Clinical trial results:
A Randomized, Double-blind, Placebo-controlled Phase 3 Study of the Bruton's Tyrosine Kinase Inhibitor, PCI-32765 (Ibrutinib), in Combination with Either Bendamustine and Rituximab (BR) or Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone (R-CHOP) in Subjects with Previously Treated Indolent Non-Hodgkin Lymphoma (iNHL)

Summary

EudraCT number	2013-003093-27
Trial protocol	SE BE GB ES IT DE PL FR
Global end of trial date	21 June 2023

Results information

Result version number	v1 (current)
This version publication date	06 July 2024
First version publication date	06 July 2024

Trial information

Trial identification

Sponsor protocol code	PCI-32765FLR3001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01974440
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Janssen Research & Development, LLC
Sponsor organisation address	920 Route 202 South, Raritan, New Jersey, United States, 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	21 June 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	21 June 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of this trial was to evaluate whether the addition of ibrutinib of either bendamustine and rituximab (BR) to the combination or rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) combination would result in prolongation of progression-free survival (PFS), as assessed by investigator, compared with either BR or R-CHOP alone in subjects with previously treated indolent Non-Hodgkin lymphoma (iNHL) (follicular lymphoma [FL] or marginal zone lymphoma [MZL]).

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 Practice and applicable regulatory requirements.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	31 January 2014
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: 10
Country: Number of subjects enrolled	Australia: 37
Country: Number of subjects enrolled	Belgium: 13
Country: Number of subjects enrolled	Brazil: 3
Country: Number of subjects enrolled	China: 57
Country: Number of subjects enrolled	Germany: 13
Country: Number of subjects enrolled	Spain: 20
Country: Number of subjects enrolled	France: 21
Country: Number of subjects enrolled	United Kingdom: 20
Country: Number of subjects enrolled	Israel: 33
Country: Number of subjects enrolled	Italy: 11
Country: Number of subjects enrolled	Japan: 42
Country: Number of subjects enrolled	Korea, Republic of: 26
Country: Number of subjects enrolled	Poland: 8
Country: Number of subjects enrolled	Russian Federation: 20
Country: Number of subjects enrolled	Sweden: 1
Country: Number of subjects enrolled	Türkiye: 20
Country: Number of subjects enrolled	Ukraine: 8

Country: Number of subjects enrolled	United States: 40
Worldwide total number of subjects	403
EEA total number of subjects	87

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)	257
From 65 to 84 years	142
85 years and over	4

Subject disposition

Recruitment

Recruitment details:

A total of 403 subjects were randomised, of which 400 subjects were treated and 126 subjects completed the study. Placebo+CIT arm subjects discontinued the study treatment post the primary analysis but were assessed for the safety till the end of the study.

Pre-assignment

Screening details:

Subjects were stratified by background chemotherapy treatment (BR or combination or R-CHOP), refractory versus relapsed disease, Indolent non-Hodgkin lymphoma histology, and number of prior lines of therapy. No further efficacy analyses were done after the primary analysis.

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo + Chemoimmunotherapy (CIT)

Arm description:

Subjects received 4 capsules of placebo matching to ibrutinib orally once daily continuously starting on Cycle 1, Day 1 until disease progression, or unacceptable toxicity, or study end, whichever occurred first. All subjects also received a background therapy for maximum of 6 cycles (each cycle = 21 days) either with BR: bendamustine hydrochloride 90 milligrams per meter square (mg/m^2) intravenously (IV) on Days 1 and 2 of each cycle and rituximab 375 mg/m^2 IV on Day 1 of each cycle; or background therapy with R-CHOP: rituximab 375 mg/m^2 IV on Day 1, cyclophosphamide 750 mg/m^2 IV on Day 1, doxorubicin 50 mg/m^2 IV on Day 1, vincristine 1.4 mg/m^2 IV (maximum total 2 mg) on Day 1, and prednisone 100 mg orally on Days 1 to 5 until disease progression or unacceptable toxicity. After treatment unblinding at the time of the primary analysis, subjects randomised to arm "Placebo + CIT" discontinued placebo treatment.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Subjects received placebo (4 capsules) matching to ibrutinib once daily continuously starting on Cycle 1, Day 1 until disease progression, or unacceptable toxicity, or study end, whichever occurred first.

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

Dosage and administration details:

As a background therapy subjects received BR regimen: rituximab 375 mg/m^2 IV on Day 1 of each cycle of 21 days.

Investigational medicinal product name	Prednisone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule

Routes of administration	Oral use

Dosage and administration details:

As a background therapy subjects received R-CHOP regimen: prednisone 100 mg on Days 1 to 5 of each cycle of 21 days.

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

Dosage and administration details:

As a background therapy subjects received R-CHOP regimen: cyclophosphamide 750 mg/m^2 IV on Day 1 of each cycle of 21 days.

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

Dosage and administration details:

As a background therapy subjects received R-CHOP regimen: doxorubicin 50 mg/m^2 IV on Day 1 of each cycle of 21 days.

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

Dosage and administration details:

As a background therapy subjects received R-CHOP regimen: vincristine 1.4 mg/m^2 IV (maximum total 2 mg) on Day 1 of each cycle of 21 days.

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

Dosage and administration details:

As a background therapy subjects received BR regimen: bendamustine hydrochloride 90 milligrams per meter square (mg/m^2) intravenously (IV) on Days 1 and 2 of each cycle of 21 days.

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

Dosage and administration details:

As a background therapy subjects received R-CHOP regimen: rituximab 375 mg/m^2 IV on Day 1 of each cycle of 21 days.

Arm title	Ibrutinib + CIT

Arm description:

Subjects received ibrutinib 560 mg capsules (4 capsules of 140 mg) orally once daily continuously starting on Cycle 1, Day 1 until disease progression, or unacceptable toxicity, or study end, whichever occurred first. All subjects also received a background therapy for maximum of 6 cycles (each cycle = 21 days) either with BR: bendamustine hydrochloride 90 mg/m^2 IV on Days 1 and 2 of each cycle and rituximab 375 mg/m^2 IV on Day 1 of each cycle; or background therapy with R-CHOP: rituximab 375 mg/m^2 IV on Day 1, cyclophosphamide 750 mg/m^2 IV on Day 1, doxorubicin 50 mg/m^2 IV on Day 1, vincristine 1.4 mg/m^2 IV (maximum total 2 mg) on Day 1, and prednisone 100 mg orally on Days 1 to 5 until disease progression or unacceptable toxicity. After treatment unblinding at the time of the primary analysis, subjects randomised to arm "Ibrutinib + CIT" continued/stopped treatment with ibrutinib at the discretion of the treating physician.

Arm type	Experimental
Investigational medicinal product name	Ibrutinib
Investigational medicinal product code	JNJ-54179060; PCI-32765
Other name	Imbruvica
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Subjects received ibrutinib 560 mg (4 capsules of 140 mg) once daily continuously starting on Cycle 1, Day 1 of each cycle of 21 days.

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

Dosage and administration details:

As a background therapy subjects received BR regimen: bendamustine hydrochloride 90 milligrams per meter square (mg/m^2) intravenously (IV) on Days 1 and 2 of each cycle of 21 days.

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

Dosage and administration details:

As a background therapy subjects received BR regimen: rituximab 375 mg/m^2 IV on Day 1 of each cycle.

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

Dosage and administration details:

As a background therapy subjects received R-CHOP regimen: prednisone 100 mg on Days 1 to 5 of each cycle of 21 days.

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

Dosage and administration details:

As a background therapy subjects received R-CHOP regimen: cyclophosphamide 750 mg/m^2 IV on Day 1 of each cycle of 21 days.

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

Dosage and administration details:

As a background therapy subjects received R-CHOP regimen: vincristine 1.4 mg/m^2 IV (maximum total 2 mg) on Day 1 of each cycle of 21 days.

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

Dosage and administration details:

As a background therapy subjects received R-CHOP regimen: rituximab 375 mg/m^2 IV on Day 1 of each cycle of 21 days.

Number of subjects in period 1	Placebo + Chemoimmunotherapy (CIT)	Ibrutinib + CIT
Started	201	202
Safety Analysis Set	199	201
Subjects With MZL	28 [1]	28 [2]
Subjects with FL	173	174
Completed	61	65
Not completed	140	137
Consent withdrawn by subject	24	20
Lost to follow-up	7	7
Sponsor decision	109	110

Notes:

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

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

Baseline characteristics

Reporting groups	
Reporting group title	Placebo + Chemoimmunotherapy (CIT)

Reporting group description:

Subjects received 4 capsules of placebo matching to ibrutinib orally once daily continuously starting on Cycle 1, Day 1 until disease progression, or unacceptable toxicity, or study end, whichever occurred first. All subjects also received a background therapy for maximum of 6 cycles (each cycle = 21 days) either with BR: bendamustine hydrochloride 90 milligrams per meter square (mg/m^2) intravenously (IV) on Days 1 and 2 of each cycle and rituximab 375 mg/m^2 IV on Day 1 of each cycle; or background therapy with R-CHOP: rituximab 375 mg/m^2 IV on Day 1, cyclophosphamide 750 mg/m^2 IV on Day 1, doxorubicin 50 mg/m^2 IV on Day 1, vincristine 1.4 mg/m^2 IV (maximum total 2 mg) on Day 1, and prednisone 100 mg orally on Days 1 to 5 until disease progression or unacceptable toxicity. After treatment unblinding at the time of the primary analysis, subjects randomised to arm "Placebo + CIT" discontinued placebo treatment.

Reporting group title	Ibrutinib + CIT

Reporting group description:

Subjects received ibrutinib 560 mg capsules (4 capsules of 140 mg) orally once daily continuously starting on Cycle 1, Day 1 until disease progression, or unacceptable toxicity, or study end, whichever occurred first. All subjects also received a background therapy for maximum of 6 cycles (each cycle = 21 days) either with BR: bendamustine hydrochloride 90 mg/m^2 IV on Days 1 and 2 of each cycle and rituximab 375 mg/m^2 IV on Day 1 of each cycle; or background therapy with R-CHOP: rituximab 375 mg/m^2 IV on Day 1, cyclophosphamide 750 mg/m^2 IV on Day 1, doxorubicin 50 mg/m^2 IV on Day 1, vincristine 1.4 mg/m^2 IV (maximum total 2 mg) on Day 1, and prednisone 100 mg orally on Days 1 to 5 until disease progression or unacceptable toxicity. After treatment unblinding at the time of the primary analysis, subjects randomised to arm "Ibrutinib + CIT" continued/stopped treatment with ibrutinib at the discretion of the treating physician.

Reporting group values	Placebo + Chemoimmunotherapy (CIT)	Ibrutinib + CIT	Total
Number of subjects	201	202	403
Title for AgeCategorical Units: subjects			
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	129	128	257
From 65 to 84 years	69	73	142
85 years and over	3	1	4
Title for AgeContinuous Units: years			
arithmetic mean	58.7	58.9	
standard deviation	± 12.7	± 11.86	-
Title for Gender Units: subjects			
Female	102	89	191
Male	99	113	212

End points

End points reporting groups

Reporting group title	Placebo + Chemoimmunotherapy (CIT)

Reporting group description:

Subjects received 4 capsules of placebo matching to ibrutinib orally once daily continuously starting on Cycle 1, Day 1 until disease progression, or unacceptable toxicity, or study end, whichever occurred first. All subjects also received a background therapy for maximum of 6 cycles (each cycle = 21 days) either with BR: bendamustine hydrochloride 90 milligrams per meter square (mg/m^2) intravenously (IV) on Days 1 and 2 of each cycle and rituximab 375 mg/m^2 IV on Day 1 of each cycle; or background therapy with R-CHOP: rituximab 375 mg/m^2 IV on Day 1, cyclophosphamide 750 mg/m^2 IV on Day 1, doxorubicin 50 mg/m^2 IV on Day 1, vincristine 1.4 mg/m^2 IV (maximum total 2 mg) on Day 1, and prednisone 100 mg orally on Days 1 to 5 until disease progression or unacceptable toxicity. After treatment unblinding at the time of the primary analysis, subjects randomised to arm "Placebo + CIT" discontinued placebo treatment.

Reporting group title	Ibrutinib + CIT

Reporting group description:

Subjects received ibrutinib 560 mg capsules (4 capsules of 140 mg) orally once daily continuously starting on Cycle 1, Day 1 until disease progression, or unacceptable toxicity, or study end, whichever occurred first. All subjects also received a background therapy for maximum of 6 cycles (each cycle = 21 days) either with BR: bendamustine hydrochloride 90 mg/m^2 IV on Days 1 and 2 of each cycle and rituximab 375 mg/m^2 IV on Day 1 of each cycle; or background therapy with R-CHOP: rituximab 375 mg/m^2 IV on Day 1, cyclophosphamide 750 mg/m^2 IV on Day 1, doxorubicin 50 mg/m^2 IV on Day 1, vincristine 1.4 mg/m^2 IV (maximum total 2 mg) on Day 1, and prednisone 100 mg orally on Days 1 to 5 until disease progression or unacceptable toxicity. After treatment unblinding at the time of the primary analysis, subjects randomised to arm "Ibrutinib + CIT" continued/stopped treatment with ibrutinib at the discretion of the treating physician.

Primary: Supplementary Analysis: Progression Free Survival: Unstratified Analysis - Subjects With Marginal Zone Lymphoma (MZL)

End point title	Supplementary Analysis: Progression Free Survival: Unstratified Analysis - Subjects With Marginal Zone Lymphoma (MZL)

End point description:

PFS in MZL:duration (in months) from date of randomisation to date of disease progression or relapse from CR or death, whichever was first reported. Per 2007 Revised Response Criteria for Malignant Lymphoma: disease progression: any new lesion or increase by >=50% of previously involved sites from nadir disease progression criteria: Appearance of new nodal lesion 1.5 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. Subjects who were progression-free and alive or had unknown status were censored at last tumor assessment. Kaplan-Meier method was used for analysis. Unstratified analysis was performed on subjects with MZL. All randomised subjects who were enrolled with MZL and were analysed according to treatment to which they were randomised. Here, 99999 represents that median and upper limit 95% CI were not calculated due to insufficient number of subjects with events.

End point type	Primary

End point timeframe:

Up to 8 years

End point values	Placebo + Chemoimmunotherapy (CIT)	Ibrutinib + CIT		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	28		
Units: Months				
median (confidence interval 95%)	91.63 (9.23 to 99999)	99999 (49.25 to 99999)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo + Chemoimmunotherapy (CIT) v Ibrutinib + CIT
Number of subjects included in analysis	56
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4505
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.725
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.312
upper limit	1.682

Primary: Primary Analysis: Progression Free Survival (PFS): Stratified Analysis

End point title	Primary Analysis: Progression Free Survival (PFS): Stratified Analysis

End point description:

PFS: duration (in months) from the date of randomisation to the date of disease progression or relapse from complete response (CR) or death, whichever was first reported. Per 2007 Revised Response Criteria for Malignant Lymphoma disease progression: any new lesion or increase by greater than or equal to (>=) 50 percent (%) of previously involved sites from nadir disease progression criteria: Appearance of new nodal lesion 1.5 centimeters (cm) in any axis, 50% increase in sum of product of diameters (SPD) of greater than (>)1 node or 50% increase in longest diameter of previously identified node 1 cm in short axis. Subjects who were progression-free and alive or had unknown status were censored at the last tumor assessment. Kaplan-Meier method and stratification factors was used for the analysis. Intent-to-treat (ITT) population: who were enrolled with follicular lymphoma (FL) or marginal zone lymphoma (MZL) and were analysed according to the treatment to which they were randomised.

End point type	Primary

End point timeframe:

Up to 8 years

End point values	Placebo + Chemoimmunotherapy (CIT)	Ibrutinib + CIT		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	201	202		
Units: Months				
median (confidence interval 95%)	23.75 (20.11 to 31.18)	40.51 (32.62 to 52.80)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo + Chemoimmunotherapy (CIT) v Ibrutinib + CIT
Number of subjects included in analysis	403
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0922
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.806
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.626
upper limit	1.037

Secondary: Supplementary Analysis: Complete Response Rate: Unstratified Analysis - Subjects With MZL

End point title	Supplementary Analysis: Complete Response Rate: Unstratified Analysis - Subjects With MZL

End point description:

CRR in MZL subjects was defined as the percentage of subjects who achieved a CR (based on investigator assessment) on or prior to the initiation of subsequent antilymphoma therapy. Criteria for CR: disappearance of all evidence of disease; 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 and no new sites of disease detected during assessment. Kaplan-Meier method was used for the analysis. For this end point, unstratified analysis was performed on subjects with MZL. All randomised subjects who were enrolled with MZL and were analysed according to the treatment to which they were randomised.

End point type	Secondary

End point timeframe:

Up to 8 years

End point values	Placebo + Chemoimmunotherapy (CIT)	Ibrutinib + CIT		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	28		
Units: Percentage of subjects				
number (not applicable)	60.7	64.3		

Statistical analyses

No statistical analyses for this end point

Secondary: Primary Analysis: Complete Response Rate (CRR): Stratified Analysis

End point title	Primary Analysis: Complete Response Rate (CRR): Stratified Analysis

End point description:

CRR was defined as the percentage of subjects who achieved a complete response (CR); (based on investigator assessment) on or prior to the initiation of subsequent antilymphoma therapy. Criteria for CR: disappearance of all evidence of disease; mass of any size permitted if positron emission tomography (PET) negative; regression to normal size on CT; spleen and liver: not palpable, nodules disappeared; bone marrow: infiltrate cleared on repeat biopsy and no new sites of disease detected during assessment. Kaplan-Meier method was used for the analysis. Stratification factors were used for the analysis. ITT population included all randomised subjects who were enrolled with FL or MZL and were analysed according to the treatment to which they were randomised.

End point type	Secondary

End point timeframe:

Up to 8 years

End point values	Placebo + Chemoimmunotherapy (CIT)	Ibrutinib + CIT		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	201	202		
Units: Percentage of subjects				
number (not applicable)	50.2	55		

Statistical analyses

No statistical analyses for this end point

Secondary: Primary Analysis: Overall Survival (OS): Stratified Analysis

End point title	Primary Analysis: Overall Survival (OS): Stratified Analysis

End point description:

OS was defined as the interval (in months) between the date of randomisation and the date of the subject's death due to any cause. Kaplan-Meier method was used for the analysis. Stratification factors were used for the analysis. ITT population included all randomised subjects who were enrolled with FL or MZL and were analysed according to the treatment to which they were randomised. Here, 99999 represents that median, upper and lower limit of 95% confidence interval (CI) were not calculated due to insufficient number of subjects with events.

End point type	Secondary

End point timeframe:

Up to 8 years

End point values	Placebo + Chemoimmunotherapy (CIT)	Ibrutinib + CIT		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	201	202		
Units: Months				
median (confidence interval 95%)	99999 (94.19 to 99999)	99999 (99999 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Supplementary Analysis: Overall Survival: Unstratified Analysis - Subjects With MZL

End point title	Supplementary Analysis: Overall Survival: Unstratified Analysis - Subjects With MZL

End point description:

OS in MZL subjects was defined as the interval (in months) between the date of randomisation and the date of the subject's death due to any cause. Kaplan-Meier method was used for the analysis. For this end point, unstratified analysis was performed on subjects with MZL. All randomised subjects who were enrolled with MZL and were analysed according to the treatment to which they were randomised. Here, 99999 represents that median, upper and lower limit of 95% CI were not calculated due to insufficient number of subjects with events.

End point type	Secondary

End point timeframe:

Up to 8 years

End point values	Placebo + Chemoimmunotherapy (CIT)	Ibrutinib + CIT		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	28		
Units: Months				
median (confidence interval 95%)	99999 (75.86 to 99999)	99999 (-99999 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Supplementary Analysis: Overall Response Rate: Unstratified Analysis - Subjects With MZL

End point title	Supplementary Analysis: Overall Response Rate: Unstratified Analysis - Subjects With MZL

End point description:

ORR in MZL subjects was defined as the percentage of subjects who achieved a CR or PR. Criteria for CR: disappearance of all evidence of disease; 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 and no new sites of disease detected during assessment. Criteria for PR: >=50% decrease in sum of the diameter of all target lesions compared with baseline, in absence of new lesions or unequivocal progression of non-target lesions. Kaplan-Meier method was used for the analysis. For this end point, unstratified analysis was performed on subjects with MZL. All randomised subjects who were enrolled with MZL and were analysed according to the treatment to which they were randomised.

End point type	Secondary

End point timeframe:

Up to 8 years

End point values	Placebo + Chemoimmunotherapy (CIT)	Ibrutinib + CIT		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	28		
Units: Percentage of subjects				
number (not applicable)	82.1	89.3		

Statistical analyses

No statistical analyses for this end point

Secondary: Primary Analysis: Overall Response Rate (ORR): Stratified Analysis

End point title	Primary Analysis: Overall Response Rate (ORR): Stratified Analysis

End point description:

ORR was defined as the percentage of subjects who achieved a CR or partial response (PR). Criteria for CR: disappearance of all evidence of disease; 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 and no new sites of disease detected during assessment. Criteria for PR: >=50% decrease in sum of the diameter of all target lesions compared with baseline, in absence of new lesions or unequivocal progression of non-target lesions. Kaplan-Meier method was used for the analysis. Stratification factors were used for the analysis. ITT population included all randomised subjects who were enrolled with FL or MZL and were analysed according to the treatment to which they were randomised.

End point type	Secondary

End point timeframe:

Up to 8 years

End point values	Placebo + Chemoimmunotherapy (CIT)	Ibrutinib + CIT		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	201	202		
Units: Percentage of subjects				
number (not applicable)	90.5	91.6		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Treatment-emergent Adverse Events (TEAEs)

End point title	Number of Subjects with Treatment-emergent Adverse Events (TEAEs)

End point description:

Number of subjects with TEAEs were reported. Adverse event (AE) was defined as any untoward medical occurrence in a clinical study subject administered a pharmaceutical (investigational or non investigational) product. An AE did not necessarily have a causal relationship with the pharmaceutical/biological agent under study. TEAEs were defined as adverse events with onset or worsening on or after date of first dose of study treatment up to and including 30 days after date of last dose of study medication. Safety analysis population included all randomised subjects who received at least 1 dose of study drug, and were analysed according to the actual treatment received.

End point type	Secondary

End point timeframe:

Placebo + Chemoimmunotherapy (CIT) arm: From Day 1 up to 30 days after date of last dose of study medication (up to 8 years); Ibrutinib + CIT arm: From Day 1 up to 30 days after date of last dose of study medication (up to 8 years 8 months)

End point values	Placebo + Chemoimmunotherapy (CIT)	Ibrutinib + CIT		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	199	201		
Units: Subjects	197	199		

Statistical analyses

No statistical analyses for this end point

Secondary: Primary Analysis: Duration of Response (DOR): Stratified Analysis

End point title	Primary Analysis: Duration of Response (DOR): Stratified Analysis

End point description:

DOR:the interval (in months) between the date of initial documentation of response (CR or PR) and the date of first documented evidence of progressive disease (or relapse for subjects who experienced CR during the study) or death, whichever occurred first. Criteria for CR: disappearance of all evidence of disease; 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 and no new sites of

disease detected during assessment. Criteria for PR: >=50% decrease in sum of the diameter of all target lesions compared with baseline, in absence of new lesions or unequivocal progression of non-target lesions. Kaplan-Meier method and stratification factors were used for the analysis. ITT population: randomised subjects enrolled with FL or MZL and were analysed according to the treatment to which they were randomised. Subjects achieved a PR or better included in this analysis.

End point type	Secondary

End point timeframe:

Up to 8 years

End point values	Placebo + Chemoimmunotherapy (CIT)	Ibrutinib + CIT		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	182	185		
Units: Months				
median (confidence interval 95%)	21.68 (17.61 to 32.36)	44.32 (32.89 to 60.02)		

Statistical analyses

No statistical analyses for this end point

Secondary: Supplementary Analysis: Duration of Response: Unstratified Analysis - Subjects With MZL

End point title	Supplementary Analysis: Duration of Response: Unstratified Analysis - Subjects With MZL

End point description:

DOR in MZL:interval (in months) between the date of initial documentation of response (CR or PR) and first evidence of progressive disease (or relapse for subjects with CR during the study) or death, whichever occurred first. CR criteria: disappearance of all evidence of disease; mass of any size permitted (PET negative); regression to normal size on CT; spleen and liver: not palpable, nodules disappeared; bone marrow: infiltrate cleared on repeat biopsy and no new disease sites detected at assessment. PR criteria:>=50% decrease in diameter of target lesions compared to baseline, in absence of new lesions or unequivocal progression of non-target lesions. Kaplan-Meier method and unstratified analysis was performed. All randomised subjects enrolled with MZL and analysed according to the treatment to which they were randomised. Subjects who achieved a PR or better were included in this analysis. 99999:median and upper limit 95% CI not calculated due to insufficient subjects with events.

End point type	Secondary

End point timeframe:

Up to 8 years

End point values	Placebo + Chemoimmunotherapy (CIT)	Ibrutinib + CIT		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	25		
Units: Months				
median (confidence interval 95%)	89.17 (42.48 to 99999)	99999 (73.23 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Primary Analysis: Time to Worsening (TTW) in the Lymphoma (Lym) Subscale of the Functional Assessment of Cancer Therapy - Lymphoma Subscale (FACT-LymS) Questionnaire

End point title	Primary Analysis: Time to Worsening (TTW) in the Lymphoma (Lym) Subscale of the Functional Assessment of Cancer Therapy - Lymphoma Subscale (FACT-LymS) Questionnaire

End point description:

Time-to-worsening in the Lymphoma subscale of the FACT-Lym was defined as the time (in months) from the date of randomisation to the start date of the worsening of subject symptoms. Worsening was defined by a 5-point decrease from baseline in subject symptoms. FACT-Lym Lymphoma subscale contains 15 questions, scores from 0 to 4 for each question (0 = not at all, 1 = a little bit, 2 = some what, 3 = quite a bit and 4 = very much, where the higher score indicated worse condition). 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 randomised subjects who were enrolled with FL or MZL and were analysed according to the treatment to which they were randomised.

End point type	Secondary

End point timeframe:

Up to 8 years

End point values	Placebo + Chemoimmunotherapy (CIT)	Ibrutinib + CIT		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	201	202		
Units: Months				
median (confidence interval 95%)	37.03 (24.21 to 48.33)	24.84 (14.95 to 31.28)		

Statistical analyses

No statistical analyses for this end point

Secondary: Supplementary Analysis: Time to Worsening (TTW) in the Lymphoma (Lym) Subscale of the Functional Assessment of Cancer Therapy - Lymphoma Subscale (FACT-LymS) Questionnaire: Subjects with MZL

End point title	Supplementary Analysis: Time to Worsening (TTW) in the Lymphoma (Lym) Subscale of the Functional Assessment of Cancer Therapy - Lymphoma Subscale (FACT-LymS) Questionnaire: Subjects with MZL

End point description:

TTW in MZL subjects in the Lymphoma subscale of the FACT-Lym was defined as the time (in months)

from the date of randomisation to the start date of the worsening of subject symptoms. Worsening was defined by a 5-point decrease from baseline in subject symptoms. FACT-Lym Lymphoma subscale contains 15 questions, scores from 0 to 4 for each question (0 = not at all, 1 = a little bit, 2 = some what, 3 = quite a bit and 4 = very much, where the higher score indicated worse condition). Lymphoma subscale score is the total of reverse scores, range 0 to 60. Higher scores indicate a better quality of life. All randomised subjects who were enrolled with MZL and were analysed according to the treatment to which they were randomised. Here, 99999 represents that upper limit of 95% CI was not calculated due to insufficient number of subjects with events.

End point type	Secondary

End point timeframe:

Up to 8 years

End point values	Placebo + Chemoimmunotherapy (CIT)	Ibrutinib + CIT		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	28		
Units: Months				
median (confidence interval 95%)	36.83 (4.86 to 99999)	58.91 (5.82 to 85.88)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with TEAEs: Subjects with MZL

End point title	Number of Subjects with TEAEs: Subjects with MZL

End point description:

Number of MZL subjects with TEAEs were reported. AE was defined as any untoward medical occurrence in a clinical study subject administered a pharmaceutical (investigational or non investigational) product. An AE did not necessarily have a causal relationship with the pharmaceutical/biological agent under study. TEAEs were defined as adverse events with onset or worsening on or after date of first dose of study treatment up to and including 30 days after date of last dose of study medication. Safety analysis population included all randomised subjects with MZL who received at least 1 dose of study drug, and were analysed according to the actual treatment received.

End point type	Secondary

End point timeframe:

Placebo + Chemoimmunotherapy (CIT) arm: From Day 1 up to 30 days after date of last dose of study medication (up to 8 years); Ibrutinib + CIT arm: From Day 1 up to 30 days after date of last dose of study medication (up to 8 years 8 months)

End point values	Placebo + Chemoimmunotherapy (CIT)	Ibrutinib + CIT		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	28		
Units: Subjects	28	28		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Serious & non-serious AEs:up to 30 days after last dose of study medication (up to 8 years for Placebo+CIT arm and 8 years 8 months for Ibrutinib+CIT arm); all cause deaths:Placebo+CIT: up to 8 years 4 months; Ibrutinib+CIT: up to 9 years 1 month

Adverse event reporting additional description:

All AEs were based on safety analysis: who received at least 1 dose of study drug, analysed as per actual treatment received. Subjects not received study drug not included in the safety analysis. Placebo+CIT arm subjects discontinued the study treatment post the primary analysis but were assessed for the safety till the end of the study.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25.0.

Reporting groups

Reporting group title	Ibrutinib + CIT

Reporting group description:

Subjects received ibrutinib 560 mg capsules (4 capsules of 140 mg) orally once daily continuously starting on Cycle 1, Day 1 until disease progression, or unacceptable toxicity, or study end, whichever occurred first. All subjects also received a background therapy for maximum of 6 cycles (each cycle = 21 days) either with BR: bendamustine hydrochloride 90 mg/m^2 IV on Days 1 and 2 of each cycle and rituximab 375 mg/m^2 IV on Day 1 of each cycle; or background therapy with R-CHOP: rituximab 375 mg/m^2 IV on Day 1, cyclophosphamide 750 mg/m^2 IV on Day 1, doxorubicin 50 mg/m^2 IV on Day 1, vincristine 1.4 mg/m^2 IV (maximum total 2 mg) on Day 1, and prednisone 100 mg orally on Days 1 to 5 until disease progression or unacceptable toxicity. After treatment unblinding at the time of the primary analysis, subjects randomised to arm "Placebo + CIT" discontinued placebo treatment.

Reporting group title	Placebo + Chemoimmunotherapy (CIT)

Reporting group description:

Subjects received 4 capsules of placebo matching to ibrutinib orally once daily continuously starting on Cycle 1, Day 1 until disease progression, or unacceptable toxicity, or study end, whichever occurred first. All subjects also received a background therapy for maximum of 6 cycles (each cycle = 21 days) either with BR: bendamustine hydrochloride 90 milligrams per meter square (mg/m^2) intravenously (IV) on Days 1 and 2 of each cycle and rituximab 375 mg/m^2 IV on Day 1 of each cycle; or background therapy with R-CHOP: rituximab 375 mg/m^2 IV on Day 1, cyclophosphamide 750 mg/m^2 IV on Day 1, doxorubicin 50 mg/m^2 IV on Day 1, vincristine 1.4 mg/m^2 IV (maximum total 2 mg) on Day 1, and prednisone 100 mg orally on Days 1 to 5 until disease progression or unacceptable toxicity. After treatment unblinding at the time of the primary analysis, subjects randomised to arm "Placebo + CIT" discontinued placebo treatment.

Serious adverse events	Ibrutinib + CIT	Placebo + Chemoimmunotherapy (CIT)	
Total subjects affected by serious adverse events			
subjects affected / exposed	113 / 201 (56.22%)	76 / 199 (38.19%)	
number of deaths (all causes)	64	61	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lung Neoplasm Malignant			

subjects affected / exposed	2 / 201 (1.00%)	2 / 199 (1.01%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 1	
Acute Myeloid Leukaemia			
subjects affected / exposed	0 / 201 (0.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Basal Cell Carcinoma			
subjects affected / exposed	2 / 201 (1.00%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder Cancer			
subjects affected / exposed	1 / 201 (0.50%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hypopharyngeal Cancer			
subjects affected / exposed	0 / 201 (0.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Myelodysplastic Syndrome			
subjects affected / exposed	1 / 201 (0.50%)	2 / 199 (1.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-Small Cell Lung Cancer			
subjects affected / exposed	1 / 201 (0.50%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-Small Cell Lung Cancer Metastatic			
subjects affected / exposed	1 / 201 (0.50%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian Cancer			

subjects affected / exposed	1 / 201 (0.50%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Plasma Cell Myeloma			
subjects affected / exposed	0 / 201 (0.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous Cell Carcinoma of Skin			
subjects affected / exposed	1 / 201 (0.50%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous Cell Carcinoma of the Tongue			
subjects affected / exposed	1 / 201 (0.50%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transitional Cell Carcinoma			
subjects affected / exposed	1 / 201 (0.50%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine Leiomyoma			
subjects affected / exposed	1 / 201 (0.50%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nasal Cavity Cancer			
subjects affected / exposed	0 / 201 (0.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Vascular disorders			
Venous Thrombosis			
subjects affected / exposed	1 / 201 (0.50%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Extremity Necrosis			

subjects affected / exposed	1 / 201 (0.50%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematoma			
subjects affected / exposed	1 / 201 (0.50%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	0 / 201 (0.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	2 / 201 (1.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Orthostatic Hypotension			
subjects affected / exposed	0 / 201 (0.00%)	2 / 199 (1.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	16 / 201 (7.96%)	5 / 199 (2.51%)	
occurrences causally related to treatment / all	0 / 19	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic Mass			
subjects affected / exposed	1 / 201 (0.50%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-Cardiac Chest Pain			
subjects affected / exposed	1 / 201 (0.50%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metaplasia			

subjects affected / exposed	1 / 201 (0.50%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hernia			
subjects affected / exposed	1 / 201 (0.50%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General Physical Health Deterioration			
subjects affected / exposed	2 / 201 (1.00%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gait Disturbance			
subjects affected / exposed	0 / 201 (0.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest Pain			
subjects affected / exposed	0 / 201 (0.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Anaphylactic Reaction			
subjects affected / exposed	0 / 201 (0.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypogammaglobulinaemia			
subjects affected / exposed	1 / 201 (0.50%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypersensitivity			
subjects affected / exposed	0 / 201 (0.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			

Benign Prostatic Hyperplasia			
subjects affected / exposed	1 / 201 (0.50%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostatomegaly			
subjects affected / exposed	1 / 201 (0.50%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine Cyst			
subjects affected / exposed	1 / 201 (0.50%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pleuritic Pain			
subjects affected / exposed	1 / 201 (0.50%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis Chronic			
subjects affected / exposed	1 / 201 (0.50%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchospasm			
subjects affected / exposed	1 / 201 (0.50%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic Obstructive Pulmonary Disease			
subjects affected / exposed	1 / 201 (0.50%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cough			
subjects affected / exposed	0 / 201 (0.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Dyspnoea			
subjects affected / exposed	3 / 201 (1.49%)	2 / 199 (1.01%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	1 / 201 (0.50%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial Lung Disease			
subjects affected / exposed	1 / 201 (0.50%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural Effusion			
subjects affected / exposed	1 / 201 (0.50%)	2 / 199 (1.01%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	2 / 201 (1.00%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary Fibrosis			
subjects affected / exposed	0 / 201 (0.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary Hypertension			
subjects affected / exposed	1 / 201 (0.50%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary Oedema			
subjects affected / exposed	0 / 201 (0.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory Failure			

subjects affected / exposed	0 / 201 (0.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Vocal Cord Leukoplakia			
subjects affected / exposed	1 / 201 (0.50%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vocal Cord Polyp			
subjects affected / exposed	1 / 201 (0.50%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary Embolism			
subjects affected / exposed	0 / 201 (0.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 201 (0.50%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bipolar Disorder			
subjects affected / exposed	0 / 201 (0.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disinhibition			
subjects affected / exposed	1 / 201 (0.50%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric Decompensation			
subjects affected / exposed	1 / 201 (0.50%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			

Neutrophil Count Decreased			
subjects affected / exposed	3 / 201 (1.49%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelet Count Decreased			
subjects affected / exposed	1 / 201 (0.50%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
White Blood Cell Count Decreased			
subjects affected / exposed	1 / 201 (0.50%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Ankle Fracture			
subjects affected / exposed	0 / 201 (0.00%)	1 / 199 (0.50%)	
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	0 / 201 (0.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hand Fracture			
subjects affected / exposed	1 / 201 (0.50%)	0 / 199 (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 / 201 (0.50%)	0 / 199 (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	3 / 201 (1.49%)	2 / 199 (1.01%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Road Traffic Accident			
subjects affected / exposed	0 / 201 (0.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal Compression Fracture			
subjects affected / exposed	1 / 201 (0.50%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal Fracture			
subjects affected / exposed	1 / 201 (0.50%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxicity to Various Agents			
subjects affected / exposed	0 / 201 (0.00%)	1 / 199 (0.50%)	
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	1 / 201 (0.50%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac Failure Chronic			
subjects affected / exposed	1 / 201 (0.50%)	0 / 199 (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 / 201 (0.50%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary Artery Disease			
subjects affected / exposed	2 / 201 (1.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left Ventricular Dysfunction			

subjects affected / exposed	0 / 201 (0.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mitral Valve Incompetence			
subjects affected / exposed	1 / 201 (0.50%)	0 / 199 (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	2 / 201 (1.00%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac Failure Acute			
subjects affected / exposed	1 / 201 (0.50%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac Failure			
subjects affected / exposed	3 / 201 (1.49%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac Dysfunction			
subjects affected / exposed	1 / 201 (0.50%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial Ischaemia			
subjects affected / exposed	2 / 201 (1.00%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial Fibrillation			
subjects affected / exposed	4 / 201 (1.99%)	2 / 199 (1.01%)	
occurrences causally related to treatment / all	0 / 4	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic Valve Incompetence			

subjects affected / exposed	1 / 201 (0.50%)	0 / 199 (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	1 / 201 (0.50%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac Arrest			
subjects affected / exposed	0 / 201 (0.00%)	2 / 199 (1.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 2	
Tricuspid Valve Incompetence			
subjects affected / exposed	1 / 201 (0.50%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular Tachycardia			
subjects affected / exposed	1 / 201 (0.50%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus Tachycardia			
subjects affected / exposed	1 / 201 (0.50%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial Effusion			
subjects affected / exposed	1 / 201 (0.50%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebral Ischaemia			
subjects affected / exposed	1 / 201 (0.50%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular Accident			

subjects affected / exposed	0 / 201 (0.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	1 / 201 (0.50%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic Stroke			
subjects affected / exposed	1 / 201 (0.50%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Post Herpetic Neuralgia			
subjects affected / exposed	0 / 201 (0.00%)	2 / 199 (1.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sciatica			
subjects affected / exposed	1 / 201 (0.50%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	0 / 201 (0.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subarachnoid Haemorrhage			
subjects affected / exposed	0 / 201 (0.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	2 / 201 (1.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			

subjects affected / exposed	0 / 201 (0.00%)	2 / 199 (1.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	5 / 201 (2.49%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			
subjects affected / exposed	1 / 201 (0.50%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile Neutropenia			
subjects affected / exposed	13 / 201 (6.47%)	7 / 199 (3.52%)	
occurrences causally related to treatment / all	0 / 14	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			
subjects affected / exposed	3 / 201 (1.49%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Tympanic Membrane Perforation			
subjects affected / exposed	1 / 201 (0.50%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear Discomfort			
subjects affected / exposed	1 / 201 (0.50%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Visual Impairment			
subjects affected / exposed	1 / 201 (0.50%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Necrotising Retinitis			

subjects affected / exposed	1 / 201 (0.50%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cataract Cortical			
subjects affected / exposed	1 / 201 (0.50%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal Artery Occlusion			
subjects affected / exposed	0 / 201 (0.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Haemorrhoids			
subjects affected / exposed	1 / 201 (0.50%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal Hernia			
subjects affected / exposed	0 / 201 (0.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal Fissure			
subjects affected / exposed	1 / 201 (0.50%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal Incontinence			
subjects affected / exposed	0 / 201 (0.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	1 / 201 (0.50%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			

subjects affected / exposed	3 / 201 (1.49%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	1 / 201 (0.50%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Crohn's Disease			
subjects affected / exposed	1 / 201 (0.50%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	2 / 201 (1.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal Haemorrhage			
subjects affected / exposed	1 / 201 (0.50%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small Intestinal Obstruction			
subjects affected / exposed	0 / 201 (0.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Rectal Stenosis			
subjects affected / exposed	1 / 201 (0.50%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal Haemorrhage			
subjects affected / exposed	0 / 201 (0.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngo-Oesophageal Diverticulum			

subjects affected / exposed	0 / 201 (0.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis Chronic			
subjects affected / exposed	1 / 201 (0.50%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis Acute			
subjects affected / exposed	2 / 201 (1.00%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	1 / 201 (0.50%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic Colitis			
subjects affected / exposed	0 / 201 (0.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	0 / 201 (0.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal Hernia			
subjects affected / exposed	3 / 201 (1.49%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper Gastrointestinal Haemorrhage			
subjects affected / exposed	1 / 201 (0.50%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			

subjects affected / exposed	2 / 201 (1.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	3 / 201 (1.49%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bile Duct Stone			
subjects affected / exposed	0 / 201 (0.00%)	1 / 199 (0.50%)	
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			
Psoriasis			
subjects affected / exposed	1 / 201 (0.50%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash			
subjects affected / exposed	2 / 201 (1.00%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urticaria			
subjects affected / exposed	1 / 201 (0.50%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute Kidney Injury			
subjects affected / exposed	5 / 201 (2.49%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Calculus Urinary			
subjects affected / exposed	0 / 201 (0.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Cystitis Noninfective			
subjects affected / exposed	1 / 201 (0.50%)	0 / 199 (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	1 / 201 (0.50%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydronephrosis			
subjects affected / exposed	0 / 201 (0.00%)	2 / 199 (1.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obstructive Nephropathy			
subjects affected / exposed	1 / 201 (0.50%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvi-Ureteric Obstruction			
subjects affected / exposed	0 / 201 (0.00%)	1 / 199 (0.50%)	
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 / 201 (0.00%)	1 / 199 (0.50%)	
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	3 / 201 (1.49%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone Pain			
subjects affected / exposed	0 / 201 (0.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Myositis			
subjects affected / exposed	0 / 201 (0.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteitis			
subjects affected / exposed	0 / 201 (0.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteonecrosis			
subjects affected / exposed	0 / 201 (0.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rotator Cuff Syndrome			
subjects affected / exposed	1 / 201 (0.50%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Diverticulitis			
subjects affected / exposed	1 / 201 (0.50%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	0 / 201 (0.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis Bacterial			
subjects affected / exposed	0 / 201 (0.00%)	1 / 199 (0.50%)	
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	1 / 201 (0.50%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Bacteraemia			

subjects affected / exposed	1 / 201 (0.50%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial Infection			
subjects affected / exposed	1 / 201 (0.50%)	0 / 199 (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 / 201 (0.50%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus Infection			
subjects affected / exposed	2 / 201 (1.00%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus Chorioretinitis			
subjects affected / exposed	0 / 201 (0.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis			
subjects affected / exposed	1 / 201 (0.50%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Covid-19 Pneumonia			
subjects affected / exposed	4 / 201 (1.99%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 6	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Coronavirus Infection			
subjects affected / exposed	1 / 201 (0.50%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic Sinusitis			

subjects affected / exposed	1 / 201 (0.50%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	5 / 201 (2.49%)	3 / 199 (1.51%)	
occurrences causally related to treatment / all	0 / 9	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Campylobacter Gastroenteritis			
subjects affected / exposed	1 / 201 (0.50%)	0 / 199 (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	3 / 201 (1.49%)	2 / 199 (1.01%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial Sepsis			
subjects affected / exposed	0 / 201 (0.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia Bacteraemia			
subjects affected / exposed	2 / 201 (1.00%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia Pyelonephritis			
subjects affected / exposed	0 / 201 (0.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia Urinary Tract Infection			
subjects affected / exposed	1 / 201 (0.50%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis Salmonella			

subjects affected / exposed	1 / 201 (0.50%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis Viral			
subjects affected / exposed	0 / 201 (0.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal Infection			
subjects affected / exposed	2 / 201 (1.00%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gingivitis			
subjects affected / exposed	0 / 201 (0.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
H1n1 Influenza			
subjects affected / exposed	0 / 201 (0.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemophilus Infection			
subjects affected / exposed	1 / 201 (0.50%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis E			
subjects affected / exposed	1 / 201 (0.50%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes Simplex			
subjects affected / exposed	0 / 201 (0.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes Zoster			

subjects affected / exposed	3 / 201 (1.49%)	4 / 199 (2.01%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	1 / 201 (0.50%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infectious Pleural Effusion			
subjects affected / exposed	1 / 201 (0.50%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infective Exacerbation of Chronic Obstructive Airways Disease			
subjects affected / exposed	1 / 201 (0.50%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral Discitis			
subjects affected / exposed	1 / 201 (0.50%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngitis			
subjects affected / exposed	1 / 201 (0.50%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower Respiratory Tract Infection			
subjects affected / exposed	2 / 201 (1.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nocardiosis			
subjects affected / exposed	1 / 201 (0.50%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Orchitis			

subjects affected / exposed	1 / 201 (0.50%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalitis			
subjects affected / exposed	0 / 201 (0.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Endocarditis			
subjects affected / exposed	0 / 201 (0.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Otitis Media			
subjects affected / exposed	2 / 201 (1.00%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic Abscess			
subjects affected / exposed	1 / 201 (0.50%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pertussis			
subjects affected / exposed	0 / 201 (0.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngitis			
subjects affected / exposed	1 / 201 (0.50%)	0 / 199 (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	2 / 201 (1.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pneumonia			

subjects affected / exposed	20 / 201 (9.95%)	9 / 199 (4.52%)	
occurrences causally related to treatment / all	0 / 30	0 / 10	
deaths causally related to treatment / all	0 / 3	0 / 1	
Pneumonia Bacterial			
subjects affected / exposed	2 / 201 (1.00%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia Cytomegaloviral			
subjects affected / exposed	1 / 201 (0.50%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia Herpes Viral			
subjects affected / exposed	1 / 201 (0.50%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia Klebsiella			
subjects affected / exposed	1 / 201 (0.50%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulpitis Dental			
subjects affected / exposed	1 / 201 (0.50%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	0 / 201 (0.00%)	1 / 199 (0.50%)	
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	2 / 201 (1.00%)	3 / 199 (1.51%)	
occurrences causally related to treatment / all	0 / 2	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhinovirus Infection			

subjects affected / exposed	2 / 201 (1.00%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Salmonella Sepsis			
subjects affected / exposed	0 / 201 (0.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Salmonellosis			
subjects affected / exposed	0 / 201 (0.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	8 / 201 (3.98%)	4 / 199 (2.01%)	
occurrences causally related to treatment / all	0 / 9	0 / 4	
deaths causally related to treatment / all	0 / 1	0 / 0	
Septic Shock			
subjects affected / exposed	3 / 201 (1.49%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Sinusitis			
subjects affected / exposed	3 / 201 (1.49%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin Infection			
subjects affected / exposed	1 / 201 (0.50%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Soft Tissue Infection			
subjects affected / exposed	1 / 201 (0.50%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal Sepsis			

subjects affected / exposed	1 / 201 (0.50%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Tonsillitis			
subjects affected / exposed	0 / 201 (0.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper Respiratory Tract Infection			
subjects affected / exposed	3 / 201 (1.49%)	2 / 199 (1.01%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary Tract Infection			
subjects affected / exposed	7 / 201 (3.48%)	3 / 199 (1.51%)	
occurrences causally related to treatment / all	0 / 7	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	1 / 201 (0.50%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Varicella			
subjects affected / exposed	1 / 201 (0.50%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular Device Infection			
subjects affected / exposed	1 / 201 (0.50%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vestibular Neuronitis			
subjects affected / exposed	1 / 201 (0.50%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral Infection			

subjects affected / exposed	0 / 201 (0.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vulvitis			
subjects affected / exposed	0 / 201 (0.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal Skin Infection			
subjects affected / exposed	1 / 201 (0.50%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Decreased Appetite			
subjects affected / exposed	2 / 201 (1.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes Mellitus			
subjects affected / exposed	0 / 201 (0.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Failure to Thrive			
subjects affected / exposed	0 / 201 (0.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hypokalaemia			
subjects affected / exposed	1 / 201 (0.50%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	2 / 201 (1.00%)	0 / 199 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malnutrition			

subjects affected / exposed	0 / 201 (0.00%)	1 / 199 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour Lysis Syndrome			
subjects affected / exposed	1 / 201 (0.50%)	2 / 199 (1.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Ibrutinib + CIT	Placebo + Chemoimmunotherapy (CIT)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	198 / 201 (98.51%)	196 / 199 (98.49%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	19 / 201 (9.45%)	17 / 199 (8.54%)	
occurrences (all)	37	38	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	16 / 201 (7.96%)	16 / 199 (8.04%)	
occurrences (all)	25	25	
Chills			
subjects affected / exposed	15 / 201 (7.46%)	9 / 199 (4.52%)	
occurrences (all)	19	15	
Fatigue			
subjects affected / exposed	73 / 201 (36.32%)	60 / 199 (30.15%)	
occurrences (all)	129	120	
Influenza Like Illness			
subjects affected / exposed	13 / 201 (6.47%)	1 / 199 (0.50%)	
occurrences (all)	15	1	
Malaise			
subjects affected / exposed	16 / 201 (7.96%)	8 / 199 (4.02%)	
occurrences (all)	26	15	
Oedema Peripheral			

subjects affected / exposed	18 / 201 (8.96%)	18 / 199 (9.05%)	
occurrences (all)	24	21	
Pyrexia			
subjects affected / exposed	60 / 201 (29.85%)	45 / 199 (22.61%)	
occurrences (all)	117	79	
Immune system disorders			
Hypogammaglobulinaemia			
subjects affected / exposed	20 / 201 (9.95%)	7 / 199 (3.52%)	
occurrences (all)	24	8	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	57 / 201 (28.36%)	40 / 199 (20.10%)	
occurrences (all)	99	58	
Dyspnoea			
subjects affected / exposed	19 / 201 (9.45%)	21 / 199 (10.55%)	
occurrences (all)	28	31	
Epistaxis			
subjects affected / exposed	16 / 201 (7.96%)	5 / 199 (2.51%)	
occurrences (all)	24	6	
Oropharyngeal Pain			
subjects affected / exposed	18 / 201 (8.96%)	20 / 199 (10.05%)	
occurrences (all)	27	23	
Productive Cough			
subjects affected / exposed	15 / 201 (7.46%)	17 / 199 (8.54%)	
occurrences (all)	21	20	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	17 / 201 (8.46%)	16 / 199 (8.04%)	
occurrences (all)	26	17	
Investigations			
Alanine Aminotransferase Increased			
subjects affected / exposed	27 / 201 (13.43%)	23 / 199 (11.56%)	
occurrences (all)	57	41	
Aspartate Aminotransferase Increased			
subjects affected / exposed	19 / 201 (9.45%)	20 / 199 (10.05%)	
occurrences (all)	25	40	

Blood Alkaline Phosphatase Increased			
subjects affected / exposed	15 / 201 (7.46%)	3 / 199 (1.51%)	
occurrences (all)	37	6	
Blood Bilirubin Increased			
subjects affected / exposed	9 / 201 (4.48%)	13 / 199 (6.53%)	
occurrences (all)	15	19	
Blood Creatinine Increased			
subjects affected / exposed	20 / 201 (9.95%)	10 / 199 (5.03%)	
occurrences (all)	43	15	
Lymphocyte Count Decreased			
subjects affected / exposed	17 / 201 (8.46%)	14 / 199 (7.04%)	
occurrences (all)	85	77	
Neutrophil Count Decreased			
subjects affected / exposed	32 / 201 (15.92%)	27 / 199 (13.57%)	
occurrences (all)	134	166	
Platelet Count Decreased			
subjects affected / exposed	35 / 201 (17.41%)	17 / 199 (8.54%)	
occurrences (all)	155	89	
Weight Decreased			
subjects affected / exposed	25 / 201 (12.44%)	11 / 199 (5.53%)	
occurrences (all)	50	19	
White Blood Cell Count Decreased			
subjects affected / exposed	31 / 201 (15.42%)	29 / 199 (14.57%)	
occurrences (all)	168	211	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	12 / 201 (5.97%)	3 / 199 (1.51%)	
occurrences (all)	16	4	
Infusion Related Reaction			
subjects affected / exposed	15 / 201 (7.46%)	18 / 199 (9.05%)	
occurrences (all)	19	23	
Cardiac disorders			
Atrial Fibrillation			
subjects affected / exposed	12 / 201 (5.97%)	5 / 199 (2.51%)	
occurrences (all)	14	7	
Nervous system disorders			

Dizziness Postural			
subjects affected / exposed	14 / 201 (6.97%)	13 / 199 (6.53%)	
occurrences (all)	14	17	
Headache			
subjects affected / exposed	35 / 201 (17.41%)	34 / 199 (17.09%)	
occurrences (all)	67	61	
Neuropathy Peripheral			
subjects affected / exposed	12 / 201 (5.97%)	10 / 199 (5.03%)	
occurrences (all)	18	12	
Paraesthesia			
subjects affected / exposed	6 / 201 (2.99%)	12 / 199 (6.03%)	
occurrences (all)	7	16	
Peripheral Sensory Neuropathy			
subjects affected / exposed	12 / 201 (5.97%)	8 / 199 (4.02%)	
occurrences (all)	20	11	
Dysgeusia			
subjects affected / exposed	12 / 201 (5.97%)	3 / 199 (1.51%)	
occurrences (all)	15	4	
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	75 / 201 (37.31%)	69 / 199 (34.67%)	
occurrences (all)	402	342	
Lymphopenia			
subjects affected / exposed	18 / 201 (8.96%)	23 / 199 (11.56%)	
occurrences (all)	90	68	
Leukopenia			
subjects affected / exposed	27 / 201 (13.43%)	26 / 199 (13.07%)	
occurrences (all)	199	107	
Anaemia			
subjects affected / exposed	50 / 201 (24.88%)	39 / 199 (19.60%)	
occurrences (all)	154	93	
Thrombocytopenia			
subjects affected / exposed	46 / 201 (22.89%)	28 / 199 (14.07%)	
occurrences (all)	187	90	
Ear and labyrinth disorders			

Vertigo			
subjects affected / exposed	12 / 201 (5.97%)	15 / 199 (7.54%)	
occurrences (all)	14	16	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	102 / 201 (50.75%)	69 / 199 (34.67%)	
occurrences (all)	225	123	
Dry Mouth			
subjects affected / exposed	13 / 201 (6.47%)	6 / 199 (3.02%)	
occurrences (all)	19	9	
Dyspepsia			
subjects affected / exposed	25 / 201 (12.44%)	15 / 199 (7.54%)	
occurrences (all)	36	16	
Nausea			
subjects affected / exposed	103 / 201 (51.24%)	78 / 199 (39.20%)	
occurrences (all)	225	180	
Vomiting			
subjects affected / exposed	57 / 201 (28.36%)	40 / 199 (20.10%)	
occurrences (all)	115	76	
Constipation			
subjects affected / exposed	33 / 201 (16.42%)	54 / 199 (27.14%)	
occurrences (all)	53	84	
Abdominal Pain Upper			
subjects affected / exposed	19 / 201 (9.45%)	13 / 199 (6.53%)	
occurrences (all)	26	14	
Abdominal Pain			
subjects affected / exposed	16 / 201 (7.96%)	18 / 199 (9.05%)	
occurrences (all)	26	23	
Stomatitis			
subjects affected / exposed	27 / 201 (13.43%)	12 / 199 (6.03%)	
occurrences (all)	58	17	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	11 / 201 (5.47%)	6 / 199 (3.02%)	
occurrences (all)	13	6	
Dry Skin			

subjects affected / exposed	13 / 201 (6.47%)	9 / 199 (4.52%)	
occurrences (all)	17	9	
Pruritus			
subjects affected / exposed	25 / 201 (12.44%)	30 / 199 (15.08%)	
occurrences (all)	33	39	
Rash			
subjects affected / exposed	68 / 201 (33.83%)	33 / 199 (16.58%)	
occurrences (all)	120	51	
Rash Maculo-Papular			
subjects affected / exposed	16 / 201 (7.96%)	12 / 199 (6.03%)	
occurrences (all)	32	15	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	28 / 201 (13.93%)	36 / 199 (18.09%)	
occurrences (all)	49	55	
Back Pain			
subjects affected / exposed	21 / 201 (10.45%)	21 / 199 (10.55%)	
occurrences (all)	28	25	
Muscle Spasms			
subjects affected / exposed	33 / 201 (16.42%)	16 / 199 (8.04%)	
occurrences (all)	60	23	
Myalgia			
subjects affected / exposed	23 / 201 (11.44%)	13 / 199 (6.53%)	
occurrences (all)	28	18	
Pain in Extremity			
subjects affected / exposed	17 / 201 (8.46%)	21 / 199 (10.55%)	
occurrences (all)	26	26	
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	10 / 201 (4.98%)	11 / 199 (5.53%)	
occurrences (all)	13	12	
Bronchitis			
subjects affected / exposed	21 / 201 (10.45%)	25 / 199 (12.56%)	
occurrences (all)	38	33	
Cellulitis			

subjects affected / exposed	16 / 201 (7.96%)	2 / 199 (1.01%)	
occurrences (all)	20	4	
Conjunctivitis			
subjects affected / exposed	11 / 201 (5.47%)	6 / 199 (3.02%)	
occurrences (all)	17	8	
Covid-19			
subjects affected / exposed	15 / 201 (7.46%)	4 / 199 (2.01%)	
occurrences (all)	16	4	
Folliculitis			
subjects affected / exposed	12 / 201 (5.97%)	3 / 199 (1.51%)	
occurrences (all)	14	3	
Herpes Zoster			
subjects affected / exposed	15 / 201 (7.46%)	22 / 199 (11.06%)	
occurrences (all)	21	24	
Influenza			
subjects affected / exposed	17 / 201 (8.46%)	16 / 199 (8.04%)	
occurrences (all)	18	18	
Nasopharyngitis			
subjects affected / exposed	23 / 201 (11.44%)	31 / 199 (15.58%)	
occurrences (all)	51	82	
Pneumonia			
subjects affected / exposed	25 / 201 (12.44%)	11 / 199 (5.53%)	
occurrences (all)	38	18	
Respiratory Tract Infection			
subjects affected / exposed	9 / 201 (4.48%)	12 / 199 (6.03%)	
occurrences (all)	13	18	
Sinusitis			
subjects affected / exposed	15 / 201 (7.46%)	12 / 199 (6.03%)	
occurrences (all)	24	16	
Skin Infection			
subjects affected / exposed	15 / 201 (7.46%)	4 / 199 (2.01%)	
occurrences (all)	24	4	
Upper Respiratory Tract Infection			
subjects affected / exposed	47 / 201 (23.38%)	49 / 199 (24.62%)	
occurrences (all)	94	93	
Urinary Tract Infection			

subjects affected / exposed	28 / 201 (13.93%)	10 / 199 (5.03%)	
occurrences (all)	82	11	
Metabolism and nutrition disorders			
Decreased Appetite			
subjects affected / exposed	44 / 201 (21.89%)	33 / 199 (16.58%)	
occurrences (all)	73	51	
Hyperglycaemia			
subjects affected / exposed	6 / 201 (2.99%)	11 / 199 (5.53%)	
occurrences (all)	18	18	
Hyperuricaemia			
subjects affected / exposed	16 / 201 (7.96%)	4 / 199 (2.01%)	
occurrences (all)	25	4	
Hypoalbuminaemia			
subjects affected / exposed	12 / 201 (5.97%)	2 / 199 (1.01%)	
occurrences (all)	21	2	
Hypokalaemia			
subjects affected / exposed	36 / 201 (17.91%)	12 / 199 (6.03%)	
occurrences (all)	89	16	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 December 2014	The purpose of this amendment was to remove requirement that only ~70% of subjects can receive 1 of the background chemotherapies as well as to implement several administrative clarifications. Updates on safety related information (eg, monitoring for ocular symptoms and atrial fibrillation; potential risks; and guidance on co-administration with certain concomitant medications) had been implemented to align with the current Investigator's Brochure (IB).
29 August 2022	The purpose of this amendment was to update the dose modification guidance and the data that was being collected after the clinical cutoff for the primary analysis.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported