors.
[49] - p-value from stratified log-rank test are adjusted for stratification factors.

Secondary: Time to engraftment after high-dose therapy (HDT)/ASCT

End point title	Time to engraftment after high-dose therapy (HDT)/ASCT

End point description:

Engraftment is defined as 1) three consecutive days when the ANC is ≥0.5x109/L and 2) an unsupported platelet count of ≥20x109/L, and the engraftment date is the date that this occurs. If engraftment was not achieved by Day 42 or the last observation, engraftment was deemed to be a failure, and censoring took place at Day 42 or at the last observation.

End point type	Secondary

End point timeframe:

From ASCT up to 42 days post-ASCT (Baseline up to approximately 4.5 months)

End point values	Rituximab + Chemotherapy	Ofatumumab + Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	83[50]	74[51]		
Units: days				
median (confidence interval 95%)	24 (16 to 99999)	99999 (26 to 99999)		

Notes:

[50] - Safety population. Only participants completing HDT/ASCT are included. 99999 represents NA.

[51] - Safety population. Only participants completing HDT/ASCT are included. 99999 represents NA.

Statistical analyses

Statistical analysis title	Analysis 1
Comparison groups	Rituximab + Chemotherapy v Ofatumumab + Chemotherapy
Number of subjects included in analysis	157
Analysis specification	Pre-specified
Analysis type	superiority[52]
P-value	= 0.035 [53]
Method	Stratified Log-Rank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.36
upper limit	1

Notes:

[52] - Confidence Interval estimated using the Brookmeyer-Crowley method. HR are estimated using the Pike estimator. A hazard ratio <1 indicates a lower probability of recovery with Ofatumumab compared to Rituximab. HR was adjusted for stratification factors.

[53] - p-value from stratified log-rank test are adjusted for stratification factors.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events (AEs) were collected up to 60 days after the last dose of study treatment, or the commencement of high-dose chemotherapy, or anti-cancer therapy, whichever occurred first (up to approximately 16 study weeks).

Adverse event reporting additional description:

Serious adverse events (SAEs) and non-serious AEs were collected in members of the Safety Population, comprised of all participants who received at least one dose of study drug.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	Rituximab + Chemotherapy

Reporting group description:

Participants received 3 cycles (21 days per cycle) of rituximab combined with salvage chemotherapy (SC): either the DHAP regimen (3 cycles of dexamethasone, cytarabine, cisplatin [DHAP]) or the DVD regimen (DHAP-VIM [etoposide, ifosfamide, mesna, methotrexate]-DHAP). Rituximab (375 milligrams per meters squared [mg/m^2]) was infused intravenously (IV) on Day (D) 1 (or up to 3 days prior to D1) and D8 (+/-2 days) of Cycle 1 of the SC, and then on D1 only of Cycles 2 and 3. The DHAP regimen (SC) contained: dexamethasone (40 mg/day) administered orally or IV on Days 1, 2, 3, or 4 of each cycle; cisplatin (100 mg/m^2/day) as an IV continuous infusion on D1 of each cycle; and cytarabine 2 grams (g)/m^2 over 3 hours every 12 hours (2 doses) for each infusion on D2 of each cycle. VIM: etoposide (90 mg/m^2 IV on Days 1, 3, and 5), ifosfamide (1200 mg/m^2 IV on Days 1, 2, 3, 4, and 5), mesna (10 or 20 mg/kilogram [kg] IV on Days 1, 2, 3, 4, and 5), methotrexate (30 mg/m^2 IV on Days 1 and 5).

Reporting group title	Ofatumumab + Chemotherapy

Reporting group description:

Participants received 3 cycles (21 days per cycle) of ofatumumab combined with SC: either the DHAP regimen (three cycles of DHAP) or the DVD regimen (DHAP-VIM-DHAP). Ofatumumab (1000 mg/1000 milliliter [mL]) was infused IV on Day 1 (or up to 3 days prior to Day 1) and Day 8 (+/-2 days) of Cycle 1 of the SC, and then on Day 1 only of Cycles 2 and 3. The DHAP regimen (SC) contained: dexamethasone (40 mg/day) administered orally or IV on Days 1, 2, 3, or 4 of each cycle; cisplatin (100 mg/[m^2]/day) as an IV continuous infusion on Day 1 of each cycle; and cytarabine 2 g/m^2 over 3 hours every 12 hours (2 doses) for each infusion on Day 2 of each cycle. VIM: etoposide (90 mg/m^2 IV on Days 1, 3, and 5), ifosfamide (1200 mg/m^2 IV on Days 1, 2, 3, 4, and 5), mesna (10 or 20 mg/kg IV on Days 1, 2, 3, 4, and 5), methotrexate (30 mg/m^2 IV on Days 1 and 5).

Serious adverse events	Rituximab + Chemotherapy	Ofatumumab + Chemotherapy	
Total subjects affected by serious adverse events			
subjects affected / exposed	115 / 223 (51.57%)	118 / 222 (53.15%)	
number of deaths (all causes)	131	122	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Papillary thyroid cancer			

subjects affected / exposed	0 / 223 (0.00%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myelodysplastic syndrome			
subjects affected / exposed	1 / 223 (0.45%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphoma			
subjects affected / exposed	1 / 223 (0.45%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 223 (0.45%)	3 / 222 (1.35%)	
occurrences causally related to treatment / all	1 / 1	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orthostatic hypotension			
subjects affected / exposed	0 / 223 (0.00%)	2 / 222 (0.90%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombosis			
subjects affected / exposed	1 / 223 (0.45%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	0 / 223 (0.00%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	0 / 223 (0.00%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemia			

subjects affected / exposed	1 / 223 (0.45%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vena cava thrombosis			
subjects affected / exposed	0 / 223 (0.00%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	11 / 223 (4.93%)	8 / 222 (3.60%)	
occurrences causally related to treatment / all	8 / 11	6 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucosal inflammation			
subjects affected / exposed	2 / 223 (0.90%)	3 / 222 (1.35%)	
occurrences causally related to treatment / all	2 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	0 / 223 (0.00%)	3 / 222 (1.35%)	
occurrences causally related to treatment / all	0 / 0	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	0 / 223 (0.00%)	2 / 222 (0.90%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	1 / 223 (0.45%)	2 / 222 (0.90%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 1	1 / 1	
Chills			
subjects affected / exposed	0 / 223 (0.00%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			

subjects affected / exposed	1 / 223 (0.45%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Euthanasia			
subjects affected / exposed	0 / 223 (0.00%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	0 / 223 (0.00%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypersensitivity			
subjects affected / exposed	0 / 223 (0.00%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Secondary immunodeficiency			
subjects affected / exposed	1 / 223 (0.45%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Reproductive system and breast disorders			
Epididymitis			
subjects affected / exposed	2 / 223 (0.90%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pleural effusion			
subjects affected / exposed	1 / 223 (0.45%)	2 / 222 (0.90%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			

subjects affected / exposed	2 / 223 (0.90%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	1 / 223 (0.45%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	1 / 223 (0.45%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			
subjects affected / exposed	0 / 223 (0.00%)	2 / 222 (0.90%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Cough			
subjects affected / exposed	0 / 223 (0.00%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	0 / 223 (0.00%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung disorder			
subjects affected / exposed	0 / 223 (0.00%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	0 / 223 (0.00%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			

subjects affected / exposed	1 / 223 (0.45%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax spontaneous			
subjects affected / exposed	1 / 223 (0.45%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	1 / 223 (0.45%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Confusional state			
subjects affected / exposed	0 / 223 (0.00%)	2 / 222 (0.90%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Completed suicide			
subjects affected / exposed	1 / 223 (0.45%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Investigations			
Blood creatinine increased			
subjects affected / exposed	5 / 223 (2.24%)	12 / 222 (5.41%)	
occurrences causally related to treatment / all	6 / 6	13 / 13	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelet count decreased			
subjects affected / exposed	2 / 223 (0.90%)	7 / 222 (3.15%)	
occurrences causally related to treatment / all	2 / 2	7 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutrophil count decreased			
subjects affected / exposed	1 / 223 (0.45%)	3 / 222 (1.35%)	
occurrences causally related to treatment / all	1 / 1	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Alanine aminotransferase increased			

subjects affected / exposed	0 / 223 (0.00%)	2 / 222 (0.90%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
White blood cell count decreased			
subjects affected / exposed	0 / 223 (0.00%)	2 / 222 (0.90%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 223 (0.00%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood bilirubin increased			
subjects affected / exposed	0 / 223 (0.00%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood potassium decreased			
subjects affected / exposed	1 / 223 (0.45%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood urea increased			
subjects affected / exposed	1 / 223 (0.45%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
C-reactive protein increased			
subjects affected / exposed	1 / 223 (0.45%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Creatinine renal clearance decreased			
subjects affected / exposed	1 / 223 (0.45%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrocardiogram change			

subjects affected / exposed	0 / 223 (0.00%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Weight increased			
subjects affected / exposed	1 / 223 (0.45%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Spinal compression fracture			
subjects affected / exposed	1 / 223 (0.45%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Contusion			
subjects affected / exposed	0 / 223 (0.00%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial bones fracture			
subjects affected / exposed	1 / 223 (0.45%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			
subjects affected / exposed	1 / 223 (0.45%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infusion related reaction			
subjects affected / exposed	0 / 223 (0.00%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 223 (0.45%)	2 / 222 (0.90%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Acute coronary syndrome			
subjects affected / exposed	1 / 223 (0.45%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	0 / 223 (0.00%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	1 / 223 (0.45%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	0 / 223 (0.00%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac failure			
subjects affected / exposed	0 / 223 (0.00%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left ventricular failure			
subjects affected / exposed	1 / 223 (0.45%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	0 / 223 (0.00%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericarditis			
subjects affected / exposed	1 / 223 (0.45%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus bradycardia			

subjects affected / exposed	1 / 223 (0.45%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	1 / 223 (0.45%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachyarrhythmia			
subjects affected / exposed	0 / 223 (0.00%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Syncope			
subjects affected / exposed	1 / 223 (0.45%)	6 / 222 (2.70%)	
occurrences causally related to treatment / all	1 / 1	2 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalopathy			
subjects affected / exposed	1 / 223 (0.45%)	2 / 222 (0.90%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage intracranial			
subjects affected / exposed	1 / 223 (0.45%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 1	1 / 1	
Headache			
subjects affected / exposed	1 / 223 (0.45%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subarachnoid haemorrhage			
subjects affected / exposed	1 / 223 (0.45%)	2 / 222 (0.90%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
VIIth nerve paralysis			

subjects affected / exposed	1 / 223 (0.45%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haemorrhage			
subjects affected / exposed	0 / 223 (0.00%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral infarction			
subjects affected / exposed	1 / 223 (0.45%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	0 / 223 (0.00%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	0 / 223 (0.00%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy			
subjects affected / exposed	1 / 223 (0.45%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral motor neuropathy			
subjects affected / exposed	1 / 223 (0.45%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Presyncope			
subjects affected / exposed	0 / 223 (0.00%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Somnolence			

subjects affected / exposed	0 / 223 (0.00%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brachial plexopathy			
subjects affected / exposed	1 / 223 (0.45%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	30 / 223 (13.45%)	28 / 222 (12.61%)	
occurrences causally related to treatment / all	26 / 33	24 / 29	
deaths causally related to treatment / all	0 / 1	0 / 0	
Thrombocytopenia			
subjects affected / exposed	11 / 223 (4.93%)	12 / 222 (5.41%)	
occurrences causally related to treatment / all	13 / 13	14 / 14	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	7 / 223 (3.14%)	6 / 222 (2.70%)	
occurrences causally related to treatment / all	7 / 8	7 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	1 / 223 (0.45%)	5 / 222 (2.25%)	
occurrences causally related to treatment / all	1 / 1	5 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			
subjects affected / exposed	3 / 223 (1.35%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	4 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			
subjects affected / exposed	2 / 223 (0.90%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone marrow failure			

subjects affected / exposed	1 / 223 (0.45%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Deafness			
subjects affected / exposed	1 / 223 (0.45%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tinnitus			
subjects affected / exposed	1 / 223 (0.45%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Blindness			
subjects affected / exposed	1 / 223 (0.45%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eyelid function disorder			
subjects affected / exposed	0 / 223 (0.00%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ocular hypertension			
subjects affected / exposed	1 / 223 (0.45%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Periorbital oedema			
subjects affected / exposed	0 / 223 (0.00%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vision blurred			
subjects affected / exposed	0 / 223 (0.00%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vitreous haemorrhage			

subjects affected / exposed	1 / 223 (0.45%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Conjunctivitis			
subjects affected / exposed	1 / 223 (0.45%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	13 / 223 (5.83%)	10 / 222 (4.50%)	
occurrences causally related to treatment / all	17 / 18	10 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	9 / 223 (4.04%)	4 / 222 (1.80%)	
occurrences causally related to treatment / all	11 / 11	4 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	1 / 223 (0.45%)	5 / 222 (2.25%)	
occurrences causally related to treatment / all	1 / 1	3 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	2 / 223 (0.90%)	2 / 222 (0.90%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	1 / 223 (0.45%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	2 / 223 (0.90%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			

subjects affected / exposed	2 / 223 (0.90%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			
subjects affected / exposed	0 / 223 (0.00%)	2 / 222 (0.90%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	1 / 223 (0.45%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	1 / 223 (0.45%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dental caries			
subjects affected / exposed	0 / 223 (0.00%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer			
subjects affected / exposed	0 / 223 (0.00%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric haemorrhage			
subjects affected / exposed	1 / 223 (0.45%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal inflammation			
subjects affected / exposed	0 / 223 (0.00%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileal stenosis			

subjects affected / exposed	1 / 223 (0.45%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower gastrointestinal haemorrhage			
subjects affected / exposed	0 / 223 (0.00%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Melaena			
subjects affected / exposed	0 / 223 (0.00%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	1 / 223 (0.45%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal varices haemorrhage			
subjects affected / exposed	1 / 223 (0.45%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	1 / 223 (0.45%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic failure			
subjects affected / exposed	0 / 223 (0.00%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	1 / 223 (0.45%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperhidrosis			

subjects affected / exposed	0 / 223 (0.00%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash maculo-papular			
subjects affected / exposed	1 / 223 (0.45%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Swelling face			
subjects affected / exposed	0 / 223 (0.00%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urticaria			
subjects affected / exposed	0 / 223 (0.00%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal failure acute			
subjects affected / exposed	12 / 223 (5.38%)	11 / 222 (4.95%)	
occurrences causally related to treatment / all	12 / 12	8 / 11	
deaths causally related to treatment / all	0 / 0	1 / 1	
Renal failure			
subjects affected / exposed	3 / 223 (1.35%)	6 / 222 (2.70%)	
occurrences causally related to treatment / all	3 / 3	4 / 6	
deaths causally related to treatment / all	0 / 0	0 / 1	
Renal impairment			
subjects affected / exposed	5 / 223 (2.24%)	2 / 222 (0.90%)	
occurrences causally related to treatment / all	5 / 5	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal injury			
subjects affected / exposed	0 / 223 (0.00%)	2 / 222 (0.90%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			

subjects affected / exposed	1 / 223 (0.45%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephropathy toxic			
subjects affected / exposed	1 / 223 (0.45%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure chronic			
subjects affected / exposed	0 / 223 (0.00%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 223 (0.00%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Neutropenic sepsis			
subjects affected / exposed	4 / 223 (1.79%)	8 / 222 (3.60%)	
occurrences causally related to treatment / all	4 / 4	8 / 9	
deaths causally related to treatment / all	0 / 0	2 / 2	
Sepsis			
subjects affected / exposed	9 / 223 (4.04%)	4 / 222 (1.80%)	
occurrences causally related to treatment / all	6 / 10	3 / 4	
deaths causally related to treatment / all	1 / 2	1 / 1	
Pneumonia			
subjects affected / exposed	2 / 223 (0.90%)	4 / 222 (1.80%)	
occurrences causally related to treatment / all	2 / 2	4 / 5	
deaths causally related to treatment / all	1 / 1	0 / 0	
Device related infection			
subjects affected / exposed	3 / 223 (1.35%)	2 / 222 (0.90%)	
occurrences causally related to treatment / all	2 / 3	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Infection			
subjects affected / exposed	0 / 223 (0.00%)	4 / 222 (1.80%)	
occurrences causally related to treatment / all	0 / 0	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	4 / 223 (1.79%)	2 / 222 (0.90%)	
occurrences causally related to treatment / all	3 / 4	1 / 2	
deaths causally related to treatment / all	3 / 4	1 / 2	
Urinary tract infection			
subjects affected / exposed	2 / 223 (0.90%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	2 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	1 / 223 (0.45%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pneumonia cytomegaloviral			
subjects affected / exposed	0 / 223 (0.00%)	2 / 222 (0.90%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	2 / 2	
Pulmonary mycosis			
subjects affected / exposed	1 / 223 (0.45%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinusitis			
subjects affected / exposed	2 / 223 (0.90%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess			
subjects affected / exposed	1 / 223 (0.45%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			

subjects affected / exposed	0 / 223 (0.00%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	1 / 223 (0.45%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridial infection			
subjects affected / exposed	1 / 223 (0.45%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	0 / 223 (0.00%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related sepsis			
subjects affected / exposed	1 / 223 (0.45%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea infectious			
subjects affected / exposed	0 / 223 (0.00%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia bacteraemia			
subjects affected / exposed	0 / 223 (0.00%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fungal endocarditis			
subjects affected / exposed	1 / 223 (0.45%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Gastrointestinal candidiasis			

subjects affected / exposed	1 / 223 (0.45%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal infection			
subjects affected / exposed	1 / 223 (0.45%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes simplex			
subjects affected / exposed	0 / 223 (0.00%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	1 / 223 (0.45%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic infection			
subjects affected / exposed	0 / 223 (0.00%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parainfluenzae virus infection			
subjects affected / exposed	1 / 223 (0.45%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia klebsiella			
subjects affected / exposed	1 / 223 (0.45%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural sepsis			
subjects affected / exposed	0 / 223 (0.00%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative wound infection			

subjects affected / exposed	1 / 223 (0.45%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhinovirus infection			
subjects affected / exposed	1 / 223 (0.45%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin infection			
subjects affected / exposed	1 / 223 (0.45%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal bacteraemia			
subjects affected / exposed	0 / 223 (0.00%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal skin infection			
subjects affected / exposed	1 / 223 (0.45%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			
subjects affected / exposed	1 / 223 (0.45%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			
subjects affected / exposed	0 / 223 (0.00%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopulmonary aspergillosis			
subjects affected / exposed	1 / 223 (0.45%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			

subjects affected / exposed	1 / 223 (0.45%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis bacterial			
subjects affected / exposed	0 / 223 (0.00%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	4 / 223 (1.79%)	3 / 222 (1.35%)	
occurrences causally related to treatment / all	3 / 4	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	3 / 223 (1.35%)	4 / 222 (1.80%)	
occurrences causally related to treatment / all	4 / 4	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	1 / 223 (0.45%)	4 / 222 (1.80%)	
occurrences causally related to treatment / all	1 / 1	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour lysis syndrome			
subjects affected / exposed	2 / 223 (0.90%)	3 / 222 (1.35%)	
occurrences causally related to treatment / all	2 / 2	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	1 / 223 (0.45%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypomagnesaemia			
subjects affected / exposed	1 / 223 (0.45%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Decreased appetite			

subjects affected / exposed	0 / 223 (0.00%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus			
subjects affected / exposed	0 / 223 (0.00%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fluid overload			
subjects affected / exposed	1 / 223 (0.45%)	0 / 222 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperlipidaemia			
subjects affected / exposed	0 / 223 (0.00%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lactic acidosis			
subjects affected / exposed	0 / 223 (0.00%)	1 / 222 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Rituximab + Chemotherapy	Ofatumumab + Chemotherapy	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	217 / 223 (97.31%)	215 / 222 (96.85%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	14 / 223 (6.28%)	18 / 222 (8.11%)	
occurrences (all)	18	19	
Hypotension			
subjects affected / exposed	11 / 223 (4.93%)	20 / 222 (9.01%)	
occurrences (all)	14	21	
Flushing			

subjects affected / exposed	7 / 223 (3.14%)	12 / 222 (5.41%)	
occurrences (all)	9	14	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	80 / 223 (35.87%)	74 / 222 (33.33%)	
occurrences (all)	108	97	
Pyrexia			
subjects affected / exposed	69 / 223 (30.94%)	60 / 222 (27.03%)	
occurrences (all)	98	78	
Oedema peripheral			
subjects affected / exposed	30 / 223 (13.45%)	31 / 222 (13.96%)	
occurrences (all)	37	39	
Oedema			
subjects affected / exposed	21 / 223 (9.42%)	24 / 222 (10.81%)	
occurrences (all)	34	31	
Mucosal inflammation			
subjects affected / exposed	28 / 223 (12.56%)	11 / 222 (4.95%)	
occurrences (all)	31	11	
Chills			
subjects affected / exposed	24 / 223 (10.76%)	13 / 222 (5.86%)	
occurrences (all)	27	15	
Malaise			
subjects affected / exposed	17 / 223 (7.62%)	9 / 222 (4.05%)	
occurrences (all)	18	17	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	39 / 223 (17.49%)	23 / 222 (10.36%)	
occurrences (all)	44	27	
Dyspnoea			
subjects affected / exposed	18 / 223 (8.07%)	27 / 222 (12.16%)	
occurrences (all)	20	35	
Epistaxis			
subjects affected / exposed	24 / 223 (10.76%)	17 / 222 (7.66%)	
occurrences (all)	28	19	
Hiccups			

subjects affected / exposed	20 / 223 (8.97%)	20 / 222 (9.01%)	
occurrences (all)	28	24	
Oropharyngeal pain			
subjects affected / exposed	13 / 223 (5.83%)	12 / 222 (5.41%)	
occurrences (all)	14	14	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	24 / 223 (10.76%)	28 / 222 (12.61%)	
occurrences (all)	34	36	
Investigations			
Platelet count decreased			
subjects affected / exposed	63 / 223 (28.25%)	64 / 222 (28.83%)	
occurrences (all)	127	116	
Blood creatinine increased			
subjects affected / exposed	31 / 223 (13.90%)	45 / 222 (20.27%)	
occurrences (all)	54	67	
White blood cell count decreased			
subjects affected / exposed	25 / 223 (11.21%)	33 / 222 (14.86%)	
occurrences (all)	63	70	
Neutrophil count decreased			
subjects affected / exposed	21 / 223 (9.42%)	34 / 222 (15.32%)	
occurrences (all)	50	58	
Weight increased			
subjects affected / exposed	22 / 223 (9.87%)	22 / 222 (9.91%)	
occurrences (all)	29	34	
Haemoglobin decreased			
subjects affected / exposed	18 / 223 (8.07%)	21 / 222 (9.46%)	
occurrences (all)	28	23	
Aspartate aminotransferase increased			
subjects affected / exposed	20 / 223 (8.97%)	17 / 222 (7.66%)	
occurrences (all)	33	27	
Alanine aminotransferase increased			
subjects affected / exposed	19 / 223 (8.52%)	15 / 222 (6.76%)	
occurrences (all)	30	24	
Weight decreased			

subjects affected / exposed	11 / 223 (4.93%)	23 / 222 (10.36%)	
occurrences (all)	12	24	
Blood potassium decreased			
subjects affected / exposed	8 / 223 (3.59%)	13 / 222 (5.86%)	
occurrences (all)	9	17	
Blood lactate dehydrogenase increased			
subjects affected / exposed	12 / 223 (5.38%)	8 / 222 (3.60%)	
occurrences (all)	21	10	
Gamma-glutamyltransferase increased			
subjects affected / exposed	10 / 223 (4.48%)	12 / 222 (5.41%)	
occurrences (all)	12	13	
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	2 / 223 (0.90%)	13 / 222 (5.86%)	
occurrences (all)	4	15	
Nervous system disorders			
Headache			
subjects affected / exposed	45 / 223 (20.18%)	46 / 222 (20.72%)	
occurrences (all)	64	59	
Dizziness			
subjects affected / exposed	31 / 223 (13.90%)	23 / 222 (10.36%)	
occurrences (all)	35	28	
Dysgeusia			
subjects affected / exposed	19 / 223 (8.52%)	16 / 222 (7.21%)	
occurrences (all)	19	18	
Lethargy			
subjects affected / exposed	12 / 223 (5.38%)	5 / 222 (2.25%)	
occurrences (all)	17	6	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	136 / 223 (60.99%)	125 / 222 (56.31%)	
occurrences (all)	219	200	
Thrombocytopenia			
subjects affected / exposed	109 / 223 (48.88%)	103 / 222 (46.40%)	
occurrences (all)	223	207	

Neutropenia			
subjects affected / exposed	71 / 223 (31.84%)	67 / 222 (30.18%)	
occurrences (all)	147	120	
Leukopenia			
subjects affected / exposed	25 / 223 (11.21%)	24 / 222 (10.81%)	
occurrences (all)	62	41	
Febrile neutropenia			
subjects affected / exposed	24 / 223 (10.76%)	21 / 222 (9.46%)	
occurrences (all)	26	24	
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	21 / 223 (9.42%)	14 / 222 (6.31%)	
occurrences (all)	23	17	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	136 / 223 (60.99%)	129 / 222 (58.11%)	
occurrences (all)	247	215	
Vomiting			
subjects affected / exposed	81 / 223 (36.32%)	68 / 222 (30.63%)	
occurrences (all)	139	96	
Constipation			
subjects affected / exposed	65 / 223 (29.15%)	76 / 222 (34.23%)	
occurrences (all)	90	87	
Diarrhoea			
subjects affected / exposed	70 / 223 (31.39%)	50 / 222 (22.52%)	
occurrences (all)	91	71	
Dyspepsia			
subjects affected / exposed	24 / 223 (10.76%)	16 / 222 (7.21%)	
occurrences (all)	27	22	
Abdominal pain			
subjects affected / exposed	19 / 223 (8.52%)	17 / 222 (7.66%)	
occurrences (all)	20	20	
Abdominal pain upper			
subjects affected / exposed	14 / 223 (6.28%)	12 / 222 (5.41%)	
occurrences (all)	16	14	
Stomatitis			

subjects affected / exposed	11 / 223 (4.93%)	12 / 222 (5.41%)	
occurrences (all)	14	12	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	19 / 223 (8.52%)	48 / 222 (21.62%)	
occurrences (all)	23	63	
Pruritus			
subjects affected / exposed	10 / 223 (4.48%)	16 / 222 (7.21%)	
occurrences (all)	10	22	
Urticaria			
subjects affected / exposed	4 / 223 (1.79%)	16 / 222 (7.21%)	
occurrences (all)	9	19	
Renal and urinary disorders			
Renal failure acute			
subjects affected / exposed	13 / 223 (5.83%)	8 / 222 (3.60%)	
occurrences (all)	15	8	
Renal impairment			
subjects affected / exposed	12 / 223 (5.38%)	6 / 222 (2.70%)	
occurrences (all)	15	7	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	30 / 223 (13.45%)	34 / 222 (15.32%)	
occurrences (all)	39	36	
Bone pain			
subjects affected / exposed	14 / 223 (6.28%)	12 / 222 (5.41%)	
occurrences (all)	16	12	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	54 / 223 (24.22%)	56 / 222 (25.23%)	
occurrences (all)	75	73	
Hypomagnesaemia			
subjects affected / exposed	46 / 223 (20.63%)	51 / 222 (22.97%)	
occurrences (all)	98	74	
Hypocalcaemia			
subjects affected / exposed	37 / 223 (16.59%)	30 / 222 (13.51%)	
occurrences (all)	54	42	

Hyponatraemia			
subjects affected / exposed	25 / 223 (11.21%)	22 / 222 (9.91%)	
occurrences (all)	45	34	
Hyperglycaemia			
subjects affected / exposed	16 / 223 (7.17%)	14 / 222 (6.31%)	
occurrences (all)	29	27	
Hypophosphataemia			
subjects affected / exposed	16 / 223 (7.17%)	12 / 222 (5.41%)	
occurrences (all)	23	17	
Hypokalaemia			
subjects affected / exposed	57 / 223 (25.56%)	58 / 222 (26.13%)	
occurrences (all)	100	87	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 February 2010	Supplementation of response criteria
16 September 2010	Adjustments to the requirements for pathological confirmation of lymphoma prior to study entry.
13 March 2012	Increase of sample size to 410 and corresponding revision of statistical rationale.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported