



Clinical trial results:

A Randomized, Double-blind, Placebo-controlled Phase 3 Study of the Bruton's Tyrosine Kinase (BTK) Inhibitor, PCI-32765 (Ibrutinib), in Combination with Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone (R-CHOP) in Subjects With Newly Diagnosed Non-Germinal Center B-Cell Subtype of Diffuse Large B-Cell Lymphoma

Summary

EudraCT number	2013-000959-40
Trial protocol	GB SE CZ DE BE HU ES FI IT DK PL NL
Global end of trial date	05 April 2019

Results information

Result version number	v1 (current)
This version publication date	12 April 2020
First version publication date	12 April 2020

Trial information

Trial identification

Sponsor protocol code	PCI-32765DBL3001
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01855750
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Janssen Research & Development, LLC
Sponsor organisation address	920 Route 202, Raritan, United States, NJ 08869
Public contact	Clinical Registry group, Janssen Research & Development, LLC, ClinicalTrialsEU@its.jnj.com
Scientific contact	Clinical Registry group, Janssen Research & Development, LLC, ClinicalTrialsEU@its.jnj.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	05 April 2019
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	05 April 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to evaluate if the addition of ibrutinib to rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) prolonged event-free survival (EFS) compared with R-CHOP alone in subjects with newly diagnosed non-germinal center B-cell-like (non GCB) subtype of diffuse large B-cell lymphoma (DLBCL) selected by immunohistochemistry (IHC) or in subjects with newly diagnosed activated B-cell-like (ABC) subtype of DLBCL identified by gene expression profiling (GEP) or both patient populations.

Protection of trial subjects:

This study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practices and applicable regulatory requirements. Safety was evaluated by adverse events, clinical laboratory tests, vital signs, body surface area, physical examinations, echocardiogram or multiple uptake gated acquisition (MUGA) scans and electrocardiograms.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	30 September 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 2
Country: Number of subjects enrolled	Australia: 20
Country: Number of subjects enrolled	Belgium: 15
Country: Number of subjects enrolled	Brazil: 12
Country: Number of subjects enrolled	Canada: 21
Country: Number of subjects enrolled	China: 200
Country: Number of subjects enrolled	Czech Republic: 30
Country: Number of subjects enrolled	Germany: 13
Country: Number of subjects enrolled	Denmark: 11
Country: Number of subjects enrolled	Spain: 12
Country: Number of subjects enrolled	Finland: 14
Country: Number of subjects enrolled	France: 11
Country: Number of subjects enrolled	United Kingdom: 31
Country: Number of subjects enrolled	Hungary: 11
Country: Number of subjects enrolled	Israel: 23
Country: Number of subjects enrolled	Italy: 42

Country: Number of subjects enrolled	Japan: 73
Country: Number of subjects enrolled	Korea, Republic of: 25
Country: Number of subjects enrolled	Mexico: 3
Country: Number of subjects enrolled	Netherlands: 6
Country: Number of subjects enrolled	Norway: 7
Country: Number of subjects enrolled	Poland: 39
Country: Number of subjects enrolled	Russian Federation: 53
Country: Number of subjects enrolled	Sweden: 1
Country: Number of subjects enrolled	Turkey: 51
Country: Number of subjects enrolled	Taiwan: 17
Country: Number of subjects enrolled	Ukraine: 19
Country: Number of subjects enrolled	United States: 76
Worldwide total number of subjects	838
EEA total number of subjects	243

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)	490
From 65 to 84 years	343
85 years and over	5

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 838 subjects were enrolled; of those, 419 subjects were randomized to Treatment Group A (placebo+ Rituximab - Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone [R CHOP]) and 419 subjects to Treatment Group B (ibrutinib+R-CHOP).

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer

Arms

Are arms mutually exclusive?	Yes
Arm title	Treatment Arm B: Ibrutinib+R-CHOP

Arm description:

Subjects received ibrutinib 560 milligram (mg) (4*140 mg) capsules orally once daily (Cycle 1 Day 1 to Day 21 of last cycle; 21-day cycles) along with R-CHOP (Rituximab - Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone) as a background chemotherapy. R-CHOP regimen included rituximab 375 milligram per square meter (mg/m²) intravenously (IV), cyclophosphamide 750 mg/m² IV, doxorubicin 50 mg/m² IV, and vincristine 1.4 mg/m² IV, administered on Day 1 and prednisone 100 mg capsules orally on Days 1 to 5 of each cycle. Subjects received background chemotherapy plus ibrutinib for 6 or 8 cycles per site preference (21 days per cycle).

Arm type	Experimental
Investigational medicinal product name	Ibrutinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Subjects received 560 mg orally once daily for 6 or 8 cycles per site preference.

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

Dosage and administration details:

Subjects were administered cyclophosphamide 750 mg/m² IV on Day 1 of each cycle for 6 or 8 cycles per site preference.

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

Dosage and administration details:

Subjects were administered rituximab 375 mg/m² intravenously (IV) on Day 1 of each cycle (21-day cycles).

Investigational medicinal product name	Doxorubicin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use
Dosage and administration details:	
Subjects were administered doxorubicin 50 mg/m ² IV on Day 1 of each cycle (21-day cycles).	
Investigational medicinal product name	Vincristine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use
Dosage and administration details:	
Subjects were administered vincristine 1.4 mg/m ² IV on Day 1 of each cycle for 6 or 8 cycles per site preference.	
Investigational medicinal product name	Prednisone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use
Dosage and administration details:	
Subjects received prednisone 100 mg orally daily on Days 1 to 5 of each cycle for 6 or 8 cycles per site preference.	
Arm title	Treatment Arm A: Placebo+R-CHOP
Arm description:	
Subjects received matching placebo (4 capsules) orally once daily (21-day cycles) along with R-CHOP background chemotherapy. R-CHOP regimen included rituximab 375 milligram per square meter (mg/m ²) intravenously (IV), cyclophosphamide 750 mg/m ² IV, doxorubicin 50 mg/m ² IV, and vincristine 1.4 mg/m ² IV, administered on Day 1 and prednisone 100 mg capsules orally on Days 1 to 5 of each cycle. Subjects received background chemotherapy plus matching placebo for 6 or 8 cycles per site preference (21 days per cycle).	
Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use
Dosage and administration details:	
Subjects received matching placebo orally once daily for 6 or 8 cycles per site preference..	
Investigational medicinal product name	Rituximab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use
Dosage and administration details:	
Subjects were administered rituximab 375 mg/m ² intravenously (IV) on Day 1 of each cycle (21-day cycles).	
Investigational medicinal product name	Cyclophosphamide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use
Dosage and administration details:	
Subjects were administered cyclophosphamide 750 mg/m ² IV on Day 1 of each cycle for 6 or 8 cycles	

per site preference.

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

Dosage and administration details:

Subjects were administered doxorubicin 50 mg/m² IV on Day 1 of each cycle (21-day cycles).

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

Dosage and administration details:

Subjects were administered vincristine 1.4 mg/m² IV on Day 1 of each cycle for 6 or 8 cycles per site preference.

Investigational medicinal product name	Prednisone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Subjects received prednisone 100 mg orally daily on Days 1 to 5 of each cycle for 6 or 8 cycles per site preference.

Number of subjects in period 1	Treatment Arm B: Ibrutinib+R-CHOP	Treatment Arm A: Placebo+R-CHOP
Started	419	419
Treated	416	418
Completed	0	0
Not completed	419	419
Consent withdrawn by subject	35	28
Death	78	78
Sponsor ends the study	297	290
Lost to follow-up	9	23

Baseline characteristics

Reporting groups

Reporting group title	Treatment Arm B: Ibrutinib+R-CHOP
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Reporting group description:

Subjects received ibrutinib 560 milligram (mg) (4*140 mg) capsules orally once daily (Cycle 1 Day 1 to Day 21 of last cycle; 21-day cycles) along with R-CHOP (Rituximab - Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone) as a background chemotherapy. R-CHOP regimen included rituximab 375 milligram per square meter (mg/m²) intravenously (IV), cyclophosphamide 750 mg/m² IV, doxorubicin 50 mg/m² IV, and vincristine 1.4 mg/m² IV, administered on Day 1 and prednisone 100 mg capsules orally on Days 1 to 5 of each cycle. Subjects received background chemotherapy plus ibrutinib for 6 or 8 cycles per site preference (21 days per cycle).

Reporting group title	Treatment Arm A: Placebo+R-CHOP
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Reporting group description:

Subjects received matching placebo (4 capsules) orally once daily (21-day cycles) along with R-CHOP background chemotherapy. R-CHOP regimen included rituximab 375 milligram per square meter (mg/m²) intravenously (IV), cyclophosphamide 750 mg/m² IV, doxorubicin 50 mg/m² IV, and vincristine 1.4 mg/m² IV, administered on Day 1 and prednisone 100 mg capsules orally on Days 1 to 5 of each cycle. Subjects received background chemotherapy plus matching placebo for 6 or 8 cycles per site preference (21 days per cycle).

Reporting group values	Treatment Arm B: Ibrutinib+R-CHOP	Treatment Arm A: Placebo+R-CHOP	Total
Number of subjects	419	419	838
Title for AgeCategorical Units: subjects			
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	231	259	490
From 65 to 84 years	186	157	343
85 years and over	2	3	5
Title for AgeContinuous Units: years			
arithmetic mean	61.1	58.8	
standard deviation	± 12.57	± 13.57	-
Title for Gender Units: subjects			
Female	198	193	391
Male	221	226	447

End points

End points reporting groups

Reporting group title	Treatment Arm B: Ibrutinib+R-CHOP
Reporting group description: Subjects received ibrutinib 560 milligram (mg) (4*140 mg) capsules orally once daily (Cycle 1 Day 1 to Day 21 of last cycle; 21-day cycles) along with R-CHOP (Rituximab - Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone) as a background chemotherapy. R-CHOP regimen included rituximab 375 milligram per square meter (mg/m ²) intravenously (IV), cyclophosphamide 750 mg/m ² IV, doxorubicin 50 mg/m ² IV, and vincristine 1.4 mg/m ² IV, administered on Day 1 and prednisone 100 mg capsules orally on Days 1 to 5 of each cycle. Subjects received background chemotherapy plus ibrutinib for 6 or 8 cycles per site preference (21 days per cycle).	
Reporting group title	Treatment Arm A: Placebo+R-CHOP
Reporting group description: Subjects received matching placebo (4 capsules) orally once daily (21-day cycles) along with R-CHOP background chemotherapy. R-CHOP regimen included rituximab 375 milligram per square meter (mg/m ²) intravenously (IV), cyclophosphamide 750 mg/m ² IV, doxorubicin 50 mg/m ² IV, and vincristine 1.4 mg/m ² IV, administered on Day 1 and prednisone 100 mg capsules orally on Days 1 to 5 of each cycle. Subjects received background chemotherapy plus matching placebo for 6 or 8 cycles per site preference (21 days per cycle).	

Primary: Event-Free Survival (EFS)-Intent-to-Treat (ITT) Population

End point title	Event-Free Survival (EFS)-Intent-to-Treat (ITT) Population
End point description: EFS:duration from randomization to PD, relapse from CR assessed by investigator, initiation of subsequent systemic antilymphoma therapy for either PET-positive/biopsy-proven residual disease on completion of ≥ 6 cycles of R-CHOP therapy/death, whichever occurred first based on Revised Response Criteria for Malignant Lymphoma. PD: any new lesion or 50% increase of previously involved sites from nadir; PD criteria: new nodal lesion 1.5cm in any axis, 50% increase in SPD of >1 node or 50% increase in longest diameter of previously identified node 1cm in short axis. CR:disappearance of all evidence of disease; CR criteria: nodal masses PET positive prior to therapy; mass of any size permitted if PET negative; regression to normal size on CT; spleen, liver: not palpable, nodules disappeared; bone marrow: infiltrate cleared on repeat biopsy. ITT population included all randomized subjects, enrolled with GCB of DLBCL subtype by IHC, and analyzed according to treatment they were randomized.	
End point type	Primary
End point timeframe: Up to 5.5 years	

End point values	Treatment Arm B: Ibrutinib+R-CHOP	Treatment Arm A: Placebo+R-CHOP		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	419 ^[1]	419		
Units: Months				
median (confidence interval 95%)	49.64 (47.47 to 99999)	54.77 (48.16 to 54.77)		

Notes:

[1] - Here '99999' signifies that upper limit of 95% CI was not estimable due to lesser number of events.

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Treatment Arm A: Placebo+R-CHOP v Treatment Arm B: Ibrutinib+R-CHOP
Number of subjects included in analysis	838
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5167
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.922
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.72
upper limit	1.18

Primary: Event-Free Survival (EFS) - Activated B-Cell (ABC) Population

End point title	Event-Free Survival (EFS) - Activated B-Cell (ABC) Population
End point description:	
EFS: duration from randomization to disease progression(PD), relapse from complete response(CR) assessed by investigator, initiation of subsequent systemic antilymphoma therapy for either positron emission tomography(PET)-positive/ biopsy-proven residual disease upon completion of >=6 cycles of R-CHOP therapy/death, whichever occurred first. Responses were based on Revised Response Criteria for Malignant Lymphoma. PD: any new lesion or increase by 50% of previously involved sites from nadir; PD criteria: Appearance of new nodal lesion 1.5 cm in any axis, 50% increase in sum of product of diameters(SPD) of >1 node or 50% increase in longest diameter of previously identified node 1 cm in short axis. CR: disappearance of all evidence of disease; CR criteria: nodal masses PET positive prior to therapy; mass of any size permitted if PET negative; regression to normal size on CT; spleen and liver: not palpable, nodules disappeared; bone marrow: infiltrate cleared on repeat biopsy.	
End point type	Primary
End point timeframe:	
Up to 4.5 years	

End point values	Treatment Arm B: Ibrutinib+R-CHOP	Treatment Arm A: Placebo+R-CHOP		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	285 ^[2]	282		
Units: Months				
median (confidence interval 95%)	48.56 (48.56 to 99999)	48.16 (48.16 to 99999)		

Notes:

[2] - Here '99999' signifies that upper limit of 95% CI was not estimable due to lesser number of events.

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Treatment Arm B: Ibrutinib+R-CHOP v Treatment Arm A: Placebo+R-CHOP

Number of subjects included in analysis	567
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7311
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.949
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.704
upper limit	1.279

Secondary: Progression-Free Survival (PFS)

End point title	Progression-Free Survival (PFS)
End point description:	
<p>PFS: duration from randomization to progression, relapse from CR, or death, whichever occurred first. Responses were as per Revised Response Criteria for Malignant Lymphoma. PD: any new lesion or increase by 50% of previously involved sites from nadir; PD criteria: appearance of new nodal lesion 1.5 centimeter (cm) in any axis, 50% increase in SPD of >1 node or 50% increase in longest diameter of previously identified node 1 cm in short axis. CR: disappearance of all evidence of disease; CR criteria: nodal masses PET positive prior to therapy; mass of any size permitted if PET negative; regression to normal size on CT; spleen and liver: not palpable, nodules disappeared; bone marrow: infiltrate cleared on repeat biopsy. ITT population included all randomized subjects, enrolled with non-GCB of DLBCL subtype by IHC, and were analyzed according to treatment to which they were randomized. 99999 signifies that median and upper limit of CI were not estimable due to lesser number of events.</p>	
End point type	Secondary
End point timeframe:	
Up to 4.5 years	

End point values	Treatment Arm B: Ibrutinib+R-CHOP	Treatment Arm A: Placebo+R-CHOP		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	419	419		
Units: Months				
median (confidence interval 95%)	48.56 (48.56 to 99999)	99999 (48.16 to 99999)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Treatment Arm B: Ibrutinib+R-CHOP v Treatment Arm A: Placebo+R-CHOP

Number of subjects included in analysis	838
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5027
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.917
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.71
upper limit	1.183

Secondary: Percentage of Subjects who Achieved Complete Response (CR)

End point title	Percentage of Subjects who Achieved Complete Response (CR)
End point description:	Percentage of subjects with measurable disease who achieved CR were reported. CR: disappearance of all evidence of disease. CR Criteria: Complete disappearance of all disease-related symptoms; all lymph nodes and nodal masses regressed to normal size (less than or equal to [\leq]1.5 cm in greatest transverse diameter [GTD] for nodes greater than [$>$]1.5 cm before therapy). Previous nodes of 1.1 to 1.5 cm in long axis and greater than ($>$)1.0 cm in short axis before treatment decreased to \leq 1.0 cm in short axis after treatment. Disappearance of all splenic and hepatic nodules and other extranodal disease; a negative PET scan. A posttreatment residual mass of any size but PET-negative; spleen and liver: not palpable, nodules disappeared; bone marrow: infiltrate cleared on repeat biopsy. ITT population included all randomized subjects, enrolled with non-GCB of DLBCL subtype by IHC, and were analyzed according to treatment to which they were randomized.
End point type	Secondary
End point timeframe:	
Up to 4.5 years	

End point values	Treatment Arm B: Ibrutinib+R-CHOP	Treatment Arm A: Placebo+R-CHOP		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	419	419		
Units: Percentage of subjects				
number (not applicable)	67.3	68.0		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Treatment Arm B: Ibrutinib+R-CHOP v Treatment Arm A: Placebo+R-CHOP

Number of subjects included in analysis	838
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8229
Method	Chi-squared
Parameter estimate	Odds ratio (OR)
Point estimate	0.967
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.722
upper limit	1.296

Secondary: Overall Survival

End point title	Overall Survival
End point description:	
Overall survival was defined as the duration from the date of randomization to the date of the subject's death. Median Overall Survival was estimated by using the Kaplan-Meier method. ITT population included all randomized subjects, who were enrolled with the non-GCB of DLBCL subtype by IHC and were analyzed according to the treatment to which they were randomized. Here, 99999 signifies that median and upper limit of CI was not estimable due to lesser number of events and -99999 signifies that lower limit of CI was not estimable due to lesser number of events.	
End point type	Secondary
End point timeframe:	
Up to 5.5 years	

End point values	Treatment Arm B: Ibrutinib+R-CHOP	Treatment Arm A: Placebo+R-CHOP		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	419	419		
Units: Months				
median (confidence interval 95%)	99999 (-99999 to 99999)	99999 (-99999 to 99999)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Treatment Arm B: Ibrutinib+R-CHOP v Treatment Arm A: Placebo+R-CHOP

Number of subjects included in analysis	838
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8549
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.754
upper limit	1.407

Secondary: Time to Worsening in the Lymphoma Subscale of Functional Assessment of Cancer Therapy-Lymphoma (FACT-Lym)

End point title	Time to Worsening in the Lymphoma Subscale of Functional Assessment of Cancer Therapy-Lymphoma (FACT-Lym)
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End point description:

Time to worsening in the Lymphoma subscale of the FACT-Lym, defined as interval from the date of randomization to the start date of worsening of subject symptoms. Worsening was defined by a 5-point decrease from baseline. FACT-Lym Lymphoma subscale contains 15 questions, scores from 0 to 4 for each question (higher the worse). Lymphoma subscale score is the total of reverse scores, range 0 to 60. Higher scores indicate a better quality of life. ITT population included all randomized subjects, enrolled with non-GCB of DLBCL subtype by IHC, and were analyzed according to treatment to which they were randomized. Here, 99999 signifies that median and upper limit of CI was not estimable due to lesser number of events.

End point type	Secondary
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End point timeframe:

Up to 4.5 years

End point values	Treatment Arm B: Ibrutinib+R-CHOP	Treatment Arm A: Placebo+R-CHOP		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	419	419		
Units: Months				
median (confidence interval 95%)	11.7 (4.9 to 23.5)	35.0 (19.8 to 99999)		

Statistical analyses

Statistical analysis title	Statistical Analysis
Comparison groups	Treatment Arm B: Ibrutinib+R-CHOP v Treatment Arm A: Placebo+R-CHOP

Number of subjects included in analysis	838
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0021
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.358
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.115
upper limit	1.654

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 5.5 years

Adverse event reporting additional description:

Safety population included all randomized subjects who received at least 1 dose of study drug.

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	20.0
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Reporting groups

Reporting group title	Treatment Arm A: Placebo+R-CHOP
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Reporting group description:

Subjects received matching placebo (4 capsules) orally once daily (21-day cycles) along with R-CHOP background chemotherapy. R-CHOP regimen included rituximab 375 milligram per square meter (mg/m²) intravenously (IV), cyclophosphamide 750 mg/m² IV, doxorubicin 50 mg/m² IV, and vincristine 1.4 mg/m² IV, administered on Day 1 and prednisone 100 mg capsules orally on Days 1 to 5 of each cycle. Subjects received background chemotherapy plus matching placebo for 6 or 8 cycles per site preference (21 days per cycle).

Reporting group title	Treatment Arm B: Ibrutinib+R-CHOP
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Reporting group description:

Subjects received ibrutinib 560 milligram (mg) (4*140 mg) capsules orally once daily (Cycle 1 Day 1 to Day 21 of last cycle; 21-day cycles) along with R-CHOP (Rituximab - Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone) as a background chemotherapy. R-CHOP regimen included rituximab 375 milligram per square meter (mg/m²) intravenously (IV), cyclophosphamide 750 mg/m² IV, doxorubicin 50 mg/m² IV, and vincristine 1.4 mg/m² IV, administered on Day 1 and prednisone 100 mg capsules orally on Days 1 to 5 of each cycle. Subjects received background chemotherapy plus ibrutinib for 6 or 8 cycles per site preference (21 days per cycle).

Serious adverse events	Treatment Arm A: Placebo+R-CHOP	Treatment Arm B: Ibrutinib+R-CHOP	
Total subjects affected by serious adverse events			
subjects affected / exposed	143 / 418 (34.21%)	221 / 416 (53.13%)	
number of deaths (all causes)	77	78	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Angioimmunoblastic T-Cell Lymphoma			
subjects affected / exposed	1 / 418 (0.24%)	0 / 416 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Basal Cell Carcinoma			

subjects affected / exposed	0 / 418 (0.00%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colorectal Adenocarcinoma			
subjects affected / exposed	1 / 418 (0.24%)	0 / 416 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngeal Cancer Metastatic			
subjects affected / exposed	0 / 418 (0.00%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant Melanoma			
subjects affected / exposed	0 / 418 (0.00%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous Cell Carcinoma of Skin			
subjects affected / exposed	0 / 418 (0.00%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Aortic Aneurysm			
subjects affected / exposed	0 / 418 (0.00%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriosclerosis			
subjects affected / exposed	0 / 418 (0.00%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep Vein Thrombosis			
subjects affected / exposed	2 / 418 (0.48%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolism			

subjects affected / exposed	1 / 418 (0.24%)	0 / 416 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	1 / 418 (0.24%)	6 / 416 (1.44%)	
occurrences causally related to treatment / all	0 / 1	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shock Haemorrhagic			
subjects affected / exposed	0 / 418 (0.00%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombophlebitis			
subjects affected / exposed	0 / 418 (0.00%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vena Cava Thrombosis			
subjects affected / exposed	1 / 418 (0.24%)	0 / 416 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 418 (0.24%)	2 / 416 (0.48%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest Pain			
subjects affected / exposed	0 / 418 (0.00%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device Related Thrombosis			
subjects affected / exposed	1 / 418 (0.24%)	0 / 416 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drowning			

subjects affected / exposed	1 / 418 (0.24%)	0 / 416 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Fatigue			
subjects affected / exposed	1 / 418 (0.24%)	5 / 416 (1.20%)	
occurrences causally related to treatment / all	0 / 1	4 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
General Physical Health Deterioration			
subjects affected / exposed	1 / 418 (0.24%)	2 / 416 (0.48%)	
occurrences causally related to treatment / all	0 / 1	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injection Site Extravasation			
subjects affected / exposed	0 / 418 (0.00%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malaise			
subjects affected / exposed	0 / 418 (0.00%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucosal Inflammation			
subjects affected / exposed	0 / 418 (0.00%)	3 / 416 (0.72%)	
occurrences causally related to treatment / all	0 / 0	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple Organ Dysfunction Syndrome			
subjects affected / exposed	1 / 418 (0.24%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	1 / 1	1 / 1	
Non-Cardiac Chest Pain			
subjects affected / exposed	1 / 418 (0.24%)	0 / 416 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema Peripheral			

subjects affected / exposed	1 / 418 (0.24%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	0 / 418 (0.00%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	11 / 418 (2.63%)	12 / 416 (2.88%)	
occurrences causally related to treatment / all	6 / 12	8 / 14	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden Death			
subjects affected / exposed	2 / 418 (0.48%)	2 / 416 (0.48%)	
occurrences causally related to treatment / all	0 / 2	1 / 2	
deaths causally related to treatment / all	0 / 2	1 / 2	
Reproductive system and breast disorders			
Vaginal Fistula			
subjects affected / exposed	0 / 418 (0.00%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute Respiratory Failure			
subjects affected / exposed	1 / 418 (0.24%)	0 / 416 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Alveolitis			
subjects affected / exposed	0 / 418 (0.00%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	1 / 1	
Atelectasis			
subjects affected / exposed	1 / 418 (0.24%)	0 / 416 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Diffuse Alveolar Damage			
subjects affected / exposed	0 / 418 (0.00%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Dyspnoea			
subjects affected / exposed	1 / 418 (0.24%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	0 / 418 (0.00%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial Lung Disease			
subjects affected / exposed	4 / 418 (0.96%)	7 / 416 (1.68%)	
occurrences causally related to treatment / all	4 / 4	8 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obliterative Bronchiolitis			
subjects affected / exposed	1 / 418 (0.24%)	0 / 416 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngeal Haemorrhage			
subjects affected / exposed	1 / 418 (0.24%)	0 / 416 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural Effusion			
subjects affected / exposed	1 / 418 (0.24%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia Aspiration			
subjects affected / exposed	0 / 418 (0.00%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			

subjects affected / exposed	3 / 418 (0.72%)	6 / 416 (1.44%)	
occurrences causally related to treatment / all	2 / 3	5 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary Embolism			
subjects affected / exposed	3 / 418 (0.72%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary Mass			
subjects affected / exposed	0 / 418 (0.00%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory Failure			
subjects affected / exposed	1 / 418 (0.24%)	2 / 416 (0.48%)	
occurrences causally related to treatment / all	1 / 1	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Sinus Polyp			
subjects affected / exposed	0 / 418 (0.00%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Bipolar I Disorder			
subjects affected / exposed	1 / 418 (0.24%)	0 / 416 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Confusional State			
subjects affected / exposed	1 / 418 (0.24%)	0 / 416 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicidal Ideation			
subjects affected / exposed	0 / 418 (0.00%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			

Alanine Aminotransferase Increased subjects affected / exposed	1 / 418 (0.24%)	0 / 416 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
C-Reactive Protein Increased subjects affected / exposed	1 / 418 (0.24%)	0 / 416 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutrophil Count Decreased subjects affected / exposed	2 / 418 (0.48%)	5 / 416 (1.20%)	
occurrences causally related to treatment / all	2 / 2	5 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelet Count Decreased subjects affected / exposed	0 / 418 (0.00%)	2 / 416 (0.48%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Weight Decreased subjects affected / exposed	0 / 418 (0.00%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
White Blood Cell Count Decreased subjects affected / exposed	0 / 418 (0.00%)	3 / 416 (0.72%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
White Blood Cell Count Increased subjects affected / exposed	0 / 418 (0.00%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Compression Fracture subjects affected / exposed	0 / 418 (0.00%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Femoral Neck Fracture			
subjects affected / exposed	1 / 418 (0.24%)	0 / 416 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fibula Fracture			
subjects affected / exposed	0 / 418 (0.00%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip Fracture			
subjects affected / exposed	2 / 418 (0.48%)	0 / 416 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus Fracture			
subjects affected / exposed	1 / 418 (0.24%)	0 / 416 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infusion Related Reaction			
subjects affected / exposed	0 / 418 (0.00%)	1 / 416 (0.24%)	
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 / 418 (0.00%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative Thrombosis			
subjects affected / exposed	0 / 418 (0.00%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pubis Fracture			
subjects affected / exposed	0 / 418 (0.00%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skull Fractured Base			

subjects affected / exposed	0 / 418 (0.00%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Spinal Compression Fracture			
subjects affected / exposed	0 / 418 (0.00%)	1 / 416 (0.24%)	
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 / 418 (0.72%)	0 / 416 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Congenital Neuropathy			
subjects affected / exposed	1 / 418 (0.24%)	0 / 416 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyloric Stenosis			
subjects affected / exposed	0 / 418 (0.00%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute Coronary Syndrome			
subjects affected / exposed	0 / 418 (0.00%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute Myocardial Infarction			
subjects affected / exposed	1 / 418 (0.24%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Angina Pectoris			
subjects affected / exposed	1 / 418 (0.24%)	2 / 416 (0.48%)	
occurrences causally related to treatment / all	0 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	

Arteriosclerosis Coronary Artery subjects affected / exposed	0 / 418 (0.00%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial Fibrillation subjects affected / exposed	2 / 418 (0.48%)	13 / 416 (3.13%)	
occurrences causally related to treatment / all	2 / 2	10 / 17	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial Flutter subjects affected / exposed	0 / 418 (0.00%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac Arrest subjects affected / exposed	0 / 418 (0.00%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac Failure subjects affected / exposed	5 / 418 (1.20%)	2 / 416 (0.48%)	
occurrences causally related to treatment / all	2 / 5	1 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac Failure Acute subjects affected / exposed	1 / 418 (0.24%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac Failure Congestive subjects affected / exposed	1 / 418 (0.24%)	2 / 416 (0.48%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiomyopathy subjects affected / exposed	1 / 418 (0.24%)	0 / 416 (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	1 / 418 (0.24%)	0 / 416 (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 / 418 (0.24%)	0 / 416 (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	1 / 418 (0.24%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	1 / 1	0 / 1	
Myocardial Ischaemia			
subjects affected / exposed	0 / 418 (0.00%)	2 / 416 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus Node Dysfunction			
subjects affected / exposed	0 / 418 (0.00%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular Tachycardia			
subjects affected / exposed	1 / 418 (0.24%)	0 / 416 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia			
subjects affected / exposed	0 / 418 (0.00%)	2 / 416 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular Tachycardia			
subjects affected / exposed	0 / 418 (0.00%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Altered State of Consciousness			

subjects affected / exposed	0 / 418 (0.00%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Central Nervous System Inflammation			
subjects affected / exposed	1 / 418 (0.24%)	0 / 416 (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	0 / 418 (0.00%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral Infarction			
subjects affected / exposed	1 / 418 (0.24%)	0 / 416 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrospinal Fluid Leakage			
subjects affected / exposed	1 / 418 (0.24%)	0 / 416 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular Disorder			
subjects affected / exposed	0 / 418 (0.00%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness Postural			
subjects affected / exposed	0 / 418 (0.00%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy			
subjects affected / exposed	1 / 418 (0.24%)	0 / 416 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile Convulsion			

subjects affected / exposed	0 / 418 (0.00%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage Intracranial			
subjects affected / exposed	0 / 418 (0.00%)	2 / 416 (0.48%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hemiparesis			
subjects affected / exposed	1 / 418 (0.24%)	0 / 416 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intracranial Hypotension			
subjects affected / exposed	1 / 418 (0.24%)	0 / 416 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nerve Compression			
subjects affected / exposed	1 / 418 (0.24%)	0 / 416 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polyneuropathy			
subjects affected / exposed	0 / 418 (0.00%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Sciatica			
subjects affected / exposed	0 / 418 (0.00%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	0 / 418 (0.00%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			

subjects affected / exposed	1 / 418 (0.24%)	5 / 416 (1.20%)	
occurrences causally related to treatment / all	0 / 2	1 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	5 / 418 (1.20%)	15 / 416 (3.61%)	
occurrences causally related to treatment / all	4 / 6	13 / 17	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile Neutropenia			
subjects affected / exposed	44 / 418 (10.53%)	78 / 416 (18.75%)	
occurrences causally related to treatment / all	42 / 55	71 / 100	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			
subjects affected / exposed	2 / 418 (0.48%)	4 / 416 (0.96%)	
occurrences causally related to treatment / all	1 / 3	2 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphopenia			
subjects affected / exposed	0 / 418 (0.00%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	13 / 418 (3.11%)	17 / 416 (4.09%)	
occurrences causally related to treatment / all	11 / 16	14 / 19	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	1 / 418 (0.24%)	0 / 416 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	1 / 418 (0.24%)	9 / 416 (2.16%)	
occurrences causally related to treatment / all	1 / 1	6 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			

Vertigo			
subjects affected / exposed	0 / 418 (0.00%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Eye Haemorrhage			
subjects affected / exposed	0 / 418 (0.00%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Glaucoma			
subjects affected / exposed	0 / 418 (0.00%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal Detachment			
subjects affected / exposed	1 / 418 (0.24%)	0 / 416 (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	2 / 418 (0.48%)	2 / 416 (0.48%)	
occurrences causally related to treatment / all	1 / 2	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	0 / 418 (0.00%)	3 / 416 (0.72%)	
occurrences causally related to treatment / all	0 / 0	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	0 / 418 (0.00%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	4 / 418 (0.96%)	15 / 416 (3.61%)	
occurrences causally related to treatment / all	5 / 5	13 / 17	
deaths causally related to treatment / all	0 / 0	0 / 0	

Diverticular Perforation			
subjects affected / exposed	0 / 418 (0.00%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal Ulcer Haemorrhage			
subjects affected / exposed	0 / 418 (0.00%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspepsia			
subjects affected / exposed	1 / 418 (0.24%)	0 / 416 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteritis			
subjects affected / exposed	0 / 418 (0.00%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric Haemorrhage			
subjects affected / exposed	1 / 418 (0.24%)	2 / 416 (0.48%)	
occurrences causally related to treatment / all	0 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric Perforation			
subjects affected / exposed	1 / 418 (0.24%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal Haemorrhage			
subjects affected / exposed	1 / 418 (0.24%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrooesophageal Reflux Disease			
subjects affected / exposed	1 / 418 (0.24%)	0 / 416 (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	2 / 418 (0.48%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal Obstruction			
subjects affected / exposed	0 / 418 (0.00%)	2 / 416 (0.48%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower Gastrointestinal Haemorrhage			
subjects affected / exposed	0 / 418 (0.00%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mechanical Ileus			
subjects affected / exposed	1 / 418 (0.24%)	0 / 416 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	3 / 418 (0.72%)	6 / 416 (1.44%)	
occurrences causally related to treatment / all	1 / 3	5 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic Colitis			
subjects affected / exposed	0 / 418 (0.00%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obstruction Gastric			
subjects affected / exposed	1 / 418 (0.24%)	0 / 416 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophagitis			
subjects affected / exposed	1 / 418 (0.24%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			

subjects affected / exposed	0 / 418 (0.00%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal Haemorrhage			
subjects affected / exposed	0 / 418 (0.00%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small Intestinal Obstruction			
subjects affected / exposed	1 / 418 (0.24%)	0 / 416 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small Intestinal Perforation			
subjects affected / exposed	1 / 418 (0.24%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			
subjects affected / exposed	0 / 418 (0.00%)	2 / 416 (0.48%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	2 / 418 (0.48%)	8 / 416 (1.92%)	
occurrences causally related to treatment / all	0 / 2	6 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholangitis			
subjects affected / exposed	1 / 418 (0.24%)	0 / 416 (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	0 / 418 (0.00%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic Failure			

subjects affected / exposed	0 / 418 (0.00%)	2 / 416 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Hepatic Function Abnormal			
subjects affected / exposed	2 / 418 (0.48%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Dermatitis Allergic			
subjects affected / exposed	0 / 418 (0.00%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute Kidney Injury			
subjects affected / exposed	1 / 418 (0.24%)	4 / 416 (0.96%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis Haemorrhagic			
subjects affected / exposed	0 / 418 (0.00%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysuria			
subjects affected / exposed	0 / 418 (0.00%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pollakiuria			
subjects affected / exposed	0 / 418 (0.00%)	1 / 416 (0.24%)	
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	2 / 418 (0.48%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary Retention			

subjects affected / exposed	0 / 418 (0.00%)	1 / 416 (0.24%)	
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	0 / 418 (0.00%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back Pain			
subjects affected / exposed	0 / 418 (0.00%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chondrocalcinosis Pyrophosphate			
subjects affected / exposed	0 / 418 (0.00%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Flank Pain			
subjects affected / exposed	1 / 418 (0.24%)	0 / 416 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular Weakness			
subjects affected / exposed	0 / 418 (0.00%)	2 / 416 (0.48%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myalgia			
subjects affected / exposed	0 / 418 (0.00%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Arteritis Infective			
subjects affected / exposed	0 / 418 (0.00%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Aspergillus Infection			
subjects affected / exposed	0 / 418 (0.00%)	2 / 416 (0.48%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	1 / 1	
Atypical Pneumonia			
subjects affected / exposed	0 / 418 (0.00%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			
subjects affected / exposed	0 / 418 (0.00%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain Abscess			
subjects affected / exposed	0 / 418 (0.00%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	0 / 418 (0.00%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopulmonary Aspergillosis			
subjects affected / exposed	1 / 418 (0.24%)	2 / 416 (0.48%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	0 / 418 (0.00%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral Aspergillosis			
subjects affected / exposed	0 / 418 (0.00%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridial Infection			

subjects affected / exposed	0 / 418 (0.00%)	2 / 416 (0.48%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cryptococcal Fungaemia			
subjects affected / exposed	0 / 418 (0.00%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus Gastrointestinal Infection			
subjects affected / exposed	1 / 418 (0.24%)	0 / 416 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device Related Infection			
subjects affected / exposed	1 / 418 (0.24%)	4 / 416 (0.96%)	
occurrences causally related to treatment / all	0 / 1	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterococcal Sepsis			
subjects affected / exposed	0 / 418 (0.00%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	1 / 418 (0.24%)	0 / 416 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	0 / 418 (0.00%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis Bacterial			
subjects affected / exposed	1 / 418 (0.24%)	0 / 416 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemophilus Infection			

subjects affected / exposed	1 / 418 (0.24%)	0 / 416 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis B			
subjects affected / exposed	1 / 418 (0.24%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis B Reactivation			
subjects affected / exposed	1 / 418 (0.24%)	0 / 416 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes Zoster			
subjects affected / exposed	3 / 418 (0.72%)	2 / 416 (0.48%)	
occurrences causally related to treatment / all	2 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incision Site Infection			
subjects affected / exposed	1 / 418 (0.24%)	0 / 416 (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 / 418 (0.48%)	3 / 416 (0.72%)	
occurrences causally related to treatment / all	1 / 2	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Klebsiella Sepsis			
subjects affected / exposed	1 / 418 (0.24%)	0 / 416 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower Respiratory Tract Infection			
subjects affected / exposed	0 / 418 (0.00%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower Respiratory Tract Infection Fungal			

subjects affected / exposed	0 / 418 (0.00%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung Abscess			
subjects affected / exposed	0 / 418 (0.00%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung Infection			
subjects affected / exposed	7 / 418 (1.67%)	14 / 416 (3.37%)	
occurrences causally related to treatment / all	5 / 8	9 / 15	
deaths causally related to treatment / all	1 / 1	0 / 0	
Lymph Gland Infection			
subjects affected / exposed	1 / 418 (0.24%)	0 / 416 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucosal Infection			
subjects affected / exposed	0 / 418 (0.00%)	1 / 416 (0.24%)	
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 / 418 (0.24%)	2 / 416 (0.48%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic Sepsis			
subjects affected / exposed	2 / 418 (0.48%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	1 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			
subjects affected / exposed	1 / 418 (0.24%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngitis			

subjects affected / exposed	0 / 418 (0.00%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumocystis Jirovecii Pneumonia			
subjects affected / exposed	0 / 418 (0.00%)	3 / 416 (0.72%)	
occurrences causally related to treatment / all	0 / 0	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pneumonia			
subjects affected / exposed	14 / 418 (3.35%)	28 / 416 (6.73%)	
occurrences causally related to treatment / all	9 / 18	20 / 34	
deaths causally related to treatment / all	1 / 1	0 / 1	
Pneumonia Cryptococcal			
subjects affected / exposed	0 / 418 (0.00%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia Cytomegaloviral			
subjects affected / exposed	0 / 418 (0.00%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia Klebsiella			
subjects affected / exposed	0 / 418 (0.00%)	2 / 416 (0.48%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia Respiratory Syncytial Viral			
subjects affected / exposed	1 / 418 (0.24%)	0 / 416 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pseudomembranous Colitis			
subjects affected / exposed	0 / 418 (0.00%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary Mycosis			

subjects affected / exposed	0 / 418 (0.00%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory Syncytial Virus Infection			
subjects affected / exposed	0 / 418 (0.00%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory Tract Infection			
subjects affected / exposed	0 / 418 (0.00%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory Tract Infection Bacterial			
subjects affected / exposed	0 / 418 (0.00%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory Tract Infection Fungal			
subjects affected / exposed	0 / 418 (0.00%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	3 / 418 (0.72%)	7 / 416 (1.68%)	
occurrences causally related to treatment / all	1 / 4	5 / 9	
deaths causally related to treatment / all	0 / 1	0 / 1	
Septic Shock			
subjects affected / exposed	1 / 418 (0.24%)	5 / 416 (1.20%)	
occurrences causally related to treatment / all	1 / 1	2 / 5	
deaths causally related to treatment / all	0 / 0	0 / 1	
Sialoadenitis			
subjects affected / exposed	1 / 418 (0.24%)	0 / 416 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinusitis			

subjects affected / exposed	2 / 418 (0.48%)	0 / 416 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper Respiratory Tract Infection			
subjects affected / exposed	1 / 418 (0.24%)	3 / 416 (0.72%)	
occurrences causally related to treatment / all	1 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary Tract Infection			
subjects affected / exposed	3 / 418 (0.72%)	5 / 416 (1.20%)	
occurrences causally related to treatment / all	0 / 3	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	1 / 418 (0.24%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral Infection			
subjects affected / exposed	0 / 418 (0.00%)	2 / 416 (0.48%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral Upper Respiratory Tract Infection			
subjects affected / exposed	0 / 418 (0.00%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound Infection			
subjects affected / exposed	1 / 418 (0.24%)	0 / 416 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Decreased Appetite			
subjects affected / exposed	2 / 418 (0.48%)	0 / 416 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			

subjects affected / exposed	2 / 418 (0.48%)	8 / 416 (1.92%)	
occurrences causally related to treatment / all	0 / 2	6 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes Mellitus			
subjects affected / exposed	1 / 418 (0.24%)	0 / 416 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fluid Overload			
subjects affected / exposed	0 / 418 (0.00%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	1 / 418 (0.24%)	0 / 416 (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	0 / 418 (0.00%)	4 / 416 (0.96%)	
occurrences causally related to treatment / all	0 / 0	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	1 / 418 (0.24%)	3 / 416 (0.72%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypophagia			
subjects affected / exposed	1 / 418 (0.24%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoproteinaemia			
subjects affected / exposed	0 / 418 (0.00%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ketoacidosis			

subjects affected / exposed	1 / 418 (0.24%)	0 / 416 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Tumour Lysis Syndrome			
subjects affected / exposed	0 / 418 (0.00%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Treatment Arm A: Placebo+R-CHOP	Treatment Arm B: Ibrutinib+R-CHOP	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	411 / 418 (98.33%)	411 / 416 (98.80%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	18 / 418 (4.31%)	23 / 416 (5.53%)	
occurrences (all)	21	34	
Hypotension			
subjects affected / exposed	10 / 418 (2.39%)	23 / 416 (5.53%)	
occurrences (all)	11	28	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	16 / 418 (3.83%)	28 / 416 (6.73%)	
occurrences (all)	29	48	
Fatigue			
subjects affected / exposed	102 / 418 (24.40%)	138 / 416 (33.17%)	
occurrences (all)	182	241	
Malaise			
subjects affected / exposed	21 / 418 (5.02%)	25 / 416 (6.01%)	
occurrences (all)	43	33	
Mucosal Inflammation			
subjects affected / exposed	23 / 418 (5.50%)	34 / 416 (8.17%)	
occurrences (all)	29	52	
Oedema Peripheral			

subjects affected / exposed occurrences (all)	29 / 418 (6.94%) 33	46 / 416 (11.06%) 66	
Pyrexia subjects affected / exposed occurrences (all)	68 / 418 (16.27%) 109	83 / 416 (19.95%) 145	
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	47 / 418 (11.24%) 53	55 / 416 (13.22%) 71	
Dyspnoea subjects affected / exposed occurrences (all)	25 / 418 (5.98%) 30	30 / 416 (7.21%) 38	
Oropharyngeal Pain subjects affected / exposed occurrences (all)	25 / 418 (5.98%) 32	32 / 416 (7.69%) 42	
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	43 / 418 (10.29%) 54	39 / 416 (9.38%) 43	
Investigations Alanine Aminotransferase Increased subjects affected / exposed occurrences (all)	24 / 418 (5.74%) 46	25 / 416 (6.01%) 36	
Lymphocyte Count Decreased subjects affected / exposed occurrences (all)	42 / 418 (10.05%) 326	44 / 416 (10.58%) 358	
Neutrophil Count Decreased subjects affected / exposed occurrences (all)	81 / 418 (19.38%) 412	99 / 416 (23.80%) 395	
Platelet Count Decreased subjects affected / exposed occurrences (all)	38 / 418 (9.09%) 171	83 / 416 (19.95%) 454	
Weight Decreased subjects affected / exposed occurrences (all)	18 / 418 (4.31%) 29	36 / 416 (8.65%) 57	
White Blood Cell Count Decreased			

subjects affected / exposed occurrences (all)	104 / 418 (24.88%) 764	107 / 416 (25.72%) 626	
Injury, poisoning and procedural complications Infusion Related Reaction subjects affected / exposed occurrences (all)	26 / 418 (6.22%) 29	23 / 416 (5.53%) 30	
Nervous system disorders Dysgeusia subjects affected / exposed occurrences (all)	19 / 418 (4.55%) 23	26 / 416 (6.25%) 27	
Headache subjects affected / exposed occurrences (all)	43 / 418 (10.29%) 70	29 / 416 (6.97%) 54	
Hypoaesthesia subjects affected / exposed occurrences (all)	22 / 418 (5.26%) 28	28 / 416 (6.73%) 35	
Neuropathy Peripheral subjects affected / exposed occurrences (all)	35 / 418 (8.37%) 49	65 / 416 (15.63%) 96	
Paraesthesia subjects affected / exposed occurrences (all)	16 / 418 (3.83%) 22	28 / 416 (6.73%) 42	
Peripheral Sensory Neuropathy subjects affected / exposed occurrences (all)	63 / 418 (15.07%) 81	77 / 416 (18.51%) 134	
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	116 / 418 (27.75%) 476	173 / 416 (41.59%) 714	
Febrile Neutropenia subjects affected / exposed occurrences (all)	22 / 418 (5.26%) 28	41 / 416 (9.86%) 56	
Leukopenia subjects affected / exposed occurrences (all)	74 / 418 (17.70%) 412	70 / 416 (16.83%) 402	
Lymphopenia			

subjects affected / exposed	36 / 418 (8.61%)	23 / 416 (5.53%)	
occurrences (all)	245	191	
Neutropenia			
subjects affected / exposed	248 / 418 (59.33%)	213 / 416 (51.20%)	
occurrences (all)	1079	865	
Thrombocytopenia			
subjects affected / exposed	53 / 418 (12.68%)	102 / 416 (24.52%)	
occurrences (all)	141	352	
Gastrointestinal disorders			
Abdominal Pain			
subjects affected / exposed	34 / 418 (8.13%)	37 / 416 (8.89%)	
occurrences (all)	47	44	
Abdominal Pain Upper			
subjects affected / exposed	34 / 418 (8.13%)	28 / 416 (6.73%)	
occurrences (all)	57	34	
Constipation			
subjects affected / exposed	110 / 418 (26.32%)	111 / 416 (26.68%)	
occurrences (all)	149	147	
Diarrhoea			
subjects affected / exposed	81 / 418 (19.38%)	149 / 416 (35.82%)	
occurrences (all)	122	291	
Dry Mouth			
subjects affected / exposed	17 / 418 (4.07%)	22 / 416 (5.29%)	
occurrences (all)	22	27	
Dyspepsia			
subjects affected / exposed	22 / 418 (5.26%)	26 / 416 (6.25%)	
occurrences (all)	27	30	
Mouth Ulceration			
subjects affected / exposed	20 / 418 (4.78%)	32 / 416 (7.69%)	
occurrences (all)	27	52	
Nausea			
subjects affected / exposed	135 / 418 (32.30%)	170 / 416 (40.87%)	
occurrences (all)	304	356	
Stomatitis			
subjects affected / exposed	47 / 418 (11.24%)	64 / 416 (15.38%)	
occurrences (all)	65	110	

Vomiting subjects affected / exposed occurrences (all)	59 / 418 (14.11%) 89	91 / 416 (21.88%) 157	
Skin and subcutaneous tissue disorders			
Alopecia subjects affected / exposed occurrences (all)	106 / 418 (25.36%) 117	69 / 416 (16.59%) 78	
Pruritus subjects affected / exposed occurrences (all)	21 / 418 (5.02%) 24	11 / 416 (2.64%) 14	
Rash subjects affected / exposed occurrences (all)	21 / 418 (5.02%) 23	22 / 416 (5.29%) 32	
Musculoskeletal and connective tissue disorders			
Back Pain subjects affected / exposed occurrences (all)	40 / 418 (9.57%) 59	34 / 416 (8.17%) 42	
Bone Pain subjects affected / exposed occurrences (all)	21 / 418 (5.02%) 29	17 / 416 (4.09%) 32	
Muscle Spasms subjects affected / exposed occurrences (all)	14 / 418 (3.35%) 21	30 / 416 (7.21%) 35	
Myalgia subjects affected / exposed occurrences (all)	24 / 418 (5.74%) 27	18 / 416 (4.33%) 26	
Infections and infestations			
Pneumonia subjects affected / exposed occurrences (all)	9 / 418 (2.15%) 11	22 / 416 (5.29%) 27	
Upper Respiratory Tract Infection subjects affected / exposed occurrences (all)	29 / 418 (6.94%) 37	35 / 416 (8.41%) 39	
Urinary Tract Infection subjects affected / exposed occurrences (all)	15 / 418 (3.59%) 19	24 / 416 (5.77%) 29	

Metabolism and nutrition disorders			
Decreased Appetite			
subjects affected / exposed	51 / 418 (12.20%)	64 / 416 (15.38%)	
occurrences (all)	71	100	
Hypoalbuminaemia			
subjects affected / exposed	9 / 418 (2.15%)	24 / 416 (5.77%)	
occurrences (all)	11	46	
Hypokalaemia			
subjects affected / exposed	23 / 418 (5.50%)	75 / 416 (18.03%)	
occurrences (all)	40	157	
Hypomagnesaemia			
subjects affected / exposed	7 / 418 (1.67%)	22 / 416 (5.29%)	
occurrences (all)	9	32	
Hyponatraemia			
subjects affected / exposed	11 / 418 (2.63%)	28 / 416 (6.73%)	
occurrences (all)	15	42	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 September 2013	Amendment INT-1: The overall reason for the amendment was to remove the biopsy/tissue requirement for confirmation of DLBCL diagnosis; update the protocol with new safety-related information and instructions; further clarify study treatment dosing instructions; revise operational aspects of the study; and perform minor modifications and formatting changes.
05 August 2015	Amendment INT-2: The overall reason for amendment was to clarify protocol recommendations for monitoring of subject subgroups who are considered, based on emerging literature, at increased risk of hepatitis B virus reactivation due to R-CHOP + ibrutinib/placebo therapy. Additionally, the protocol was updated with new safety-related information for consistency with the ibrutinib Investigator's Brochure.
16 October 2017	Amendment INT-3: The overall reason for the amendment was to omit the interim analysis due to a lower than expected event-free survival event rate observed. To change retrospective analysis of the activated B cell like (ABC) diffuse large B cell lymphoma (DLBCL) population by gene expression profiling (GEP) from a secondary objective to a co-primary objective (ie, in addition to the already pre specified non germinal center B cell-like [non GCB] DLBCL population by immunohistochemistry [IHC]). The hypothesis and primary endpoint analysis were updated to include the ABC by GEP population and the statistical method was clarified.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Sponsor decided to stop the study as all participants had concluded study treatment and outcomes were not expected to change and study was considered as completed.

Notes: