

**Clinical trial results:****A Study of Obinutuzumab in Combination With CHOP Chemotherapy Versus Rituximab With CHOP in Participants With CD20-Positive Diffuse Large B-Cell Lymphoma (GOYA)****Summary**

EudraCT number	2010-024194-39
Trial protocol	ES GB SK CZ HU IT DE AT DK PL
Global end of trial date	31 January 2018

Results information

Result version number	v3 (current)
This version publication date	10 February 2019
First version publication date	23 April 2017
Version creation reason	

Trial information**Trial identification**

Sponsor protocol code	BO21005
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01287741
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, global.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	31 January 2018
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	31 January 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective was to demonstrate superiority in progression-free survival (PFS) with obinutuzumab (GA101) plus cyclophosphamide, doxorubicin, vincristine, and prednisone/prednisolone (G-CHOP), compared with rituximab plus chemotherapy (R-CHOP) in previously untreated subjects with CD20-positive diffuse large B-cell lymphoma (DLBCL), based on investigator-assessed PFS.

Protection of trial subjects:

Each subject, or the subject's representative, signed an informed consent form prior to screening.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	26 July 2011
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	78 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	China: 248
Country: Number of subjects enrolled	Hong Kong: 3
Country: Number of subjects enrolled	Japan: 111
Country: Number of subjects enrolled	Korea, Republic of: 59
Country: Number of subjects enrolled	Thailand: 86
Country: Number of subjects enrolled	Taiwan: 7
Country: Number of subjects enrolled	Argentina: 3
Country: Number of subjects enrolled	Brazil: 2
Country: Number of subjects enrolled	Colombia: 6
Country: Number of subjects enrolled	Mexico: 9
Country: Number of subjects enrolled	Panama: 4
Country: Number of subjects enrolled	Peru: 8
Country: Number of subjects enrolled	Hungary: 68
Country: Number of subjects enrolled	Poland: 15
Country: Number of subjects enrolled	Russian Federation: 31
Country: Number of subjects enrolled	Serbia: 5
Country: Number of subjects enrolled	Slovakia: 3
Country: Number of subjects enrolled	Canada: 120

Country: Number of subjects enrolled	United States: 96
Country: Number of subjects enrolled	Australia: 22
Country: Number of subjects enrolled	South Africa: 8
Country: Number of subjects enrolled	Austria: 6
Country: Number of subjects enrolled	Switzerland: 21
Country: Number of subjects enrolled	Germany: 23
Country: Number of subjects enrolled	Denmark: 11
Country: Number of subjects enrolled	Spain: 79
Country: Number of subjects enrolled	United Kingdom: 27
Country: Number of subjects enrolled	Italy: 259
Country: Number of subjects enrolled	Czech Republic: 74
Worldwide total number of subjects	1414
EEA total number of subjects	565

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)	848
From 65 to 84 years	564
85 years and over	2

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Eleven subjects withdrew from the study after randomization but prior to receiving study treatment.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
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Arm title	Rituximab+Chemotherapy
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Arm description:

Subjects received eight 21-day cycles of rituximab, combined with six or eight cycles of standard cyclophosphamide, doxorubicin, vincristine, and prednisone/prednisolone (CHOP) chemotherapy (21-day cycles). Prior to study start, study centers chose whether they planned to administer 6 or 8 cycles of CHOP chemotherapy.

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

Dosage and administration details:

Rituximab at a dose of 375 milligrams per square metre (mg/m^2), administered by intravenous (IV) infusion on Day 1 of each 21-day cycle for 8 cycles.

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

Dosage and administration details:

Cyclophosphamide $750 \text{ mg}/\text{m}^2$, administered intravenously (IV) on Day 1 of each 21-day cycle.

Investigational medicinal product name	Vincristine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Vincristine $1.4 \text{ mg}/\text{m}^2$ (maximum 2 mg) IV, administered on Day 1 of each 21-day cycle.

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

Dosage and administration details:

Doxorubicin $50 \text{ mg}/\text{m}^2$ IV, administered on Day 1 of each 21-day cycle.

Investigational medicinal product name	Prednisone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Prednisone 100 mg (or equivalent prednisolone or methylprednisolone), administered orally on Days 1-5 of each 21-day cycle.

Arm title	Obinutuzumab+Chemotherapy
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Arm description:

Subjects received eight 21-day cycles of obinutuzumab, combined with six or eight cycles of standard cyclophosphamide, doxorubicin, vincristine, and prednisone/prednisolone (CHOP) chemotherapy (21-day cycles). Subjects received an additional two doses of obinutuzumab on Days 8 and 15 of Cycle 1. Prior to study start, study centers chose whether they planned to administer 6 or 8 cycles of CHOP chemotherapy.

Arm type	Experimental
Investigational medicinal product name	Obinutuzumab
Investigational medicinal product code	
Other name	GA101, RO5072759
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Obinutuzumab 1000 mg IV infusion, administered on Day 1 of each 21-day cycle for 8 cycles. During Cycle 1, obinutuzumab was also infused on Days 8 and 15.

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

Dosage and administration details:

Cyclophosphamide 750 milligrams per square metre (mg/m²), administered intravenously (IV) on Day 1 of each 21-day cycle.

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

Dosage and administration details:

Doxorubicin 50 mg/m² IV, administered on Day 1 of each 21-day cycle.

Investigational medicinal product name	Vincristine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Vincristine 1.4 mg/m² (maximum 2 mg) IV, administered on Day 1 of each 21-day cycle.

Investigational medicinal product name	Prednisone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Prednisone 100 mg (or equivalent prednisolone or methylprednisolone), administered orally on Days 1-5 of each 21-day cycle.

Number of subjects in period 1	Rituximab+Chemotherapy	Obinutuzumab+Chemotherapy
Started	710	704
Completed	86	91
Not completed	624	613
Adverse event, serious fatal	32	44
Consent withdrawn by subject	35	38
Physician decision	15	23
Study terminated by Sponsor	307	315
Adverse event, non-fatal	4	6
Non-compliance	6	4
Lost to follow-up	10	8
Progressive disease	190	166
Reason not specified	23	9
Protocol deviation	2	-

Baseline characteristics

Reporting groups

Reporting group title	Rituximab+Chemotherapy
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Reporting group description:

Subjects received eight 21-day cycles of rituximab, combined with six or eight cycles of standard cyclophosphamide, doxorubicin, vincristine, and prednisone/prednisolone (CHOP) chemotherapy (21-day cycles). Prior to study start, study centers chose whether they planned to administer 6 or 8 cycles of CHOP chemotherapy.

Reporting group title	Obinutuzumab+Chemotherapy
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Reporting group description:

Subjects received eight 21-day cycles of obinutuzumab, combined with six or eight cycles of standard cyclophosphamide, doxorubicin, vincristine, and prednisone/prednisolone (CHOP) chemotherapy (21-day cycles). Subjects received an additional two doses of obinutuzumab on Days 8 and 15 of Cycle 1. Prior to study start, study centers chose whether they planned to administer 6 or 8 cycles of CHOP chemotherapy.

Reporting group values	Rituximab+Chemotherapy	Obinutuzumab+Chemotherapy	Total
Number of subjects	710	704	1414
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	431	417	848
From 65-84 years	279	285	564
85 years and over	0	2	2
Age Continuous			
Units: years			
arithmetic mean	59.1	59.4	
standard deviation	± 13.6	± 13.3	-
Sex: Female, Male			
Units: Subjects			
Female	328	336	664
Male	382	368	750

End points

End points reporting groups

Reporting group title	Rituximab+Chemotherapy
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Reporting group description:

Subjects received eight 21-day cycles of rituximab, combined with six or eight cycles of standard cyclophosphamide, doxorubicin, vincristine, and prednisone/prednisolone (CHOP) chemotherapy (21-day cycles). Prior to study start, study centers chose whether they planned to administer 6 or 8 cycles of CHOP chemotherapy.

Reporting group title	Obinutuzumab+Chemotherapy
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Reporting group description:

Subjects received eight 21-day cycles of obinutuzumab, combined with six or eight cycles of standard cyclophosphamide, doxorubicin, vincristine, and prednisone/prednisolone (CHOP) chemotherapy (21-day cycles). Subjects received an additional two doses of obinutuzumab on Days 8 and 15 of Cycle 1. Prior to study start, study centers chose whether they planned to administer 6 or 8 cycles of CHOP chemotherapy.

Primary: Median Time to Progression-Free Survival (PFS), Investigator-Assessed

End point title	Median Time to Progression-Free Survival (PFS), Investigator-Assessed
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End point description:

Kaplan Meier estimate of median PFS was defined as time at which half of subjects have progressed. Progression-free survival was defined as time from randomization until first documented day of disease progression or relapse, using modified version of Revised Response Criteria for Malignant Lymphoma, or death from any cause, whichever occurred first, on investigator assessments. Progression was defined as at least 50% increase in nodal lesions or $\geq 50\%$ increase in any node > 1 centimeter(cm) or $\geq 50\%$ increase in other target measurable lesions (ex. splenic or hepatic nodules) and/or appearance of any new bone marrow involvement and/or appearance of any new lesion > 1.5 cm or $\geq 50\%$ increase in any previously involved node with a diameter ≤ 1 cm such that it is now > 1.5 cm. Tumor measurements were obtained by computed tomography or magnetic resonance imaging. 9.999 and 9999 = Confidence intervals not reached at time of analysis due to too few subjects had an event.

End point type	Primary
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End point timeframe:

Baseline up to data cut-off (up to 31 January 2018)

End point values	Rituximab+Chemotherapy	Obinutuzumab+Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	710	704		
Units: months				
median (confidence interval 95%)	74.5 (9.999 to 9999)	68.3 (68.3 to 9999)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Obinutuzumab+Chemotherapy v Rituximab+Chemotherapy

Number of subjects included in analysis	1414
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.4753
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.94
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.78
upper limit	1.12

Secondary: Median Time to Progression-Free Survival (PFS), Independent Review Committee (IRC)-Assessed

End point title	Median Time to Progression-Free Survival (PFS), Independent Review Committee (IRC)-Assessed
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End point description:

Kaplan Meier estimate of the median PFS was defined as the time at which half of the subjects have progressed (progressive disease [PD]). Progression-free survival was defined as the time from randomization until the first documented day of disease progression or relapse, using a modified version of the Revised Response Criteria for Malignant Lymphoma, or death from any cause, whichever occurred first, on the basis of IRC assessments. Progression was defined as at least 50% increase in nodal lesions or $\geq 50\%$ increase in any node > 1 centimeter (cm) or $\geq 50\%$ increase in other target measurable lesions (e.g., splenic or hepatic nodules) and/or appearance of any new bone marrow involvement and/or appearance of any new lesion > 1.5 cm or $\geq 50\%$ increase in any previously involved node with a diameter ≤ 1 cm such that it is now > 1.5 cm. Tumor measurements were obtained by computed tomography (CT) or magnetic resonance imaging (MRI). 9999 = PFS event not reached at time of analysis.

End point type	Secondary
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End point timeframe:

Baseline up to clinical cut off date of 29 April 2016

End point values	Rituximab+Chemotherapy	Obinutuzumab+Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	710	704		
Units: months				
median (confidence interval 95%)	9999 (9999 to 9999)	9999 (9999 to 9999)		

Statistical analyses

Statistical analysis title	Statistical Analysis 2
Comparison groups	Rituximab+Chemotherapy v Obinutuzumab+Chemotherapy

Number of subjects included in analysis	1414
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.2736
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.89
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.72
upper limit	1.1

Secondary: Median Time to Overall Survival (OS)

End point title	Median Time to Overall Survival (OS)
End point description:	Kaplan Meier estimate of median OS was defined as the time at which half of the subjects had died, regardless of the cause of death. Overall survival in the overall study population was defined as the time from the date of randomization to the date of death from any cause. 9999 = PFS event not reached at time of analysis.
End point type	Secondary
End point timeframe:	Baseline up to data cut-off (up to 31 January 2018)

End point values	Rituximab+Chemotherapy	Obinutuzumab+Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	710	704		
Units: months				
median (confidence interval 95%)	9999 (9999 to 9999)	9999 (9999 to 9999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Response Rate (ORR), Investigator-Assessed

End point title	Overall Response Rate (ORR), Investigator-Assessed
End point description:	Overall response was determined on the basis of investigator assessments according to the International Working Group (IWG) Revised Response Criteria for Malignant Lymphoma, 2007. Tumor assessments were performed with CT/MRI with or without PET. Overall response was defined as the disappearance of all evidence of disease, regression of measurable disease, and no new sites.
End point type	Secondary

End point timeframe:

Baseline up to data cut-off (up to 31 January 2018)

End point values	Rituximab+Chemotherapy	Obinutuzumab+Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	710	704		
Units: percentage of subjects				
number (not applicable)				
Without PET (n= 710, 704)	80.1	81.4		
With PET (n=665, 669)	77.6	77.1		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Response Rate (ORR), IRC-Assessed

End point title	Overall Response Rate (ORR), IRC-Assessed
End point description:	Overall response was determined on the basis of IRC assessments according to the International Working Group (IWG) Revised Response Criteria for Malignant Lymphoma, 2007. Tumor assessments were performed with CT/MRI with or without PET. Overall response was defined as the disappearance of all evidence of disease, regression of measurable disease, and no new sites. The analysis of ORR, IRC-Assessed was based on the primary analysis that occurred on 29 April 2016.
End point type	Secondary
End point timeframe:	Baseline up to clinical cut off date of 29 April 2016

End point values	Rituximab+Chemotherapy	Obinutuzumab+Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	710	704		
Units: percentage of subjects				
number (not applicable)				
Without PET (n= 712, 706)	80.2	82.3		
With PET (n=665, 669)	81.1	82.1		

Statistical analyses

No statistical analyses for this end point

Secondary: Complete Response (CR) at the End of Treatment, Investigator-Assessed

End point title	Complete Response (CR) at the End of Treatment, Investigator-Assessed
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End point description:

Percentage of subjects with complete response was determined on the basis of investigator assessments according to the International Working Group (IWG) Revised Response Criteria for Malignant Lymphoma, 2007. Tumor assessments were performed with CT/MRI with or without PET. Complete response was defined as the disappearance of all evidence of disease.

End point type	Secondary
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End point timeframe:

Baseline up to data cut-off (up to 31 January 2018)

End point values	Rituximab+Chemotherapy	Obinutuzumab+Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	710	704		
Units: percentage of subjects				
number (not applicable)				
Without PET (n= 710, 704)	33.9	35.4		
With PET (n=665, 669)	59.1	56.5		

Statistical analyses

No statistical analyses for this end point

Secondary: Complete Response (CR) at the End of Treatment, IRC-Assessed

End point title	Complete Response (CR) at the End of Treatment, IRC-Assessed
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End point description:

Percentage of subjects with complete response was determined on the basis of IRC assessments according to the International Working Group (IWG) Revised Response Criteria for Malignant Lymphoma, 2007. Tumor assessments were performed with CT/MRI with or without PET. Complete response was defined as the disappearance of all evidence of disease. The analysis of CR, IRC-Assessed was based on the primary analysis that occurred on 29 April 2016.

End point type	Secondary
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End point timeframe:

Baseline up to clinical cut off date of 29 April 2016

End point values	Rituximab+Chemotherapy	Obinutuzumab+Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	710	704		
Units: percentage of subjects				
number (not applicable)				
Without PET (n= 712, 706)	34.4	39.1		

With PET (n=665, 669)	65.3	66.7		
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Statistical analyses

No statistical analyses for this end point

Secondary: Median Time to Event-Free Survival (EFS), Investigator-Assessed

End point title	Median Time to Event-Free Survival (EFS), Investigator-Assessed
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End point description:

Kaplan Meier estimate of median EFS is the time at which half of the subjects have progressed. Event-free survival was defined as the time from the date of randomization until the date of disease progression, relapse, initiation of a new non-protocol-specified anti-lymphoma treatment, or death from any cause on the basis of investigator assessments with the use of Revised Response Criteria for Malignant Lymphoma. Disease progression/relapse was defined as at least 50% increase in nodal lesions or $\geq 50\%$ increase in any node > 1 centimeter (cm) or $\geq 50\%$ increase in other target measurable lesions (e.g., splenic or hepatic nodules) and/or appearance of any new bone marrow involvement and/or appearance of any new lesion > 1.5 cm or $\geq 50\%$ increase in any previously involved node with a diameter ≤ 1 cm such that it is now > 1.5 cm. Tumor measurements were obtained by CT/MRI. 9.999 and 9999 = The confidence intervals could not be estimated as too few subjects had an event.

End point type	Secondary
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End point timeframe:

Baseline up to death or disease progression, or initiation of new anti-lymphoma treatment (NALT), whichever occurred first, to data cut-off (up to 31 January 2018)

End point values	Rituximab+Chemotherapy	Obinutuzumab+Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	710	704		
Units: months				
median (confidence interval 95%)	74.5 (9.999 to 9999)	68.3 (68.3 to 9999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Median Time to Disease-Free Survival (DFS), Investigator-Assessed

End point title	Median Time to Disease-Free Survival (DFS), Investigator-Assessed
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End point description:

Kaplan Meier estimate of median DFS was defined as time at which half of subjects have disease progression/relapse or death from any cause. Disease-free survival was defined as time from date of first occurrence of a documented CR to date of disease progression/relapse or death from any cause on basis of investigator assessments with use of Revised Response Criteria for Malignant Lymphoma. Tumor assessments were performed with CT/MRI. CR was defined as disappearance of all target lesions.

Progression/relapse was defined as at least 50% increase in nodal lesions or $\geq 50\%$ increase in any node $>1\text{cm}$ or $\geq 50\%$ increase in other target measurable lesions (ex. splenic or hepatic nodules) and/or appearance of any new bone marrow involvement and/or appearance of any new lesion $> 1.5\text{cm}$ or $\geq 50\%$ increase in any previously involved node with a diameter $\leq 1\text{cm}$ such that it is now $>1.5\text{cm}$. 9.999 and 9999 = Median and corresponding 95% CI could not be estimated as too few subjects had an event.

End point type	Secondary
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End point timeframe:

Baseline up to death or disease progression, whichever occurred first, to data cut-off (up to 31 January 2018)

End point values	Rituximab+Chemotherapy	Obinutuzumab+Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	394	417		
Units: months				
median (confidence interval 95%)	9999 (9999 to 9999)	65.4 (9.999 to 9999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR), Investigator-Assessed

End point title	Duration of Response (DOR), Investigator-Assessed
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End point description:

DOR: time from first occurrence of CR or PR to disease progression/relapse, or death from any cause for subjects with a response of CR or PR. CR: disappearance of all target lesions. PR: $\geq 50\%$ decrease target lesions in up to six dominant lesions identified at baseline, no new lesions & no increase in size of the liver, spleen, or other nodes. Splenic & hepatic nodule regression $\geq 50\%$. Progression/relapse: at least 50% increase in nodal lesions or $\geq 50\%$ increase in any node $>1\text{ cm}$ or $\geq 50\%$ increase in other target lesions (ex, splenic or hepatic nodules) and/or any new bone marrow involvement and/or any new lesion $>1.5\text{ cm}$ or $\geq 50\%$ increase in any previously involved node with a diameter $\leq 1\text{ cm}$ such that it is now $>1.5\text{ cm}$. A subject in Rituximab+CHOP arm with longest follow-up, 53 months, had an event. Criterion for median was minimum time when survival went below 50%. 9.999 and 9999 =Not enough events to calculate median and range of confidence interval.

End point type	Secondary
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End point timeframe:

Baseline up to death or disease progression, whichever occurred first, to data cut-off (up to 31 January 2018)

End point values	Rituximab+Chemotherapy	Obinutuzumab+Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	641	657		
Units: months				
median (confidence interval 95%)	71.9 (9.999 to 9999)	9999 (65.4 to 9999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Next Anti-Lymphoma Treatment (TTNALT)

End point title	Time to Next Anti-Lymphoma Treatment (TTNALT)
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End point description:

Time to next anti-lymphoma treatment was defined as the time from the date of randomization to the start date of the next anti-lymphoma treatment or death from any cause. 9999 = Not enough events to calculate median and range of confidence interval.

End point type	Secondary
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End point timeframe:

Baseline up to start of next anti-lymphoma treatment or death due to any cause, whichever occurred first, to data cut-off (31 January 2018)

End point values	Rituximab+Chemotherapy	Obinutuzumab+Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	710	704		
Units: months				
median (confidence interval 95%)	9999 (74.5 to 9999)	9999 (9999 to 9999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Functional Assessment of Cancer Therapy-Lymphoma (FACT-Lym) Subscale Score

End point title	Change From Baseline in Functional Assessment of Cancer Therapy-Lymphoma (FACT-Lym) Subscale Score
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End point description:

The FACT-Lym subscale was developed to assess health-related quality of life in patients with non-Hodgkin lymphoma. The score range is 0-60, with higher scores indicating better outcomes. A positive change from baseline indicates an improvement. 9999=NE=Not estimable based on 0 or 1 subject evaluated.

End point type	Secondary
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End point timeframe:

Baseline (pre-dose [Hour 0] on C1D1), C3D1, end of treatment (up to Month 6), every 12 months thereafter up to data cut-off of 31 January 2018, (cycle length = 21 days)

End point values	Rituximab+Chemotherapy	Obinutuzumab+Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	710	704		
Units: score on a scale				
arithmetic mean (standard deviation)				
Baseline (n=607, 639)	45.34 (± 10.16)	45.18 (± 9.86)		
Score Change, Cycle 3 Day 1 (n=553, 563)	3.83 (± 8.65)	3.70 (± 9.13)		
Score Change, Study Compl./Discont. (n=526, 527)	5.03 (± 10.21)	4.35 (± 11.03)		
Score Change, Follow-Up Month 12 (n=371, 411)	6.37 (± 10.12)	6.18 (± 10.51)		
Score Change, Follow-Up Month 24 (n=335, 372)	7.07 (± 10.35)	6.66 (± 10.50)		
Score Change, Follow-Up Month 30 (n=0, 1)	9999 (± 9999)	25.00 (± 9999)		
Score Change, Follow-Up Month 36 (n=317, 353)	7.57 (± 10.16)	7.31 (± 10.67)		
Score Change, Follow-Up Month 48 (n=167, 192)	8.22 (± 9.65)	7.37 (± 10.45)		
Score Change, Follow-Up Term./Compl. (n=121, 135)	5.51 (± 10.04)	5.55 (± 10.62)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in European Organization for Research and Treatment of Cancer Quality of Life Core 30 (EORTC QLQ-C30) Domain Scores

End point title	Change From Baseline in European Organization for Research and Treatment of Cancer Quality of Life Core 30 (EORTC QLQ-C30) Domain Scores
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End point description:

The EORTC QLQ-C30 is a health-related quality of life questionnaire. A higher score indicates better quality of life, with changes of 5 to 10 points considered to be a minimally important difference to participants. 9999=NE=Not estimable based on 0 or 1 subject evaluated.

End point type	Secondary
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End point timeframe:

Baseline (pre-dose [Hour 0] on C1D1), C3D1, end of treatment (up to Month 6), every 12 months thereafter up to data cut-off of 31 January 2018, (cycle length = 21 days)

End point values	Rituximab+Chemotherapy	Obinutuzumab+Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	710	704		
Units: score on a scale				
arithmetic mean (standard deviation)				
Baseline (n=610, 641)	59.81 (± 24.39)	58.55 (± 25.23)		
Change Baseline, C1 D1 (n=0, 0)	9999 (± 9999)	9999 (± 9999)		
Change Baseline, C3 D1 (n=556, 565)	6.37 (± 23.77)	7.51 (± 25.99)		
Change Baseline, Study Completion (n=526, 530)	9.84 (± 25.96)	10.22 (± 30.17)		
Change Baseline, Follow Up Month 12 (n=371, 413)	12.67 (± 26.31)	13.84 (± 29.97)		
Change Baseline, Foll-Up Month 24 (n=337, 370)	14.74 (± 26.33)	15.81 (± 29.24)		
Change Baseline, Foll-Up Month 30 (n=0, 1)	9999 (± 9999)	58.33 (± 9999)		
Change Baseline, Foll-Up Month 36 (n=321, 352)	15.01 (± 26.85)	17.99 (± 28.85)		
Change Baseline, Foll-Up Month 48 (n=168, 193)	16.62 (± 27.49)	17.53 (± 30.31)		
Change Baseline, Foll-Up Completion (n=122, 136)	8.74 (± 29.40)	8.46 (± 28.71)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Adverse Events (AEs)

End point title	Percentage of Subjects With Adverse Events (AEs)
End point description:	
An adverse event is any untoward medical occurrence in a subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with the treatment. An adverse event can therefore be any unfavorable 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. Preexisting conditions which worsen during a study are also considered as adverse events.	
End point type	Secondary
End point timeframe:	
Baseline up to data cut-off (up to 31 January 2018)	

End point values	Rituximab+Chemotherapy	Obinutuzumab+Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	701	702		
Units: percentage of subjects				
number (not applicable)	95.3	98.1		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Human Anti-Human Antibodies (HAHAs) to Obinutuzumab

End point title	Percentage of Subjects With Human Anti-Human Antibodies (HAHAs) to Obinutuzumab ^[1]
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End point description:

The presence of HAHAs to obinutuzumab was assessed in the first 100 randomized subjects.

End point type	Secondary
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End point timeframe:

Pre-dose (Hour 0) on Cycle (C) 4 Day (D) 1, at end of treatment/early termination (up to Month 6), every 6 months thereafter for 30 months (cycle length = 21 days)

Notes:

[1] - 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: There is no statistics associated with this endpoint.

End point values	Obinutuzumab + Chemotherapy			
Subject group type	Reporting group			
Number of subjects analysed	100			
Units: percentage of subjects				
number (not applicable)				
Screening (n=100)	2.0			
Cycle 4 Day 1 (n=86)	0			
Study Completion / Early Discontinuation (n=65)	0			
Follow-Up Month 6 (n=40)	0			
Follow-Up Month 12 (n=40)	0			
Follow-Up Month 18 (n=27)	0			
Follow-Up Month 24 (n=25)	0			
Follow-Up Month 30 (n=19)	0			
Follow-Up Completion/ Early Discontinuation (n=46)	0			
Unscheduled (n=3)	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Serum Concentrations of Obinutuzumab in Japanese Subjects with Diffuse Large B-Cell Lymphoma (DLBCL)

End point title	Serum Concentrations of Obinutuzumab in Japanese Subjects with Diffuse Large B-Cell Lymphoma (DLBCL) ^[2]
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End point description:

Serum samples for assessment of obinutuzumab serum concentrations were collected only from a subset of Japanese subjects following administration of 1000 mg obinutuzumab. The analysis of this endpoint was based on the primary analysis that occurred on 29 April 2016.

End point type	Secondary
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End point timeframe:

C1: D1 post-infusion and 20-28 and 66-80 hours after end of infusion, D8 and D15 pre-and post-infusion; C2: D1 pre- and post-infusion; C4: D1 pre- and post-infusion; C6: D1 pre- and post-infusion; C8: D1 pre- and post-infusion (cycle length = 21 days)

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: There is no statistics associated with this endpoint.

End point values	Obinutuzumab +Chemotherapy			
Subject group type	Reporting group			
Number of subjects analysed	39			
Units: micrograms per milliliter (µg/mL)				
geometric mean (geometric coefficient of variation)				
Cycle 1, Day 8 pre-infusion	174 (± 38.7)			
Cycle 1, Day 15 pre-infusion	320 (± 39.2)			
Cycle 2, Day 1 pre-infusion	431 (± 39.8)			
Cycle 4, Day 1 pre-infusion	352 (± 42.1)			
Cycle 6, Day 1 pre-infusion	378 (± 45.9)			
Cycle 8, Day 1 pre-infusion	478 (± 43.9)			
Cycle 1, Day 1 post-infusion	435 (± 32.3)			
Cycle 1, Day 1 20-28 hours after end of infusion	259 (± 56.3)			
Cycle 1, Day 1 66-80 hours after end of infusion	219 (± 51.2)			
Cycle 1, Day 8 post-infusion	578 (± 37.8)			
Cycle 1, Day 15 post-infusion	718 (± 32.9)			
Cycle 2, Day 1 post-infusion	938 (± 31.3)			
Cycle 4, Day 1 post-infusion	817 (± 28.6)			
Cycle 6, Day 1 post-infusion	813 (± 32.6)			
Cycle 8, Day 1 post-infusion	881 (± 35.9)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

6 years and 7 months

Adverse event reporting additional description:

The safety analysis population included all participants who received at least one dose of study drug (i.e., obinutuzumab, rituximab, or CHOP). Because of serious Good Clinical Practice non-compliance at a single study site in China, all 4 patients enrolled at the site (2 in each treatment arm) were excluded from the final analysis.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	21.0
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Reporting groups

Reporting group title	Obinutuzumab+Chemotherapy
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Reporting group description:

Participants received eight 21-day cycles of obinutuzumab, combined with six or eight cycles of standard cyclophosphamide, doxorubicin, vincristine, and prednisone/prednisolone (CHOP) chemotherapy (21-day cycles). Participants received an additional two doses of obinutuzumab on Days 8 and 15 of Cycle 1. Prior to study start, study centers chose whether they planned to administer 6 or 8 cycles of CHOP chemotherapy.

Reporting group title	Rituximab+Chemotherapy
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Reporting group description:

Participants received eight 21-day cycles of rituximab, combined with six or eight cycles of standard cyclophosphamide, doxorubicin, vincristine, and prednisone/prednisolone (CHOP) chemotherapy (21-day cycles). Prior to study start, study centers chose whether they planned to administer 6 or 8 cycles of CHOP chemotherapy.

Serious adverse events	Obinutuzumab+Chemotherapy	Rituximab+Chemotherapy	
Total subjects affected by serious adverse events			
subjects affected / exposed	312 / 702 (44.44%)	269 / 701 (38.37%)	
number of deaths (all causes)	149	141	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute myeloid leukaemia			
subjects affected / exposed	1 / 702 (0.14%)	2 / 701 (0.29%)	
occurrences causally related to treatment / all	0 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Adenocarcinoma of colon			
subjects affected / exposed	0 / 702 (0.00%)	2 / 701 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

B-cell lymphoma			
subjects affected / exposed	0 / 702 (0.00%)	1 / 701 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cancer			
subjects affected / exposed	1 / 702 (0.14%)	3 / 701 (0.43%)	
occurrences causally related to treatment / all	0 / 1	1 / 3	
deaths causally related to treatment / all	0 / 1	0 / 0	
Colon adenoma			
subjects affected / exposed	1 / 702 (0.14%)	0 / 701 (0.00%)	
occurrences causally related to treatment / all	0 / 10	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon cancer			
subjects affected / exposed	0 / 702 (0.00%)	2 / 701 (0.29%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Colorectal cancer			
subjects affected / exposed	1 / 702 (0.14%)	1 / 701 (0.14%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liposarcoma			
subjects affected / exposed	1 / 702 (0.14%)	0 / 701 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung adenocarcinoma			
subjects affected / exposed	3 / 702 (0.43%)	2 / 701 (0.29%)	
occurrences causally related to treatment / all	1 / 3	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Marginal zone lymphoma			
subjects affected / exposed	0 / 702 (0.00%)	1 / 701 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal carcinoma			

subjects affected / exposed	0 / 702 (0.00%)	1 / 701 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Papillary cystadenoma lymphomatosum			
subjects affected / exposed	1 / 702 (0.14%)	0 / 701 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer			
subjects affected / exposed	2 / 702 (0.28%)	2 / 701 (0.29%)	
occurrences causally related to treatment / all	0 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small cell lung cancer metastatic			
subjects affected / exposed	1 / 702 (0.14%)	0 / 701 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour perforation			
subjects affected / exposed	1 / 702 (0.14%)	0 / 701 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatocellular carcinoma			
subjects affected / exposed	2 / 702 (0.28%)	1 / 701 (0.14%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 2	0 / 1	
Angioimmunoblastic T-cell lymphoma			
subjects affected / exposed	1 / 702 (0.14%)	0 / 701 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myelodysplastic syndrome			
subjects affected / exposed	1 / 702 (0.14%)	0 / 701 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Squamous cell carcinoma of pharynx			

subjects affected / exposed	0 / 702 (0.00%)	1 / 701 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Lung neoplasm malignant			
subjects affected / exposed	1 / 702 (0.14%)	0 / 701 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Plasma cell myeloma			
subjects affected / exposed	0 / 702 (0.00%)	1 / 701 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	2 / 702 (0.28%)	0 / 701 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage			
subjects affected / exposed	1 / 702 (0.14%)	0 / 701 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Hypertension			
subjects affected / exposed	1 / 702 (0.14%)	0 / 701 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	3 / 702 (0.43%)	2 / 701 (0.29%)	
occurrences causally related to treatment / all	1 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orthostatic hypotension			
subjects affected / exposed	0 / 702 (0.00%)	1 / 701 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Phlebitis			

subjects affected / exposed	1 / 702 (0.14%)	0 / 701 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombophlebitis			
subjects affected / exposed	0 / 702 (0.00%)	2 / 701 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombophlebitis superficial			
subjects affected / exposed	1 / 702 (0.14%)	0 / 701 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous occlusion			
subjects affected / exposed	1 / 702 (0.14%)	0 / 701 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous thrombosis limb			
subjects affected / exposed	1 / 702 (0.14%)	0 / 701 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Axillary vein thrombosis			
subjects affected / exposed	0 / 702 (0.00%)	1 / 701 (0.14%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jugular vein thrombosis			
subjects affected / exposed	0 / 702 (0.00%)	1 / 701 (0.14%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subclavian vein thrombosis			
subjects affected / exposed	0 / 702 (0.00%)	1 / 701 (0.14%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			

subjects affected / exposed	2 / 702 (0.28%)	4 / 701 (0.57%)	
occurrences causally related to treatment / all	2 / 2	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Axillary pain			
subjects affected / exposed	1 / 702 (0.14%)	0 / 701 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	0 / 702 (0.00%)	2 / 701 (0.29%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chills			
subjects affected / exposed	2 / 702 (0.28%)	1 / 701 (0.14%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	3 / 702 (0.43%)	2 / 701 (0.29%)	
occurrences causally related to treatment / all	0 / 3	2 / 2	
deaths causally related to treatment / all	0 / 3	2 / 2	
Extravasation			
subjects affected / exposed	0 / 702 (0.00%)	1 / 701 (0.14%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	4 / 702 (0.57%)	5 / 701 (0.71%)	
occurrences causally related to treatment / all	1 / 4	4 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	2 / 702 (0.28%)	1 / 701 (0.14%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hernia			

subjects affected / exposed	1 / 702 (0.14%)	0 / 701 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Hyperpyrexia		
subjects affected / exposed	1 / 702 (0.14%)	0 / 701 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Incarcerated hernia		
subjects affected / exposed	1 / 702 (0.14%)	0 / 701 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Malaise		
subjects affected / exposed	2 / 702 (0.28%)	0 / 701 (0.00%)
occurrences causally related to treatment / all	3 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Mucosal inflammation		
subjects affected / exposed	1 / 702 (0.14%)	1 / 701 (0.14%)
occurrences causally related to treatment / all	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Non-cardiac chest pain		
subjects affected / exposed	0 / 702 (0.00%)	2 / 701 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Oedema peripheral		
subjects affected / exposed	2 / 702 (0.28%)	0 / 701 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Pain		
subjects affected / exposed	0 / 702 (0.00%)	1 / 701 (0.14%)
occurrences causally related to treatment / all	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Peripheral swelling		

subjects affected / exposed	0 / 702 (0.00%)	1 / 701 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	17 / 702 (2.42%)	11 / 701 (1.57%)	
occurrences causally related to treatment / all	11 / 23	10 / 14	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden death			
subjects affected / exposed	1 / 702 (0.14%)	1 / 701 (0.14%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	1 / 1	1 / 1	
Reproductive system and breast disorders			
Uterine haemorrhage			
subjects affected / exposed	1 / 702 (0.14%)	0 / 701 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acquired tracheo-oesophageal fistula			
subjects affected / exposed	1 / 702 (0.14%)	0 / 701 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute pulmonary oedema			
subjects affected / exposed	1 / 702 (0.14%)	0 / 701 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory distress syndrome			
subjects affected / exposed	1 / 702 (0.14%)	1 / 701 (0.14%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	1 / 1	0 / 0	
Acute respiratory failure			
subjects affected / exposed	1 / 702 (0.14%)	3 / 701 (0.43%)	
occurrences causally related to treatment / all	0 / 2	1 / 3	
deaths causally related to treatment / all	0 / 1	1 / 1	

Alveolitis			
subjects affected / exposed	1 / 702 (0.14%)	0 / 701 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthma			
subjects affected / exposed	1 / 702 (0.14%)	0 / 701 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchial obstruction			
subjects affected / exposed	0 / 702 (0.00%)	1 / 701 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchospasm			
subjects affected / exposed	1 / 702 (0.14%)	1 / 701 (0.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	2 / 702 (0.28%)	1 / 701 (0.14%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	2 / 702 (0.28%)	1 / 701 (0.14%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Dyspnoea exertional			
subjects affected / exposed	1 / 702 (0.14%)	0 / 701 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Emphysema			
subjects affected / exposed	2 / 702 (0.28%)	0 / 701 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			

subjects affected / exposed	1 / 702 (0.14%)	0 / 701 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Haemothorax		
subjects affected / exposed	1 / 702 (0.14%)	0 / 701 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Hypoxia		
subjects affected / exposed	1 / 702 (0.14%)	1 / 701 (0.14%)
occurrences causally related to treatment / all	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Interstitial lung disease		
subjects affected / exposed	3 / 702 (0.43%)	6 / 701 (0.86%)
occurrences causally related to treatment / all	3 / 3	4 / 6
deaths causally related to treatment / all	0 / 0	0 / 1
Lung infiltration		
subjects affected / exposed	1 / 702 (0.14%)	0 / 701 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Organising pneumonia		
subjects affected / exposed	0 / 702 (0.00%)	1 / 701 (0.14%)
occurrences causally related to treatment / all	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Pleural effusion		
subjects affected / exposed	4 / 702 (0.57%)	2 / 701 (0.29%)
occurrences causally related to treatment / all	0 / 4	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Pneumonia aspiration		
subjects affected / exposed	1 / 702 (0.14%)	0 / 701 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Pneumonitis		

subjects affected / exposed	5 / 702 (0.71%)	1 / 701 (0.14%)	
occurrences causally related to treatment / all	3 / 5	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	1 / 702 (0.14%)	1 / 701 (0.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	4 / 702 (0.57%)	4 / 701 (0.57%)	
occurrences causally related to treatment / all	1 / 4	0 / 4	
deaths causally related to treatment / all	0 / 2	0 / 0	
Pulmonary fibrosis			
subjects affected / exposed	1 / 702 (0.14%)	0 / 701 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			
subjects affected / exposed	1 / 702 (0.14%)	0 / 701 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Respiratory failure			
subjects affected / exposed	0 / 702 (0.00%)	2 / 701 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cough			
subjects affected / exposed	1 / 702 (0.14%)	0 / 701 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 702 (0.14%)	0 / 701 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Completed suicide			

subjects affected / exposed	1 / 702 (0.14%)	0 / 701 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Delirium			
subjects affected / exposed	1 / 702 (0.14%)	0 / 701 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
subjects affected / exposed	0 / 702 (0.00%)	1 / 701 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Emotional distress			
subjects affected / exposed	1 / 702 (0.14%)	0 / 701 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental status changes			
subjects affected / exposed	1 / 702 (0.14%)	0 / 701 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Ejection fraction decreased			
subjects affected / exposed	1 / 702 (0.14%)	0 / 701 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HIV antibody positive			
subjects affected / exposed	1 / 702 (0.14%)	0 / 701 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oxygen saturation decreased			
subjects affected / exposed	0 / 702 (0.00%)	1 / 701 (0.14%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			

Abdominal wound dehiscence			
subjects affected / exposed	0 / 702 (0.00%)	1 / 701 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Facial bones fracture			
subjects affected / exposed	0 / 702 (0.00%)	1 / 701 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	1 / 702 (0.14%)	0 / 701 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral neck fracture			
subjects affected / exposed	0 / 702 (0.00%)	1 / 701 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	1 / 702 (0.14%)	2 / 701 (0.29%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fracture			
subjects affected / exposed	1 / 702 (0.14%)	0 / 701 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	1 / 702 (0.14%)	1 / 701 (0.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infusion related reaction			
subjects affected / exposed	8 / 702 (1.14%)	1 / 701 (0.14%)	
occurrences causally related to treatment / all	8 / 8	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Kidney rupture			

subjects affected / exposed	0 / 702 (0.00%)	1 / 701 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar vertebral fracture			
subjects affected / exposed	0 / 702 (0.00%)	1 / 701 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nerve injury			
subjects affected / exposed	1 / 702 (0.14%)	0 / 701 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic fracture			
subjects affected / exposed	1 / 702 (0.14%)	0 / 701 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative respiratory failure			
subjects affected / exposed	1 / 702 (0.14%)	0 / 701 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural complication			
subjects affected / exposed	1 / 702 (0.14%)	0 / 701 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal compression fracture			
subjects affected / exposed	0 / 702 (0.00%)	1 / 701 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haematoma			
subjects affected / exposed	3 / 702 (0.43%)	0 / 701 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Toxicity to various agents			

subjects affected / exposed	1 / 702 (0.14%)	0 / 701 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular pseudoaneurysm			
subjects affected / exposed	0 / 702 (0.00%)	1 / 701 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound haemorrhage			
subjects affected / exposed	1 / 702 (0.14%)	0 / 701 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Compression fracture			
subjects affected / exposed	1 / 702 (0.14%)	0 / 701 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	1 / 702 (0.14%)	0 / 701 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	2 / 702 (0.28%)	5 / 701 (0.71%)	
occurrences causally related to treatment / all	0 / 2	2 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	0 / 702 (0.00%)	2 / 701 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	9 / 702 (1.28%)	4 / 701 (0.57%)	
occurrences causally related to treatment / all	3 / 10	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			

subjects affected / exposed	1 / 702 (0.14%)	1 / 701 (0.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			
subjects affected / exposed	1 / 702 (0.14%)	0 / 701 (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	1 / 702 (0.14%)	1 / 701 (0.14%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 1	1 / 1	
Cardiac failure			
subjects affected / exposed	7 / 702 (1.00%)	3 / 701 (0.43%)	
occurrences causally related to treatment / all	3 / 7	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac failure congestive			
subjects affected / exposed	3 / 702 (0.43%)	1 / 701 (0.14%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac perforation			
subjects affected / exposed	1 / 702 (0.14%)	0 / 701 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiomyopathy			
subjects affected / exposed	1 / 702 (0.14%)	0 / 701 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiopulmonary failure			
subjects affected / exposed	0 / 702 (0.00%)	1 / 701 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Congestive cardiomyopathy			

subjects affected / exposed	0 / 702 (0.00%)	1 / 701 (0.14%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease			
subjects affected / exposed	0 / 702 (0.00%)	1 / 701 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery thrombosis			
subjects affected / exposed	1 / 702 (0.14%)	0 / 701 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hypertensive heart disease			
subjects affected / exposed	1 / 702 (0.14%)	0 / 701 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left ventricular dysfunction			
subjects affected / exposed	1 / 702 (0.14%)	0 / 701 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mitral valve disease			
subjects affected / exposed	1 / 702 (0.14%)	0 / 701 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	3 / 702 (0.43%)	2 / 701 (0.29%)	
occurrences causally related to treatment / all	2 / 3	0 / 2	
deaths causally related to treatment / all	1 / 1	0 / 0	
Myocardial ischaemia			
subjects affected / exposed	0 / 702 (0.00%)	1 / 701 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial effusion			

subjects affected / exposed	1 / 702 (0.14%)	0 / 701 (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	0 / 702 (0.00%)	1 / 701 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular flutter			
subjects affected / exposed	1 / 702 (0.14%)	0 / 701 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Amyotrophic lateral sclerosis			
subjects affected / exposed	1 / 702 (0.14%)	0 / 701 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haemorrhage			
subjects affected / exposed	1 / 702 (0.14%)	0 / 701 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral infarction			
subjects affected / exposed	0 / 702 (0.00%)	1 / 701 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral ischaemia			
subjects affected / exposed	1 / 702 (0.14%)	1 / 701 (0.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	3 / 702 (0.43%)	2 / 701 (0.29%)	
occurrences causally related to treatment / all	0 / 3	1 / 2	
deaths causally related to treatment / all	0 / 2	1 / 2	
Depressed level of consciousness			

subjects affected / exposed	1 / 702 (0.14%)	0 / 701 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Dizziness		
subjects affected / exposed	2 / 702 (0.28%)	0 / 701 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Embolic stroke		
subjects affected / exposed	0 / 702 (0.00%)	1 / 701 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Epilepsy		
subjects affected / exposed	0 / 702 (0.00%)	1 / 701 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Headache		
subjects affected / exposed	3 / 702 (0.43%)	2 / 701 (0.29%)
occurrences causally related to treatment / all	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Hemiparesis		
subjects affected / exposed	1 / 702 (0.14%)	0 / 701 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Iiird nerve paralysis		
subjects affected / exposed	1 / 702 (0.14%)	0 / 701 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Ischaemic stroke		
subjects affected / exposed	1 / 702 (0.14%)	0 / 701 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Loss of consciousness		

subjects affected / exposed	0 / 702 (0.00%)	1 / 701 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuropathy peripheral			
subjects affected / exposed	1 / 702 (0.14%)	1 / 701 (0.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral motor neuropathy			
subjects affected / exposed	0 / 702 (0.00%)	1 / 701 (0.14%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 702 (0.00%)	1 / 701 (0.14%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polyneuropathy			
subjects affected / exposed	0 / 702 (0.00%)	1 / 701 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Presyncope			
subjects affected / exposed	2 / 702 (0.28%)	1 / 701 (0.14%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stroke in evolution			
subjects affected / exposed	1 / 702 (0.14%)	0 / 701 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	0 / 702 (0.00%)	3 / 701 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxic encephalopathy			

subjects affected / exposed	0 / 702 (0.00%)	1 / 701 (0.14%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Transient ischaemic attack			
subjects affected / exposed	0 / 702 (0.00%)	1 / 701 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vocal cord paralysis			
subjects affected / exposed	0 / 702 (0.00%)	1 / 701 (0.14%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	1 / 702 (0.14%)	0 / 701 (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			
Anaemia			
subjects affected / exposed	9 / 702 (1.28%)	6 / 701 (0.86%)	
occurrences causally related to treatment / all	7 / 10	6 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	85 / 702 (12.11%)	71 / 701 (10.13%)	
occurrences causally related to treatment / all	101 / 107	85 / 88	
deaths causally related to treatment / all	1 / 1	0 / 0	
Haemolytic anaemia			
subjects affected / exposed	0 / 702 (0.00%)	1 / 701 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Histiocytosis haematophagic			
subjects affected / exposed	1 / 702 (0.14%)	0 / 701 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Immune thrombocytopenic purpura			

subjects affected / exposed	1 / 702 (0.14%)	0 / 701 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			
subjects affected / exposed	14 / 702 (1.99%)	6 / 701 (0.86%)	
occurrences causally related to treatment / all	14 / 14	6 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	54 / 702 (7.69%)	38 / 701 (5.42%)	
occurrences causally related to treatment / all	56 / 60	39 / 40	
deaths causally related to treatment / all	0 / 0	0 / 0	
Splenic haematoma			
subjects affected / exposed	1 / 702 (0.14%)	0 / 701 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	12 / 702 (1.71%)	2 / 701 (0.29%)	
occurrences causally related to treatment / all	13 / 15	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone Marrow Failure			
subjects affected / exposed	0 / 702 (0.00%)	1 / 701 (0.14%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo positional			
subjects affected / exposed	1 / 702 (0.14%)	0 / 701 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Cataract			
subjects affected / exposed	0 / 702 (0.00%)	2 / 701 (0.29%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lacrimation increased			

subjects affected / exposed	1 / 702 (0.14%)	0 / 701 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	4 / 702 (0.57%)	6 / 701 (0.86%)	
occurrences causally related to treatment / all	2 / 5	1 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	2 / 702 (0.28%)	1 / 701 (0.14%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal fistula			
subjects affected / exposed	0 / 702 (0.00%)	1 / 701 (0.14%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	2 / 702 (0.28%)	2 / 701 (0.29%)	
occurrences causally related to treatment / all	1 / 2	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	0 / 702 (0.00%)	1 / 701 (0.14%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	5 / 702 (0.71%)	6 / 701 (0.86%)	
occurrences causally related to treatment / all	3 / 7	2 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	1 / 702 (0.14%)	0 / 701 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric haemorrhage			

subjects affected / exposed	1 / 702 (0.14%)	2 / 701 (0.29%)
occurrences causally related to treatment / all	1 / 1	2 / 2
deaths causally related to treatment / all	0 / 0	1 / 1
Gastric perforation		
subjects affected / exposed	1 / 702 (0.14%)	3 / 701 (0.43%)
occurrences causally related to treatment / all	0 / 1	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0
Gastric ulcer		
subjects affected / exposed	1 / 702 (0.14%)	0 / 701 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Gastritis		
subjects affected / exposed	1 / 702 (0.14%)	0 / 701 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Gastritis haemorrhagic		
subjects affected / exposed	1 / 702 (0.14%)	0 / 701 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Gastrointestinal haemorrhage		
subjects affected / exposed	2 / 702 (0.28%)	3 / 701 (0.43%)
occurrences causally related to treatment / all	2 / 2	2 / 3
deaths causally related to treatment / all	0 / 0	0 / 1
Haematemesis		
subjects affected / exposed	1 / 702 (0.14%)	0 / 701 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Haematochezia		
subjects affected / exposed	0 / 702 (0.00%)	1 / 701 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Haemorrhoids		

subjects affected / exposed	2 / 702 (0.28%)	0 / 701 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Ileal perforation		
subjects affected / exposed	1 / 702 (0.14%)	0 / 701 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Ileus		
subjects affected / exposed	1 / 702 (0.14%)	2 / 701 (0.29%)
occurrences causally related to treatment / all	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Ileus paralytic		
subjects affected / exposed	0 / 702 (0.00%)	1 / 701 (0.14%)
occurrences causally related to treatment / all	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Impaired gastric emptying		
subjects affected / exposed	0 / 702 (0.00%)	1 / 701 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1
Inguinal hernia		
subjects affected / exposed	1 / 702 (0.14%)	1 / 701 (0.14%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Intestinal ischaemia		
subjects affected / exposed	1 / 702 (0.14%)	0 / 701 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0
Intestinal obstruction		
subjects affected / exposed	2 / 702 (0.28%)	5 / 701 (0.71%)
occurrences causally related to treatment / all	1 / 2	3 / 5
deaths causally related to treatment / all	0 / 0	1 / 1
Intestinal perforation		

subjects affected / exposed	3 / 702 (0.43%)	3 / 701 (0.43%)	
occurrences causally related to treatment / all	2 / 3	2 / 3	
deaths causally related to treatment / all	0 / 0	1 / 1	
Large intestine polyp			
subjects affected / exposed	2 / 702 (0.28%)	0 / 701 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower gastrointestinal haemorrhage			
subjects affected / exposed	0 / 702 (0.00%)	1 / 701 (0.14%)	
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 / 702 (0.00%)	1 / 701 (0.14%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	1 / 702 (0.14%)	2 / 701 (0.29%)	
occurrences causally related to treatment / all	1 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	1 / 702 (0.14%)	0 / 701 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumoperitoneum			
subjects affected / exposed	1 / 702 (0.14%)	0 / 701 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	2 / 702 (0.28%)	1 / 701 (0.14%)	
occurrences causally related to treatment / all	1 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal perforation			

subjects affected / exposed	1 / 702 (0.14%)	1 / 701 (0.14%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			
subjects affected / exposed	0 / 702 (0.00%)	1 / 701 (0.14%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subileus			
subjects affected / exposed	1 / 702 (0.14%)	1 / 701 (0.14%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	3 / 702 (0.43%)	1 / 701 (0.14%)	
occurrences causally related to treatment / all	1 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	2 / 702 (0.28%)	2 / 701 (0.29%)	
occurrences causally related to treatment / all	3 / 3	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Bile duct obstruction			
subjects affected / exposed	1 / 702 (0.14%)	0 / 701 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	1 / 702 (0.14%)	2 / 701 (0.29%)	
occurrences causally related to treatment / all	0 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			
subjects affected / exposed	1 / 702 (0.14%)	1 / 701 (0.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			

subjects affected / exposed	0 / 702 (0.00%)	1 / 701 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic function abnormal			
subjects affected / exposed	0 / 702 (0.00%)	1 / 701 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Diabetic foot			
subjects affected / exposed	0 / 702 (0.00%)	1 / 701 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin ulcer			
subjects affected / exposed	2 / 702 (0.28%)	1 / 701 (0.14%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	2 / 702 (0.28%)	2 / 701 (0.29%)	
occurrences causally related to treatment / all	1 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis glandularis			
subjects affected / exposed	1 / 702 (0.14%)	0 / 701 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	2 / 702 (0.28%)	0 / 701 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal colic			
subjects affected / exposed	0 / 702 (0.00%)	1 / 701 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			

subjects affected / exposed	1 / 702 (0.14%)	1 / 701 (0.14%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal impairment			
subjects affected / exposed	1 / 702 (0.14%)	0 / 701 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	1 / 702 (0.14%)	0 / 701 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Addison's disease			
subjects affected / exposed	1 / 702 (0.14%)	0 / 701 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Goitre			
subjects affected / exposed	0 / 702 (0.00%)	1 / 701 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 702 (0.14%)	2 / 701 (0.29%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	2 / 702 (0.28%)	1 / 701 (0.14%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Costochondritis			
subjects affected / exposed	0 / 702 (0.00%)	1 / 701 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Intervertebral disc protrusion			
subjects affected / exposed	1 / 702 (0.14%)	0 / 701 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint swelling			
subjects affected / exposed	0 / 702 (0.00%)	1 / 701 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myalgia			
subjects affected / exposed	1 / 702 (0.14%)	0 / 701 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	1 / 702 (0.14%)	0 / 701 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	0 / 702 (0.00%)	1 / 701 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Anal abscess			
subjects affected / exposed	2 / 702 (0.28%)	0 / 701 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendiceal abscess			
subjects affected / exposed	1 / 702 (0.14%)	0 / 701 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	1 / 702 (0.14%)	3 / 701 (0.43%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atypical pneumonia			

subjects affected / exposed	0 / 702 (0.00%)	2 / 701 (0.29%)
occurrences causally related to treatment / all	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Bacterial infection		
subjects affected / exposed	0 / 702 (0.00%)	1 / 701 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Bacterial sepsis		
subjects affected / exposed	1 / 702 (0.14%)	0 / 701 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Bronchitis		
subjects affected / exposed	1 / 702 (0.14%)	4 / 701 (0.57%)
occurrences causally related to treatment / all	0 / 1	2 / 4
deaths causally related to treatment / all	0 / 0	0 / 0
Bronchopulmonary aspergillosis		
subjects affected / exposed	1 / 702 (0.14%)	1 / 701 (0.14%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 1
Candida sepsis		
subjects affected / exposed	0 / 702 (0.00%)	1 / 701 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1
Cellulitis		
subjects affected / exposed	2 / 702 (0.28%)	2 / 701 (0.29%)
occurrences causally related to treatment / all	1 / 2	2 / 3
deaths causally related to treatment / all	0 / 0	0 / 0
Cholecystitis infective		
subjects affected / exposed	1 / 702 (0.14%)	0 / 701 (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	1 / 702 (0.14%)	1 / 701 (0.14%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile infection			
subjects affected / exposed	1 / 702 (0.14%)	0 / 701 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus chorioretinitis			
subjects affected / exposed	3 / 702 (0.43%)	1 / 701 (0.14%)	
occurrences causally related to treatment / all	3 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus colitis			
subjects affected / exposed	1 / 702 (0.14%)	0 / 701 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus infection			
subjects affected / exposed	0 / 702 (0.00%)	2 / 701 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	1 / 702 (0.14%)	2 / 701 (0.29%)	
occurrences causally related to treatment / all	0 / 2	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related sepsis			
subjects affected / exposed	1 / 702 (0.14%)	0 / 701 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic foot infection			
subjects affected / exposed	0 / 702 (0.00%)	1 / 701 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea infectious			

subjects affected / exposed	2 / 702 (0.28%)	0 / 701 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Diverticulitis		
subjects affected / exposed	1 / 702 (0.14%)	0 / 701 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Enterocolitis infectious		
subjects affected / exposed	1 / 702 (0.14%)	0 / 701 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Escherichia sepsis		
subjects affected / exposed	0 / 702 (0.00%)	1 / 701 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1
Fungal infection		
subjects affected / exposed	0 / 702 (0.00%)	1 / 701 (0.14%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Gastroenteritis		
subjects affected / exposed	2 / 702 (0.28%)	3 / 701 (0.43%)
occurrences causally related to treatment / all	2 / 4	2 / 3
deaths causally related to treatment / all	0 / 0	0 / 0
H1N1 influenza		
subjects affected / exposed	1 / 702 (0.14%)	0 / 701 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Hepatitis B Reactivation		
subjects affected / exposed	1 / 702 (0.14%)	0 / 701 (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	1 / 702 (0.14%)	0 / 701 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Herpes virus infection		
subjects affected / exposed	2 / 702 (0.28%)	0 / 701 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Herpes zoster		
subjects affected / exposed	4 / 702 (0.57%)	3 / 701 (0.43%)
occurrences causally related to treatment / all	3 / 4	3 / 4
deaths causally related to treatment / all	0 / 0	0 / 0
Herpes zoster disseminated		
subjects affected / exposed	1 / 702 (0.14%)	0 / 701 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Infected lymphocele		
subjects affected / exposed	1 / 702 (0.14%)	0 / 701 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Infection		
subjects affected / exposed	2 / 702 (0.28%)	0 / 701 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0
Infectious pleural effusion		
subjects affected / exposed	2 / 702 (0.28%)	0 / 701 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Infective glossitis		
subjects affected / exposed	1 / 702 (0.14%)	0 / 701 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Influenza		

subjects affected / exposed	1 / 702 (0.14%)	2 / 701 (0.29%)	
occurrences causally related to treatment / all	1 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Klebsiella sepsis			
subjects affected / exposed	1 / 702 (0.14%)	1 / 701 (0.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngitis			
subjects affected / exposed	1 / 702 (0.14%)	0 / 701 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Localised infection			
subjects affected / exposed	0 / 702 (0.00%)	1 / 701 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	3 / 702 (0.43%)	1 / 701 (0.14%)	
occurrences causally related to treatment / all	3 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	6 / 702 (0.85%)	3 / 701 (0.43%)	
occurrences causally related to treatment / all	5 / 6	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Measles			
subjects affected / exposed	1 / 702 (0.14%)	0 / 701 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis			
subjects affected / exposed	1 / 702 (0.14%)	0 / 701 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis cryptococcal			

subjects affected / exposed	0 / 702 (0.00%)	1 / 701 (0.14%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis viral			
subjects affected / exposed	1 / 702 (0.14%)	0 / 701 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Nasopharyngitis			
subjects affected / exposed	0 / 702 (0.00%)	2 / 701 (0.29%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Necrotising fasciitis			
subjects affected / exposed	0 / 702 (0.00%)	1 / 701 (0.14%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic infection			
subjects affected / exposed	1 / 702 (0.14%)	1 / 701 (0.14%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic sepsis			
subjects affected / exposed	3 / 702 (0.43%)	3 / 701 (0.43%)	
occurrences causally related to treatment / all	3 / 3	5 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oral infection			
subjects affected / exposed	0 / 702 (0.00%)	2 / 701 (0.29%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orchitis			
subjects affected / exposed	0 / 702 (0.00%)	1 / 701 (0.14%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis			

subjects affected / exposed	1 / 702 (0.14%)	1 / 701 (0.14%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	1 / 1	0 / 0	
Peritonitis			
subjects affected / exposed	2 / 702 (0.28%)	2 / 701 (0.29%)	
occurrences causally related to treatment / all	0 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Pharyngitis streptococcal			
subjects affected / exposed	1 / 702 (0.14%)	0 / 701 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumocystis jirovecii pneumonia			
subjects affected / exposed	1 / 702 (0.14%)	3 / 701 (0.43%)	
occurrences causally related to treatment / all	1 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	43 / 702 (6.13%)	33 / 701 (4.71%)	
occurrences causally related to treatment / all	27 / 45	23 / 36	
deaths causally related to treatment / all	2 / 5	3 / 5	
Pneumonia bacterial			
subjects affected / exposed	1 / 702 (0.14%)	0 / 701 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Progressive multifocal leukoencephalopathy			
subjects affected / exposed	1 / 702 (0.14%)	0 / 701 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostatic abscess			
subjects affected / exposed	0 / 702 (0.00%)	1 / 701 (0.14%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pseudomonal sepsis			

subjects affected / exposed	0 / 702 (0.00%)	1 / 701 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary sepsis			
subjects affected / exposed	0 / 702 (0.00%)	1 / 701 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal abscess			
subjects affected / exposed	1 / 702 (0.14%)	1 / 701 (0.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	2 / 702 (0.28%)	0 / 701 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Scrotal abscess			
subjects affected / exposed	0 / 702 (0.00%)	1 / 701 (0.14%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	16 / 702 (2.28%)	10 / 701 (1.43%)	
occurrences causally related to treatment / all	10 / 17	8 / 10	
deaths causally related to treatment / all	1 / 1	2 / 3	
Sepsis syndrome			
subjects affected / exposed	1 / 702 (0.14%)	0 / 701 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	12 / 702 (1.71%)	3 / 701 (0.43%)	
occurrences causally related to treatment / all	6 / 12	2 / 3	
deaths causally related to treatment / all	3 / 6	0 / 0	
Sinusitis fungal			

subjects affected / exposed	1 / 702 (0.14%)	0 / 701 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Soft tissue infection			
subjects affected / exposed	0 / 702 (0.00%)	1 / 701 (0.14%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subcutaneous abscess			
subjects affected / exposed	1 / 702 (0.14%)	0 / 701 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tuberculosis			
subjects affected / exposed	0 / 702 (0.00%)	1 / 701 (0.14%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tuberculosis of central nervous system			
subjects affected / exposed	0 / 702 (0.00%)	1 / 701 (0.14%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	1 / 702 (0.14%)	1 / 701 (0.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	3 / 702 (0.43%)	3 / 701 (0.43%)	
occurrences causally related to treatment / all	2 / 5	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	1 / 702 (0.14%)	1 / 701 (0.14%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Varicella			

subjects affected / exposed	1 / 702 (0.14%)	1 / 701 (0.14%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			
subjects affected / exposed	1 / 702 (0.14%)	0 / 701 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral pharyngitis			
subjects affected / exposed	0 / 702 (0.00%)	1 / 701 (0.14%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			
subjects affected / exposed	1 / 702 (0.14%)	0 / 701 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterobacter infection			
subjects affected / exposed	1 / 702 (0.14%)	0 / 701 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anorectal cellulitis			
subjects affected / exposed	0 / 702 (0.00%)	1 / 701 (0.14%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal Infect			
subjects affected / exposed	0 / 702 (0.00%)	1 / 701 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Cachexia			
subjects affected / exposed	1 / 702 (0.14%)	0 / 701 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Decreased appetite			

subjects affected / exposed	2 / 702 (0.28%)	1 / 701 (0.14%)	
occurrences causally related to treatment / all	2 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	5 / 702 (0.71%)	4 / 701 (0.57%)	
occurrences causally related to treatment / all	3 / 5	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus			
subjects affected / exposed	1 / 702 (0.14%)	0 / 701 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Failure to thrive			
subjects affected / exposed	0 / 702 (0.00%)	3 / 701 (0.43%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hyperglycaemia			
subjects affected / exposed	0 / 702 (0.00%)	1 / 701 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	1 / 702 (0.14%)	0 / 701 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	2 / 702 (0.28%)	2 / 701 (0.29%)	
occurrences causally related to treatment / all	1 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	0 / 702 (0.00%)	2 / 701 (0.29%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypophosphataemia			

subjects affected / exposed	0 / 702 (0.00%)	1 / 701 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malnutrition			
subjects affected / exposed	1 / 702 (0.14%)	2 / 701 (0.29%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour lysis syndrome			
subjects affected / exposed	1 / 702 (0.14%)	2 / 701 (0.29%)	
occurrences causally related to treatment / all	1 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Obinutuzumab+Chemotherapy	Rituximab+Chemotherapy	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	646 / 702 (92.02%)	613 / 701 (87.45%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	40 / 702 (5.70%)	27 / 701 (3.85%)	
occurrences (all)	46	34	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	76 / 702 (10.83%)	74 / 701 (10.56%)	
occurrences (all)	95	84	
Chills			
subjects affected / exposed	132 / 702 (18.80%)	37 / 701 (5.28%)	
occurrences (all)	141	38	
Fatigue			
subjects affected / exposed	136 / 702 (19.37%)	124 / 701 (17.69%)	
occurrences (all)	184	152	
Mucosal inflammation			
subjects affected / exposed	45 / 702 (6.41%)	36 / 701 (5.14%)	
occurrences (all)	56	41	
Oedema peripheral			

subjects affected / exposed occurrences (all)	35 / 702 (4.99%) 38	40 / 701 (5.71%) 48	
Pyrexia subjects affected / exposed occurrences (all)	137 / 702 (19.52%) 183	75 / 701 (10.70%) 95	
Respiratory, thoracic and mediastinal disorders			
Cough subjects affected / exposed occurrences (all)	88 / 702 (12.54%) 100	66 / 701 (9.42%) 76	
Dyspnoea subjects affected / exposed occurrences (all)	52 / 702 (7.41%) 57	31 / 701 (4.42%) 31	
Oropharyngeal pain subjects affected / exposed occurrences (all)	43 / 702 (6.13%) 48	38 / 701 (5.42%) 40	
Psychiatric disorders			
Insomnia subjects affected / exposed occurrences (all)	79 / 702 (11.25%) 82	61 / 701 (8.70%) 66	
Investigations			
Alanine Aminotransferase Increased subjects affected / exposed occurrences (all)	39 / 702 (5.56%) 53	29 / 701 (4.14%) 36	
Injury, poisoning and procedural complications			
Infusion related reaction subjects affected / exposed occurrences (all)	251 / 702 (35.75%) 312	162 / 701 (23.11%) 192	
Nervous system disorders			
Dizziness subjects affected / exposed occurrences (all)	48 / 702 (6.84%) 53	29 / 701 (4.14%) 34	
Dysgeusia subjects affected / exposed occurrences (all)	44 / 702 (6.27%) 53	38 / 701 (5.42%) 42	
Headache			

subjects affected / exposed occurrences (all)	75 / 702 (10.68%) 83	58 / 701 (8.27%) 70	
Neuropathy peripheral subjects affected / exposed occurrences (all)	87 / 702 (12.39%) 95	88 / 701 (12.55%) 94	
Paraesthesia subjects affected / exposed occurrences (all)	55 / 702 (7.83%) 65	50 / 701 (7.13%) 53	
Peripheral sensory neuropathy subjects affected / exposed occurrences (all)	54 / 702 (7.69%) 62	57 / 701 (8.13%) 61	
Blood and lymphatic system disorders			
Anaemia subjects affected / exposed occurrences (all)	96 / 702 (13.68%) 142	101 / 701 (14.41%) 130	
Febrile neutropenia subjects affected / exposed occurrences (all)	52 / 702 (7.41%) 68	44 / 701 (6.28%) 61	
Leukopenia subjects affected / exposed occurrences (all)	117 / 702 (16.67%) 315	90 / 701 (12.84%) 263	
Neutropenia subjects affected / exposed occurrences (all)	315 / 702 (44.87%) 737	269 / 701 (38.37%) 707	
Thrombocytopenia subjects affected / exposed occurrences (all)	58 / 702 (8.26%) 73	16 / 701 (2.28%) 21	
Gastrointestinal disorders			
Abdominal pain subjects affected / exposed occurrences (all)	47 / 702 (6.70%) 54	47 / 701 (6.70%) 56	
Abdominal pain upper subjects affected / exposed occurrences (all)	38 / 702 (5.41%) 46	41 / 701 (5.85%) 45	
Constipation			

subjects affected / exposed occurrences (all)	167 / 702 (23.79%) 191	177 / 701 (25.25%) 212	
Diarrhoea subjects affected / exposed occurrences (all)	113 / 702 (16.10%) 149	91 / 701 (12.98%) 114	
Dyspepsia subjects affected / exposed occurrences (all)	44 / 702 (6.27%) 51	43 / 701 (6.13%) 47	
Nausea subjects affected / exposed occurrences (all)	210 / 702 (29.91%) 330	199 / 701 (28.39%) 274	
Stomatitis subjects affected / exposed occurrences (all)	47 / 702 (6.70%) 58	65 / 701 (9.27%) 82	
Vomiting subjects affected / exposed occurrences (all)	105 / 702 (14.96%) 145	75 / 701 (10.70%) 102	
Skin and subcutaneous tissue disorders			
Alopecia subjects affected / exposed occurrences (all)	148 / 702 (21.08%) 151	144 / 701 (20.54%) 146	
Rash subjects affected / exposed occurrences (all)	17 / 702 (2.42%) 20	45 / 701 (6.42%) 47	
Musculoskeletal and connective tissue disorders			
Back pain subjects affected / exposed occurrences (all)	58 / 702 (8.26%) 70	41 / 701 (5.85%) 48	
Arthralgia subjects affected / exposed occurrences (all)	37 / 702 (5.27%) 43	28 / 701 (3.99%) 34	
Infections and infestations			
Upper respiratory tract infection subjects affected / exposed occurrences (all)	43 / 702 (6.13%) 55	49 / 701 (6.99%) 57	
Metabolism and nutrition disorders			

Decreased appetite subjects affected / exposed occurrences (all)	98 / 702 (13.96%) 122	74 / 701 (10.56%) 85	
Hypokalaemia subjects affected / exposed occurrences (all)	67 / 702 (9.54%) 93	55 / 701 (7.85%) 82	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 July 2011	Protocol Amendment 1 included the following: an early futility analysis of the end-of-treatment complete response rate for the first 200 randomized subjects; inclusion of fluorodeoxyglucose positron-emission tomography (FDG-PET) information for determination of the overall response rate and complete response rate at the end of treatment for subjects for whom FDG-PET information was available; inclusion of a pharmacokinetic sampling schedule and analysis plan for a subset of up to 40 Japanese subjects enrolled and treated in the obinutuzumab+chemotherapy arm.
31 August 2012	Protocol Amendment 2 included updated guidelines for dose-delays and modifications due to toxicities to make the modifications more consistent with standard practice.
22 May 2013	Protocol Amendment 3 included the following: removal of the existing cap on the recruitment of subjects with occult or prior hepatitis B infection; progression-free survival (PFS), as assessed by the independent review committee (IRC), was added to the primary outcome measure to clarify that it would be analyzed to support the primary analysis and that, in the United States, IRC-assessed PFS would be the basis for regulatory decisions.
24 March 2014	Protocol Amendment 4 included new guidelines regarding the management of subjects with thrombocytopenia, especially during the first cycle of obinutuzumab, including those subjects receiving concomitant anticoagulants or platelet inhibitors.
20 June 2017	Protocol Amendment 5 included to consider second malignancies as an adverse event of special interest and report these events indefinitely, regardless of relationship to study treatment, to add that the length of time the DNA materials used to determine polymorphism will be kept prior to being destroyed, to collect full information about the extent of events of second malignancies in real time and to clarify the timing of the follow-up completion visit at Month 60.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported