Clinical trial results:
RIAltO: A Randomised Investigation of Alternative Ofatumumab-containing regimens in less fit patients with CLL

Summary

EudraCT number	2011-000919-22
Trial protocol	GB
Global end of trial date	24 May 2023

Results information

Result version number	v1 (current)
This version publication date	15 February 2025
First version publication date	15 February 2025
Summary attachment (see zip file)	RIAltO Final Statistical Analysis Report (RIAltO Final Statistical Analysis 2.0 Report_V1.0_30052024.pdf)

Trial information

Trial identification

Sponsor protocol code	OMB114578

Additional study identifiers

ISRCTN number	ISRCTN09988575
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Royal Liverpool Hospital, Liverpool University Hospitals NHS Foundation Trust
Sponsor organisation address	4th Floor Linda McCartney, Royal Liverpool Hospital, Prescot Street, Liverpool, United Kingdom, L7 8XP
Public contact	Charlotte Rawcliffe, CR:UK Liverpool Cancer Trials Unit, 44 01517948167, c.rawcliffe@liv.ac.uk
Scientific contact	Charlotte Rawcliffe, CR:UK Liverpool Cancer Trials Unit, 44 01517948167, c.rawcliffe@liv.ac.uk
Sponsor organisation name	The University of Liverpool, Research Support Office,
Sponsor organisation address	2nd Floor Block C, Waterhouse Building, 3 Brownlow Street, Liverpool, United Kingdom, L69 3GL
Public contact	Charlotte Rawcliffe , CR:UK Liverpool Cancer Trials Unit, 44 01517948285, c.rawcliffe@liv.ac.uk
Scientific contact	Charlotte Rawcliffe , CR:UK Liverpool Cancer Trials Unit, 44 01517948285, c.rawcliffe@liv.ac.uk

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	No

1901/2006 apply to this trial?	

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	30 May 2024
Is this the analysis of the primary completion data?	Yes
Primary completion date	24 May 2023
Global end of trial reached?	Yes
Global end of trial date	24 May 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess whether progression free survival (PFS) time (i.e. the length of time during and after medication or treatment during which the disease being treated does not get worse) using ofatumumab plus bendamustine is longer than that using ofatumumab plus chlorambucil.

Protection of trial subjects:

Risks were minimised by the exclusion of very frail patients with a WHO performance status of more than 3 and those patients with extensive co-morbidity. All patients were screened for significant liver dysfunction, HBsAg and HBcAb (together with antibodies to HIV and hepatitis C), and those who were positive for any of these tests were excluded from the study.
In addition, bendamustine was administered at the slightly lower dose (70mg/m2 rather than 90mg/m2) that has been used with good effect as part of immunochemotherapy regimens in previously treated patients. Patients who developped grade 3-4 infection or encounter haematological toxicity of sufficient severity to delay the next cycle of treatment received subsequent cycles at an attenuated dose, with G-CSF support in the event of severe neutropenia.

Background therapy: -	
Evidence for comparator: -	
Actual start date of recruitment	07 December 2011
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	United Kingdom: 521
Worldwide total number of subjects	521
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
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)	19
From 65 to 84 years	476
85 years and over	26

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Patient notes were screened by the research team prior to the patient being approached. Screening was performed for potential study patients after they had consented to trial participation and within 42 days prior to the first dose of treatment. Patients who fulfilled the screening requirements were eligible for enrolment.

Period 1

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

Arms

Are arms mutually exclusive?	No
Arm title	Bendamustine (Including Placebo)

Arm description:

Ofatumumab + Bendamustine (Including Placebo)

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

Dosage and administration details:

Ofatumumab + Bendamustine (experimental arm)
• Ofatumumab cycle 1: 300mg iv day 1, 1000mg iv day 8
cycle 2 onwards: 1000mg iv day 1
• Bendamustine 70mg/m2 iv days 1 and 2
• Cycles to be repeated every 28 days (± 4 days)

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

Dosage and administration details:

Ofatumumab + Bendamustine (experimental arm)
• Ofatumumab cycle 1: 300mg iv day 1, 1000mg iv day 8
cycle 2 onwards: 1000mg iv day 1
• Bendamustine 70mg/m2 iv days 1 and 2
• Cycles to be repeated every 28 days (± 4 days)

Arm title	Chlorambucil (Including Placebo)

Arm description:

Ofatumumab + Chlorambucil (Including Placebo)

Arm type	Standard Therapeutic

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

Dosage and administration details:

Ofatumumab + Chlorambucil (standard therapeutic arm)
• Ofatumumab cycle 1: 300mg iv day 1, 1000mg iv day 8
cycle 2 onwards: 1000mg iv day 1
• Chlorambucil 10mg/m2 po days 1 to 7
• Cycles to be repeated every 28 days (± 4 days)

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

Dosage and administration details:

Ofatumumab + Chlorambucil (standard therapeutic arm)
• Ofatumumab cycle 1: 300mg iv day 1, 1000mg iv day 8
cycle 2 onwards: 1000mg iv day 1
• Chlorambucil 10mg/m2 po days 1 to 7
• Cycles to be repeated every 28 days (± 4 days)

Arm title	Idelalisib

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Idelalisib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Idelalisib will be provided in tablets intended for oral administration. Each tablet contains 150 mg or 100 mg of active idelalisib. The 150 mg tablets will be used for the third and subsequent cycles of therapy; the 100mg tablets are provided for the second cycle of therapy and for use by those subjects who require a dose reduction. The 150 mg tablets are pink, film-coated, and include the following inactive excipients: microcrystalline cellulose, hydroxypropyl cellulose, croscarmellose sodium, sodium starch glycolate, magnesium stearate, red iron oxide, polyethylene glycol, talc, polyvinyl alcohol (PVA), and titanium dioxide. The 100 mg tablets are orange, film-coated, and include the following inactive excipients: microcrystalline cellulose, hydroxypropyl cellulose, croscarmellose sodium, sodium starch glycolate, magnesium stearate, yellow iron oxide, polyethylene glycol, talc, PVA, and titanium dioxide.

Number of subjects in period 1	Bendamustine (Including Placebo)	Chlorambucil (Including Placebo)	Idelalisib
Started	223	225	73
Completed	79	92	28
Not completed	144	133	45
Adverse event, serious fatal	64	54	16
Consent withdrawn by subject	13	19	7
Other	65	56	22
Lost to follow-up	2	4	-

Baseline characteristics

Reporting groups	
Reporting group title	Bendamustine (Including Placebo)
Reporting group description: Ofatumumab + Bendamustine (Including Placebo)	
Reporting group title	Chlorambucil (Including Placebo)
Reporting group description: Ofatumumab + Chlorambucil (Including Placebo)	
Reporting group title	Idelalisib
Reporting group description: -	

Reporting group values	Bendamustine (Including Placebo)	Chlorambucil (Including Placebo)	Idelalisib
Number of subjects	223	225	73
Age categorical Units: Subjects			
<=70	41	47	16
>70	182	178	57
Age continuous Units: years			
median	76.0	76.0	76.0
inter-quartile range (Q1-Q3)	72.0 to 80.0	72.0 to 79.0	71.0 to 80.0
Gender categorical Units: Subjects			
Female	79	82	17
Male	144	143	56
Who Performance Status, n Units: Subjects			
0/1	186	187	65
2/3	37	38	8
Missing	0	0	0
Cumulative Illness Rating Score, n Units: Subjects			
<=6	173	174	59
>6	50	51	14
Missing	0	0	0
Disease Stage, n Units: Subjects			
Stage A	28	26	13
Stage B	73	73	20
Stage C	116	123	40
Missing	6	3	0
VES-13 Assessment, n Units: Subjects			
<3	124	131	41
>=3	72	77	24
Missing	27	17	8
GFI Assessment, n			

Units: Subjects			
<4	121	137	37
>=4	72	71	28
Missing	30	17	8
Timed Up & Go Assessment, n Units: Subjects			
<10 seconds	84	73	29
>=10 seconds	92	105	30
Missing	47	47	14
IGHV Status, n Units: Subjects			
Mutated	67	73	19
Unmutated	71	79	30
Missing	85	73	24
FISH Status, n Units: Subjects			
17p-	12	6	3
11q-	23	29	11
+12	46	55	15
13q-	69	64	19
No FISH defect	53	51	20
Missing	20	20	5
Days to treatment since registration Units: Days			
median	9.0	7.0	8.5
inter-quartile range (Q1-Q3)	6.0 to 17.0	5.0 to 15.0	6.0 to 19.5
Cumulative Illness Rating Score Units: Score			
median	4.0	4.0	4.0
inter-quartile range (Q1-Q3)	2.0 to 6.0	2.0 to 6.0	2.0 to 5.0
VES-13 Assessment Units: Score			
median	1.0	1.0	1.0
inter-quartile range (Q1-Q3)	1.0 to 4.0	1.0 to 3.0	1.0 to 3.0
GFI Assessment Units: Score			
median	3.0	2.0	3.0
inter-quartile range (Q1-Q3)	1.0 to 5.0	1.0 to 4.0	2.0 to 4.0
Timed Up & Go Assessment Units: Seconds			
median	10.0	10.5	10.0
inter-quartile range (Q1-Q3)	8.2 to 14.4	8.2 to 16.0	7.5 to 12.7

Reporting group values	Total		
Number of subjects	521		
Age categorical Units: Subjects			
<=70	104		
>70	417		

Age continuous Units: years median inter-quartile range (Q1-Q3)	- 		
Gender categorical Units: Subjects			
Female	178		
Male	343		
Who Performance Status, n Units: Subjects			
0/1	438		
2/3	83		
Missing	0		
Cumulative Illness Rating Score, n Units: Subjects			
<=6	406		
>6	115		
Missing	0		
Disease Stage, n Units: Subjects			
Stage A	67		
Stage B	166		
Stage C	279		
Missing	9		
VES-13 Assessment, n Units: Subjects			
<3	296		
>=3	173		
Missing	52		
GFI Assessment, n Units: Subjects			
<4	295		
>=4	171		
Missing	55		
Timed Up & Go Assessment, n Units: Subjects			
<10 seconds	186		
>=10 seconds	227		
Missing	108		
IGHV Status, n Units: Subjects			
Mutated	159		
Unmutated	180		
Missing	182		
FISH Status, n Units: Subjects			
17p-	21		
11q-	63		
+12	116		
13q-	152		
No FISH defect	124		

Missing	45		

Days to treatment since registration Units: Days median inter-quartile range (Q1-Q3)	- -		
Cumulative Illness Rating Score Units: Score median inter-quartile range (Q1-Q3)	- -		
VES-13 Assessment Units: Score median inter-quartile range (Q1-Q3)	- -		
GFI Assessment Units: Score median inter-quartile range (Q1-Q3)	- -		
Timed Up & Go Assessment Units: Seconds median inter-quartile range (Q1-Q3)	- -		

End points reporting groups

Reporting group title	Bendamustine (Including Placebo)
Reporting group description: Ofatumumab + Bendamustine (Including Placebo)	
Reporting group title	Chlorambucil (Including Placebo)
Reporting group description: Ofatumumab + Chlorambucil (Including Placebo)	
Reporting group title	Idelalisib
Reporting group description: -	
Subject analysis set title	Bendamustine (Including Idelalisib & Placebo) (Randomised)
Subject analysis set type	Full analysis
Subject analysis set description: Ofatumumab + Bendamustine (Including Idelalisib & Placebo) (All Randomised)	
Subject analysis set title	Chlorambucil (Including Idelalisib & Placebo) (Randomised)
Subject analysis set type	Full analysis
Subject analysis set description: Ofatumumab + Chlorambucil (Including Idelalisib & Placebo) (All Randomised)	
Subject analysis set title	Bendamustine (Including Placebo) (Per protocol)
Subject analysis set type	Per protocol
Subject analysis set description: Ofatumumab + Bendamustine (Including Placebo) (Per protocol)	
Subject analysis set title	Chlorambucil (Including Placebo) (Per protocol)
Subject analysis set type	Per protocol
Subject analysis set description: Ofatumumab + Chlorambucil (Including Placebo) (Per protocol)	
Subject analysis set title	Bendamustine (Including Placebo) (Intention-to-treat)
Subject analysis set type	Intention-to-treat
Subject analysis set description: Ofatumumab + Bendamustine (Including Placebo) (Intention-to-treat)	
Subject analysis set title	Chlorambucil (Including Placebo) (Intention-to-treat)
Subject analysis set type	Intention-to-treat
Subject analysis set description: Ofatumumab + Chlorambucil (Including Placebo) (Intention-to-treat)	
Subject analysis set title	Bendamustine (Including Placebo) (Safety)
Subject analysis set type	Safety analysis
Subject analysis set description: Ofatumumab + Bendamustine (Including Placebo) (Safety)	
Subject analysis set title	Chlorambucil (Including Placebo) (Safety)
Subject analysis set type	Safety analysis
Subject analysis set description: Ofatumumab + Chlorambucil (Including Placebo) (Safety)	
Subject analysis set title	Idelalisib (Per protocol)
Subject analysis set type	Per protocol
Subject analysis set description: Idelalisib (Per protocol)	
Subject analysis set title	Placebo (Per protocol)
Subject analysis set type	Per protocol

Subject analysis set description: Placebo (Per protocol)	
Subject analysis set title	Idelalisib (Intention-to-treat)
Subject analysis set type	Intention-to-treat
Subject analysis set description: Idelalisib (Intention-to-treat)	
Subject analysis set title	Placebo (Intention-to-treat)
Subject analysis set type	Intention-to-treat
Subject analysis set description: Placebo (Intention-to-treat)	
Subject analysis set title	Idelalisib (Safety)
Subject analysis set type	Safety analysis
Subject analysis set description: Idelalisib (Safety)	
Subject analysis set title	Placebo (Safety)
Subject analysis set type	Safety analysis
Subject analysis set description: Placebo (Safety)	

Primary: Progression Free Survival (PFS) - Primary Analysis - Bendamustine vs. Chlorambucil (Including Placebo)

End point title	Progression Free Survival (PFS) - Primary Analysis - Bendamustine vs. Chlorambucil (Including Placebo)
End point description:	
End point type	Primary
End point timeframe: Unless they with withdrew, participants were followed up until progression, death or end of trial.	

End point values	Bendamustine (Including Placebo) (Intention-to-treat)	Chlorambucil (Including Placebo) (Intention-to-treat)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	222	223		
Units: PFS in months				
median (confidence interval 95%)	37.71 (32.85 to 44.55)	29.89 (26.38 to 34.66)		

Attachments (see zip file)	PFS - Forest Plot - Subgroup Analysis/10-3.png Kaplan Meier Plot: Progression Free Survival/10-1.png PFS - Cumulative Illness Rating Score (≤6 vs. >6)/17-1.png PFS - Cumulative Illness Rating Score (≤6)/17-2.png PFS - Cumulative Illness Rating Score (>6)/17-3.png PFS - Performance Status (0 vs. 1 vs. 2 vs. 3)/17-4.png

PFS - Performance Status (0)/17-5.png
PFS - Performance Status (1)/17-6.png
PFS - Performance Status (2)/17-7.png
PFS - Performance Status (3)/17-8.png
PFS - VES-13 (<3 vs. ≥3)/17-9.png
PFS - VES-13 (<3)/17-10.png
PFS - VES-13 (≥3) /17-11.png
PFS - GFI (<4 vs. ≥4)/17-12.png
PFS - GFI (<4)/17-13.png
PFS - GFI (≥4)/17-14.png
PFS - Timed Up and Go (<10 vs. ≥10)/17-15.png
PFS - Timed Up and Go (<10)/17-16.png
PFS - Timed Up and Go (≥10)/17-17.png
PFS – IGHV Status/18-1.png
PFS - IGHV (Mutated)/18-2.png
PFS - IGHV (Unmutated)/18-3.png
PFS - FISH Status/18-4.png
PFS - FISH (17p-)/18-5.png
PFS - FISH (11q-)/18-6.png
PFS - FISH (+12)/18-7.png
PFS - FISH (13q-)/18-8.png
PFS - FISH (No FISH Defect)/18-9.png

Statistical analyses

Statistical analysis title	Stratified Cox PH model
Comparison groups	Bendamustine (Including Placebo) (Intention-to-treat) v Chlorambucil (Including Placebo) (Intention-to-treat)
Number of subjects included in analysis	445
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	0.72
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.57
upper limit	0.9

Statistical analysis title	Stratified log rank test
Comparison groups	Bendamustine (Including Placebo) (Intention-to-treat) v Chlorambucil (Including Placebo) (Intention-to-treat)

Number of subjects included in analysis	445
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.004
Method	Logrank

Secondary: Exploratory Analysis - PFS - Idelalisib vs. Placebo

End point title	Exploratory Analysis - PFS - Idelalisib vs. Placebo

End point description:

End point type	Secondary

End point timeframe:

Unless they with withdrew, participants were followed up until progression, death or end of trial.

End point values	Idelalisib (Intention-to-treat)	Placebo (Intention-to-treat)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	73	70		
Units: PFS in months				
median (confidence interval 95%)	43.46 (32.42 to 59.92)	26.84 (22.34 to 39.13)		

Attachments (see zip file)	Kaplan Meier Plot: Progression Free Survival/10-2.png

Statistical analyses

Statistical analysis title	Stratified Cox PH model
Comparison groups	Idelalisib (Intention-to-treat) v Placebo (Intention-to-treat)
Number of subjects included in analysis	143
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	0.69
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.45
upper limit	1.05

Statistical analysis title	Stratified log rank test
Comparison groups	Idelalisib (Intention-to-treat) v Placebo (Intention-to-treat)

Number of subjects included in analysis	143
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.082
Method	Logrank

Secondary: Sensitivity Analysis 2 - PFS - All Randomised - Bendamustine vs. Chlorambucil (Including Idelalisib & Placebo)

End point title	Sensitivity Analysis 2 - PFS - All Randomised - Bendamustine vs. Chlorambucil (Including Idelalisib & Placebo)

End point description:

End point type	Secondary

End point timeframe:

Unless they with withdrew, participants were followed up until progression, death or end of trial.

End point values	Bendamustine (Including Idelalisib & Placebo) (Randomised)	Chlorambucil (Including Idelalisib & Placebo) (Randomised)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	260	261		
Units: PFS in months				
median (confidence interval 95%)	41.33 (35.45 to 48.39)	28.58 (26.38 to 33.67)		

Statistical analyses

Statistical analysis title	Stratified Cox PH model
Comparison groups	Bendamustine (Including Idelalisib & Placebo) (Randomised) v Chlorambucil (Including Idelalisib & Placebo) (Randomised)
Number of subjects included in analysis	521
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	0.67
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.54
upper limit	0.83

Statistical analysis title	Stratified log rank test
Comparison groups	Bendamustine (Including Idelalisib & Placebo) (Randomised) v Chlorambucil (Including Idelalisib & Placebo) (Randomised)
Number of subjects included in analysis	521
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Logrank

Secondary: Overall Survival (OS) - Primary Analysis – Bendamustine vs. Chlorambucil (Including Placebo)

End point title	Overall Survival (OS) - Primary Analysis – Bendamustine vs. Chlorambucil (Including Placebo)

End point description:

End point type	Secondary

End point timeframe:

Unless they withdrew, participants were followed up until death or end of trial.

End point values	Bendamustine (Including Placebo) (Intention-to-treat)	Chlorambucil (Including Placebo) (Intention-to-treat)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	222	223		
Units: OS in months				
median (confidence interval 95%)	75.03 (63.45 to 90.07)	70.10 (59.93 to 93.13)		

Attachments (see zip file)	Kaplan Meier Plot: Overall Survival/11-1.png OS - Forest Plot - Subgroup Analysis/11-3.png OS - Cumulative Illness Rating Score (≤6 vs. >6)/17-18.png OS - Cumulative Illness Rating Score (≤6)/17-19.png OS - Cumulative Illness Rating Score (>6)/17-20.png OS - Performance Status (0 vs. 1 vs. 2 vs. 3)/17-21.png OS - Performance Status (0)/17-22.png OS - Performance Status (1)/17-23.png OS - Performance Status (2)/17-24.png OS - Performance Status (3)/17-25.png OS - VES-13 (<3 vs. ≥3)/17-26.png

OS - VES-13 (<3)/17-27.png
OS - VES-13 (≥3)/17-28.png
OS - GFI (<4 vs. ≥4)/17-29.png
OS - GFI (<4)/17-30.png
OS - GFI (≥4)/17-31.png
OS - Timed Up and Go (<10 vs. ≥10)/17-32.png
OS - Timed Up and Go (<10)/17-33.png
OS - Timed Up and Go (≥10)/17-34.png
OS - IGHV Status/18-10.png
OS - IGHV (Mutated)/18-11.png
OS - IGHV (Unmutated)/18-12.png
OS - FISH Status/18-13.png
OS - FISH (17p-)/18-14.png
OS - FISH (11q-)/18-15.png
OS - FISH (+12)/18-16.png
OS - FISH (13q-)/18-17.png
OS - FISH (No FISH Defect)/18-18.png

Statistical analyses

Statistical analysis title	Stratified Cox PH model
Comparison groups	Bendamustine (Including Placebo) (Intention-to-treat) v Chlorambucil (Including Placebo) (Intention-to-treat)
Number of subjects included in analysis	445
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	1.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.78
upper limit	1.48

Statistical analysis title	Stratified log rank test
Comparison groups	Bendamustine (Including Placebo) (Intention-to-treat) v Chlorambucil (Including Placebo) (Intention-to-treat)
Number of subjects included in analysis	445
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.65
Method	Logrank

Secondary: Overall Survival (OS) - Exploratory Analysis – Idelalisib vs. Placebo	
End point title	Overall Survival (OS) - Exploratory Analysis – Idelalisib vs. Placebo

End point description:

End point type	Secondary

End point timeframe:

Unless they withdrew, participants were followed up until death or end of trial.

End point values	Idelalisib (Intention-to-treat)	Placebo (Intention-to-treat)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	73	70		
Units: No. OS events	20	26		

Attachments (see zip file)	Kaplan Meier Plot: Overall Survival/11-2.png

Statistical analyses

Statistical analysis title	Stratified Cox PH model
Comparison groups	Idelalisib (Intention-to-treat) v Placebo (Intention-to-treat)
Number of subjects included in analysis	143
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.38
upper limit	1.29

Statistical analysis title	Stratified log rank test
Comparison groups	Idelalisib (Intention-to-treat) v Placebo (Intention-to-treat)

Number of subjects included in analysis	143
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.251
Method	Logrank

Secondary: Response Including MRD Negativity - Primary Analysis – Bendamustine vs. Chlorambucil (Including Placebo) - Overall Response

End point title	Response Including MRD Negativity - Primary Analysis – Bendamustine vs. Chlorambucil (Including Placebo) - Overall Response
End point description:	
Overall Response (Complete Remission & Partial Remission)	
End point type	Secondary
End point timeframe:	
Response was assessed at end of treatment.	

End point values	Bendamustine (Including Placebo) (Intention-to-treat)	Chlorambucil (Including Placebo) (Intention-to-treat)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	143	141		
Units: Events	112	102		

Statistical analyses

Statistical analysis title	Logistic regression model
Statistical analysis description:	
Overall Response (Complete Remission & Partial Remission) - Logistic Regression Model	
Comparison groups	Bendamustine (Including Placebo) (Intention-to-treat) v Chlorambucil (Including Placebo) (Intention-to-treat)
Number of subjects included in analysis	284
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.334
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.31
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.76
upper limit	2.26

Secondary: Duration of Response - Primary Analysis – Bendamustine vs. Chlorambucil (Including Placebo)

End point title	Duration of Response - Primary Analysis – Bendamustine vs. Chlorambucil (Including Placebo)

End point description:

End point type	Secondary

End point timeframe:

Unless they withdrew, participants were followed up until progression or end of trial.

End point values	Bendamustine (Including Placebo) (Intention-to-treat)	Chlorambucil (Including Placebo) (Intention-to-treat)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	112	102		
Units: Response duration in months				
median (confidence interval 95%)	44.44 (32.57 to 49.80)	30.20 (23.19 to 34.90)		

Attachments (see zip file)	Kaplan Meier Plot: Duration of Response/13-1.png

Statistical analyses

Statistical analysis title	Stratified Cox PH model
Comparison groups	Bendamustine (Including Placebo) (Intention-to-treat) v Chlorambucil (Including Placebo) (Intention-to-treat)
Number of subjects included in analysis	214
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	0.58
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.4
upper limit	0.84

Statistical analysis title	Stratified log rank test
Comparison groups	Bendamustine (Including Placebo) (Intention-to-treat) v Chlorambucil (Including Placebo) (Intention-to-treat)

Number of subjects included in analysis	214
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.004
Method	Logrank

Secondary: Time to Treatment Failure (TTF) - Primary Analysis – Bendamustine vs. Chlorambucil (Including Placebo)

End point title	Time to Treatment Failure (TTF) - Primary Analysis – Bendamustine vs. Chlorambucil (Including Placebo)
End point description: Unless they withdrew, participants were followed up until treatment failure or end of trial.	
End point type	Secondary
End point timeframe: 12 months	

End point values	Bendamustine (Including Placebo) (Intention-to-treat)	Chlorambucil (Including Placebo) (Intention-to-treat)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	215	219		
Units: TTF in months				
median (confidence interval 95%)	37.73 (32.76 to 44.61)	28.09 (26.18 to 33.59)		

Attachments (see zip file)	Kaplan Meier Plot: Time to Treatment Failure/14-1.png TTF - Forest Plot - Subgroup Analysis/14-2.png TTF - Cumulative Illness Rating Score (≤6 vs. >6)/17-35.png TTF - Cumulative Illness Rating Score (≤6)/17-36.png TTF - Cumulative Illness Rating Score (>6)/17-37.png TTF - Performance Status (0 vs. 1 vs. 2 vs. 3)/17-38.png TTF - Performance Status (0)/17-39.png TTF - Performance Status (1)/17-40.png TTF - Performance Status (2)/17-41.png TTF - Performance Status (3)/17-42.png TTF - VES-13 (<3 vs. ≥3)/17-43.png TTF - VES-13 (<3)/17-44.png TTF - VES-13 (≥3)/17-45.png TTF - GFI (<4 vs. ≥4)/17-46.png

TTF - GFI (<4)/17-47.png
TTF - GFI (≥4)/17-48.png
TTF - Timed Up and Go (<10 vs. ≥10)/17-49.png
TTF - Timed Up and Go (<10)/17-50.png
TTF - Timed Up and Go (≥10)/17-51.png
TTF - IGHV Status/18-19.png
TTF - IGHV (Mutated)/18-20.png
TTF - IGHV (Unmutated)/18-21.png
TTF - FISH Status/18-22.png
TTF - FISH (17p-)/18-23.png
TTF - FISH (11q-)/18-24.png
TTF - FISH (+12)/18-25.png
TTF - FISH (No FISH Defect)/18-26.png

Statistical analyses

Statistical analysis title	Stratified Cox PH model
Comparison groups	Bendamustine (Including Placebo) (Intention-to-treat) v Chlorambucil (Including Placebo) (Intention-to-treat)
Number of subjects included in analysis	434
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	0.68
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.54
upper limit	0.86

Statistical analysis title	Stratified log rank test
Comparison groups	Bendamustine (Including Placebo) (Intention-to-treat) v Chlorambucil (Including Placebo) (Intention-to-treat)
Number of subjects included in analysis	434
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001
Method	Logrank

Secondary: Toxicity - Primary Analysis – Bendamustine vs. Chlorambucil (Including Placebo) - Toxicity Summary

End point title	Toxicity - Primary Analysis – Bendamustine vs. Chlorambucil (Including Placebo) - Toxicity Summary

End point description:

End point type	Secondary

End point timeframe:

Toxicity reported up to 28 days after last dose of treatment except for grade 3 and 4 infection which was reported until 6 months after last dose of treatment.

End point values	Bendamustine (Including Placebo) (Safety)	Chlorambucil (Including Placebo) (Safety)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	215	219		
Units: Events				
Grade 3+ AE	108	102		
SAE	139	127		
Either Grade 3+ AE or SAE	175	166		

Statistical analyses

No statistical analyses for this end point

Secondary: Toxicity - Exploratory Analysis – Idelalisib vs. Placebo - Toxicity Summary

End point title	Toxicity - Exploratory Analysis – Idelalisib vs. Placebo - Toxicity Summary

End point description:

End point type	Secondary

End point timeframe:

Toxicity reported up to 28 days after last dose of treatment except for grade 3 and 4 infection which was reported until 6 months after last dose of treatment.

End point values	Idelalisib (Safety)	Placebo (Safety)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	72	67		
Units: Events				
Grade 3+ AE	41	37		
SAE	60	38		
Either Grade 3+ AE or SAE	69	56		

Statistical analyses

No statistical analyses for this end point

Secondary: Toxicity - Primary Analysis – Bendamustine vs. Chlorambucil (Including Placebo) - Adverse Events by Severity

End point title	Toxicity - Primary Analysis – Bendamustine vs. Chlorambucil (Including Placebo) - Adverse Events by Severity

End point description:

End point type	Secondary

End point timeframe:

Toxicity reported up to 28 days after last dose of treatment except for grade 3 and 4 infection which was reported until 6 months after last dose of treatment.

End point values	Bendamustine (Including Placebo) (Safety)	Chlorambucil (Including Placebo) (Safety)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	215	219		
Units: Adverse Events				
Severity 1	1162	1105		
Severity 2	694	704		
Severity 3	219	222		
Severity 4	43	32		
Severity 5	0	1		
Missing	17	19		

Statistical analyses

No statistical analyses for this end point

Secondary: Toxicity - Primary Analysis – Bendamustine vs. Chlorambucil (Including Placebo) - Serious Adverse Events by Severity

End point title	Toxicity - Primary Analysis – Bendamustine vs. Chlorambucil (Including Placebo) - Serious Adverse Events by Severity

End point description:

End point type	Secondary

End point timeframe:

Toxicity reported up to 28 days after last dose of treatment except for grade 3 and 4 infection which was reported until 6 months after last dose of treatment.

End point values	Bendamustine (Including Placebo) (Safety)	Chlorambucil (Including Placebo) (Safety)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	215	219		
Units: Serious Adverse Events				
Severity 1	58	41		
Severity 2	89	69		
Severity 3	93	85		
Severity 4	18	18		
Severity 5	9	3		
Missing	40	18		

Statistical analyses

No statistical analyses for this end point

Secondary: Toxicity - Exploratory Analysis – Idelalisib vs. Placebo - Adverse Events by Severity

End point title	Toxicity - Exploratory Analysis – Idelalisib vs. Placebo - Adverse Events by Severity

End point description:

End point type	Secondary

End point timeframe:

Toxicity reported up to 28 days after last dose of treatment except for grade 3 and 4 infection which was reported until 6 months after last dose of treatment.

End point values	Idelalisib (Safety)	Placebo (Safety)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	72	67		
Units: Adverse Events				
Severity 1	460	493		
Severity 2	259	278		
Severity 3	114	80		
Severity 4	14	7		
Severity 5	1	0		
Missing	2	6		

Statistical analyses

No statistical analyses for this end point

Secondary: Toxicity - Exploratory Analysis – Idelalisib vs. Placebo - Serious Adverse

Events by Severity

End point title	Toxicity - Exploratory Analysis – Idelalisib vs. Placebo - Serious Adverse Events by Severity

End point description:

End point type	Secondary

End point timeframe:

Toxicity reported up to 28 days after last dose of treatment except for grade 3 and 4 infection which was reported until 6 months after last dose of treatment.

End point values	Idelalisib (Safety)	Placebo (Safety)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	72	67		
Units: Serious Adverse Events				
Severity 1	32	15		
Severity 2	42	38		
Severity 3	34	23		
Severity 4	9	4		
Severity 5	4	1		
Missing	20	18		

Statistical analyses

No statistical analyses for this end point

Secondary: Response Including MRD Negativity - Primary Analysis – Bendamustine vs. Chlorambucil (Including Placebo) - Response by Treatment

End point title	Response Including MRD Negativity - Primary Analysis – Bendamustine vs. Chlorambucil (Including Placebo) - Response by Treatment

End point description:

End point type	Secondary

End point timeframe:

Response was assessed at end of treatment.

End point values	Bendamustine (Including Placebo) (Intention-to-treat)	Chlorambucil (Including Placebo) (Intention-to-treat)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	143	141		
Units: Patients				
Complete Remission	1	1		

Partial Remission	111	101		
Stable Disease	23	36		
Progressive Disease	8	3		

Statistical analyses

No statistical analyses for this end point

Secondary: Response Including MRD Negativity - Primary Analysis – Bendamustine vs. Chlorambucil (Including Placebo) - MRD by Treatment

End point title	Response Including MRD Negativity - Primary Analysis – Bendamustine vs. Chlorambucil (Including Placebo) - MRD by Treatment

End point description:

End point type	Secondary

End point timeframe:

Response was assessed at end of treatment.

End point values	Bendamustine (Including Placebo) (Intention-to-treat)	Chlorambucil (Including Placebo) (Intention-to-treat)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	79	88		
Units: Patients				
MRD+ve	59	84		
MRD-ve	20	4		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Sensitivity Analysis 1 - PFS - Per Protocol Set - Bendamustine vs. Chlorambucil (Including Placebo)

End point title	Sensitivity Analysis 1 - PFS - Per Protocol Set - Bendamustine vs. Chlorambucil (Including Placebo)

End point description:

End point type	Other pre-specified

End point timeframe:

Unless they with withdrew, participants were followed up until progression, death or end of trial.

End point values	Bendamustine (Including Placebo) (Per protocol)	Chlorambucil (Including Placebo) (Per protocol)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	134	158		
Units: PFS in months				
median (confidence interval 95%)	37.71 (32.29 to 48.39)	28.32 (25.53 to 34.86)		

Statistical analyses

Statistical analysis title	Stratified Cox PH model
Comparison groups	Bendamustine (Including Placebo) (Per protocol) v Chlorambucil (Including Placebo) (Per protocol)
Number of subjects included in analysis	292
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	0.73
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.55
upper limit	0.99

Statistical analysis title	Stratified log rank test
Comparison groups	Bendamustine (Including Placebo) (Per protocol) v Chlorambucil (Including Placebo) (Per protocol)
Number of subjects included in analysis	292
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.042
Method	Logrank

Post-hoc: Additional Analysis - Time to Second Line Treatment - Bendamustine vs. Chlorambucil (Including Placebo)

End point title	Additional Analysis - Time to Second Line Treatment - Bendamustine vs. Chlorambucil (Including Placebo)

End point description:

End point type	Post-hoc

End point timeframe:
Time to Second Line Treatment (From Initiation of Study Treatment)

End point values	Bendamustine (Including Placebo) (Intention-to-treat)	Chlorambucil (Including Placebo) (Intention-to-treat)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	79	108		
Units: Events in months				
median (confidence interval 95%)	27.93 (23.52 to 35.59)	26.32 (21.45 to 29.87)		

Attachments (see zip file)	Time to Second Line Treatment/19-1.png

Statistical analyses

Statistical analysis title	Stratified Cox PH model
Comparison groups	Bendamustine (Including Placebo) (Intention-to-treat) v Chlorambucil (Including Placebo) (Intention-to-treat)
Number of subjects included in analysis	187
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	0.72
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.53
upper limit	0.98

Statistical analysis title	Stratified log rank test
Comparison groups	Bendamustine (Including Placebo) (Intention-to-treat) v Chlorambucil (Including Placebo) (Intention-to-treat)
Number of subjects included in analysis	187
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.034
Method	Logrank

Post-hoc: Additional Analysis - Time to Third Line Treatment (From Randomisation) - Bendamustine vs. Chlorambucil (Including Placebo)

End point title	Additional Analysis - Time to Third Line Treatment (From Randomisation) - Bendamustine vs. Chlorambucil (Including Placebo)

End point description:

End point type	Post-hoc

End point timeframe:

Time to Third Line Treatment (From Randomisation)

End point values	Bendamustine (Including Placebo) (Intention-to-treat)	Chlorambucil (Including Placebo) (Intention-to-treat)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	222	223		
Units: Events	21	37		

Attachments (see zip file)	Time to Third Line Treatment/19-2.png

Statistical analyses

Statistical analysis title	Stratified Cox PH model
Comparison groups	Bendamustine (Including Placebo) (Intention-to-treat) v Chlorambucil (Including Placebo) (Intention-to-treat)
Number of subjects included in analysis	445
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	0.49
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.28
upper limit	0.84

Statistical analysis title	Stratified log rank test
Comparison groups	Bendamustine (Including Placebo) (Intention-to-treat) v Chlorambucil (Including Placebo) (Intention-to-treat)
Number of subjects included in analysis	445
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.009
Method	Logrank

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Toxicity reported up to 28 days after last dose of treatment except for grade 3 and 4 infection which was reported until 6 months after last dose of treatment.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.0

Reporting groups

Reporting group title	Bendamustine

Reporting group description:

Adverse events are reported for the safety set (SS) which consists of all patients who received any trial treatment.
For "Total number of deaths (all causes)", the number provided is for the Intention-to-treat set rather than the Safety set.

Reporting group title	Chlorambucil

Reporting group description:

Adverse events are reported for the safety set (SS) which consists of all patients who received any trial treatment.
For "Total number of deaths (all causes)", the number provided is for the Intention-to-treat set rather than the Safety set.

Serious adverse events	Bendamustine	Chlorambucil	
Total subjects affected by serious adverse events			
subjects affected / exposed	139 / 215 (64.65%)	127 / 219 (57.99%)	
number of deaths (all causes)	83	76	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bladder transitional cell carcinoma stage I	Additional description: Relatedness has not been included in the report Fatalities number not included in the report		
subjects affected / exposed	1 / 215 (0.47%)	0 / 219 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangiocarcinoma	Additional description: Relatedness has not been included in the report Fatalities number not included in the report		
subjects affected / exposed	1 / 215 (0.47%)	0 / 219 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon cancer stage II	Additional description: Relatedness has not been included in the report Fatalities number not included in the report		

subjects affected / exposed	1 / 215 (0.47%)	0 / 219 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0

Hepatic cancer	Additional description: Relatedness has not been included in the report Fatalities number not included in the report	
subjects affected / exposed	1 / 215 (0.47%)	0 / 219 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0

Lentigo maligna	Additional description: Relatedness has not been included in the report Fatalities number not included in the report	
subjects affected / exposed	0 / 215 (0.00%)	1 / 219 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0

Lung neoplasm malignant	Additional description: Relatedness has not been included in the report Fatalities number not included in the report	
subjects affected / exposed	1 / 215 (0.47%)	0 / 219 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0

Acute myeloid leukaemia	Additional description: Relatedness has not been included in the report Fatalities number not included in the report	
subjects affected / exposed	0 / 215 (0.00%)	1 / 219 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0

Adenocarcinoma	Additional description: Relatedness has not been included in the report Fatalities number not included in the report	
subjects affected / exposed	1 / 215 (0.47%)	0 / 219 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0

Adenocarcinoma of colon	Additional description: Relatedness has not been included in the report Fatalities number not included in the report	
subjects affected / exposed	1 / 215 (0.47%)	0 / 219 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0

Basal cell carcinoma	Additional description: Relatedness has not been included in the report Fatalities number not included in the report	
subjects affected / exposed	5 / 215 (2.33%)	7 / 219 (3.20%)
occurrences causally related to treatment / all	0 / 5	0 / 7
deaths causally related to treatment / all	0 / 0	0 / 0

Bladder cancer	Additional description: Relatedness has not been included in the report Fatalities number not included in the report		
subjects affected / exposed	0 / 215 (0.00%)	1 / 219 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bowen's disease	Additional description: Relatedness has not been included in the report Fatalities number not included in the report		
subjects affected / exposed	5 / 215 (2.33%)	1 / 219 (0.46%)	
occurrences causally related to treatment / all	0 / 6	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cancer fatigue	Additional description: Relatedness has not been included in the report Fatalities number not included in the report		
subjects affected / exposed	0 / 215 (0.00%)	1 / 219 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic lymphocytic leukaemia transformation	Additional description: Relatedness has not been included in the report Fatalities number not included in the report		
subjects affected / exposed	1 / 215 (0.47%)	0 / 219 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon cancer	Additional description: Relatedness has not been included in the report Fatalities number not included in the report		
subjects affected / exposed	0 / 215 (0.00%)	1 / 219 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colorectal adenocarcinoma	Additional description: Relatedness has not been included in the report Fatalities number not included in the report		
subjects affected / exposed	0 / 215 (0.00%)	2 / 219 (0.91%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diffuse large B-cell lymphoma	Additional description: Relatedness has not been included in the report Fatalities number not included in the report		
subjects affected / exposed	0 / 215 (0.00%)	1 / 219 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
External ear neoplasm malignant	Additional description: Relatedness has not been included in the report Fatalities number not included in the report		

subjects affected / exposed	3 / 215 (1.40%)	3 / 219 (1.37%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gallbladder cancer	Additional description: Relatedness has not been included in the report Fatalities number not included in the report		
subjects affected / exposed	1 / 215 (0.47%)	0 / 219 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric cancer	Additional description: Relatedness has not been included in the report Fatalities number not included in the report		
subjects affected / exposed	1 / 215 (0.47%)	0 / 219 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatocellular carcinoma	Additional description: Relatedness has not been included in the report Fatalities number not included in the report		
subjects affected / exposed	2 / 215 (0.93%)	0 / 219 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hodgkin's disease	Additional description: Relatedness has not been included in the report Fatalities number not included in the report		
subjects affected / exposed	1 / 215 (0.47%)	0 / 219 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intraductal proliferative breast lesion	Additional description: Relatedness has not been included in the report Fatalities number not included in the report		
subjects affected / exposed	1 / 215 (0.47%)	0 / 219 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Invasive ductal breast carcinoma	Additional description: Relatedness has not been included in the report Fatalities number not included in the report		
subjects affected / exposed	3 / 215 (1.40%)	0 / 219 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung cancer metastatic	Additional description: Relatedness has not been included in the report Fatalities number not included in the report		
subjects affected / exposed	0 / 215 (0.00%)	1 / 219 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Lymphoma	Additional description: Relatedness has not been included in the report Fatalities number not included in the report		
subjects affected / exposed	1 / 215 (0.47%)	0 / 219 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Malignant melanoma	Additional description: Relatedness has not been included in the report Fatalities number not included in the report		
subjects affected / exposed	2 / 215 (0.93%)	0 / 219 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Meningioma	Additional description: Relatedness has not been included in the report Fatalities number not included in the report		
subjects affected / exposed	1 / 215 (0.47%)	0 / 219 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Metastatic malignant melanoma	Additional description: Relatedness has not been included in the report Fatalities number not included in the report		
subjects affected / exposed	1 / 215 (0.47%)	0 / 219 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Myeloproliferative neoplasm	Additional description: Relatedness has not been included in the report Fatalities number not included in the report		
subjects affected / exposed	1 / 215 (0.47%)	1 / 219 (0.46%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Neuroendocrine carcinoma	Additional description: Relatedness has not been included in the report Fatalities number not included in the report		
subjects affected / exposed	3 / 215 (1.40%)	0 / 219 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pancreatic carcinoma	Additional description: Relatedness has not been included in the report Fatalities number not included in the report

subjects affected / exposed	1 / 215 (0.47%)	1 / 219 (0.46%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleomorphic malignant fibrous histiocytoma	Additional description: Relatedness has not been included in the report Fatalities number not included in the report		
subjects affected / exposed	1 / 215 (0.47%)	0 / 219 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer	Additional description: Relatedness has not been included in the report Fatalities number not included in the report		
subjects affected / exposed	2 / 215 (0.93%)	2 / 219 (0.91%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal adenocarcinoma	Additional description: Relatedness has not been included in the report Fatalities number not included in the report		
subjects affected / exposed	0 / 215 (0.00%)	1 / 219 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Second primary malignancy	Additional description: Relatedness has not been included in the report Fatalities number not included in the report		
subjects affected / exposed	2 / 215 (0.93%)	2 / 219 (0.91%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin cancer	Additional description: Relatedness has not been included in the report Fatalities number not included in the report		
subjects affected / exposed	0 / 215 (0.00%)	1 / 219 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma	Additional description: Relatedness has not been included in the report Fatalities number not included in the report		
subjects affected / exposed	4 / 215 (1.86%)	3 / 219 (1.37%)	
occurrences causally related to treatment / all	0 / 9	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma of skin	Additional description: Relatedness has not been included in the report Fatalities number not included in the report		

subjects affected / exposed	12 / 215 (5.58%)	8 / 219 (3.65%)	
occurrences causally related to treatment / all	0 / 20	0 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urethral neoplasm	Additional description: Relatedness has not been included in the report Fatalities number not included in the report		
subjects affected / exposed	0 / 215 (0.00%)	1 / 219 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis	Additional description: Relatedness has not been included in the report Fatalities number not included in the report		
subjects affected / exposed	1 / 215 (0.47%)	0 / 219 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral artery embolism	Additional description: Relatedness has not been included in the report Fatalities number not included in the report		
subjects affected / exposed	0 / 215 (0.00%)	1 / 219 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematoma	Additional description: Relatedness has not been included in the report Fatalities number not included in the report		
subjects affected / exposed	1 / 215 (0.47%)	0 / 219 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension	Additional description: Relatedness has not been included in the report Fatalities number not included in the report		
subjects affected / exposed	0 / 215 (0.00%)	1 / 219 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension	Additional description: Relatedness has not been included in the report Fatalities number not included in the report		
subjects affected / exposed	1 / 215 (0.47%)	1 / 219 (0.46%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest pain	Additional description: Relatedness has not been included in the report Fatalities number not included in the report		

subjects affected / exposed	0 / 215 (0.00%)	1 / 219 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chills	Additional description: Relatedness has not been included in the report Fatalities number not included in the report		
subjects affected / exposed	2 / 215 (0.93%)	0 / 219 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration	Additional description: Relatedness has not been included in the report Fatalities number not included in the report		
subjects affected / exposed	0 / 215 (0.00%)	1 / 219 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza like illness	Additional description: Relatedness has not been included in the report Fatalities number not included in the report		
subjects affected / exposed	1 / 215 (0.47%)	0 / 219 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malaise	Additional description: Relatedness has not been included in the report Fatalities number not included in the report		
subjects affected / exposed	0 / 215 (0.00%)	1 / 219 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia	Additional description: Relatedness has not been included in the report Fatalities number not included in the report		
subjects affected / exposed	11 / 215 (5.12%)	5 / 219 (2.28%)	
occurrences causally related to treatment / all	0 / 11	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Amyloidosis senile	Additional description: Relatedness has not been included in the report Fatalities number not included in the report		
subjects affected / exposed	1 / 215 (0.47%)	0 / 219 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaphylactic reaction	Additional description: Relatedness has not been included in the report Fatalities number not included in the report		

subjects affected / exposed	1 / 215 (0.47%)	0 / 219 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaphylactoid reaction	Additional description: Relatedness has not been included in the report Fatalities number not included in the report		
subjects affected / exposed	1 / 215 (0.47%)	0 / 219 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Contrast media allergy	Additional description: Relatedness has not been included in the report Fatalities number not included in the report		
subjects affected / exposed	0 / 215 (0.00%)	1 / 219 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug hypersensitivity	Additional description: Relatedness has not been included in the report Fatalities number not included in the report		
subjects affected / exposed	2 / 215 (0.93%)	0 / 219 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypersensitivity	Additional description: Relatedness has not been included in the report Fatalities number not included in the report		
subjects affected / exposed	3 / 215 (1.40%)	2 / 219 (0.91%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Testicular swelling	Additional description: Relatedness has not been included in the report Fatalities number not included in the report		
subjects affected / exposed	0 / 215 (0.00%)	1 / 219 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease	Additional description: Relatedness has not been included in the report Fatalities number not included in the report		
subjects affected / exposed	3 / 215 (1.40%)	0 / 219 (0.00%)	
occurrences causally related to treatment / all	0 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea	Additional description: Relatedness has not been included in the report Fatalities number not included in the report		

subjects affected / exposed	1 / 215 (0.47%)	2 / 219 (0.91%)
occurrences causally related to treatment / all	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0

Epistaxis	Additional description: Relatedness has not been included in the report Fatalities number not included in the report	
subjects affected / exposed	0 / 215 (0.00%)	1 / 219 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0

Interstitial lung disease	Additional description: Relatedness has not been included in the report Fatalities number not included in the report	
subjects affected / exposed	0 / 215 (0.00%)	1 / 219 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0

Pleural effusion	Additional description: Relatedness has not been included in the report Fatalities number not included in the report	
subjects affected / exposed	3 / 215 (1.40%)	0 / 219 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0

Pneumonitis	Additional description: Relatedness has not been included in the report Fatalities number not included in the report	
subjects affected / exposed	1 / 215 (0.47%)	0 / 219 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0

Pneumothorax	Additional description: Relatedness has not been included in the report Fatalities number not included in the report	
subjects affected / exposed	0 / 215 (0.00%)	1 / 219 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0

Pulmonary embolism	Additional description: Relatedness has not been included in the report Fatalities number not included in the report	
subjects affected / exposed	3 / 215 (1.40%)	1 / 219 (0.46%)
occurrences causally related to treatment / all	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0

Respiratory distress	Additional description: Relatedness has not been included in the report Fatalities number not included in the report	
subjects affected / exposed	0 / 215 (0.00%)	1 / 219 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0

Psychiatric disorders			
Confusional state	Additional description: Relatedness has not been included in the report Fatalities number not included in the report		
subjects affected / exposed	1 / 215 (0.47%)	0 / 219 (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	Additional description: Relatedness has not been included in the report Fatalities number not included in the report		
subjects affected / exposed	0 / 215 (0.00%)	1 / 219 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Weight decreased	Additional description: Relatedness has not been included in the report Fatalities number not included in the report		
subjects affected / exposed	0 / 215 (0.00%)	1 / 219 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
X-ray with contrast upper gastrointestinal tract	Additional description: Relatedness has not been included in the report Fatalities number not included in the report		
subjects affected / exposed	1 / 215 (0.47%)	0 / 219 (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			
Expired product administered	Additional description: Relatedness has not been included in the report Fatalities number not included in the report		
subjects affected / exposed	1 / 215 (0.47%)	0 / 219 (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	Additional description: Relatedness has not been included in the report Fatalities number not included in the report		
subjects affected / exposed	25 / 215 (11.63%)	21 / 219 (9.59%)	
occurrences causally related to treatment / all	0 / 27	0 / 24	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haematuria	Additional description: Relatedness has not been included in the report Fatalities number not included in the report		
subjects affected / exposed	0 / 215 (0.00%)	1 / 219 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal compression fracture	Additional description: Relatedness has not been included in the report Fatalities number not included in the report		

subjects affected / exposed	1 / 215 (0.47%)	0 / 219 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haematoma	Additional description: Relatedness has not been included in the report Fatalities number not included in the report		
subjects affected / exposed	0 / 215 (0.00%)	2 / 219 (0.91%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Traumatic haematoma	Additional description: Relatedness has not been included in the report Fatalities number not included in the report		
subjects affected / exposed	1 / 215 (0.47%)	0 / 219 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction	Additional description: Relatedness has not been included in the report Fatalities number not included in the report		
subjects affected / exposed	2 / 215 (0.93%)	1 / 219 (0.46%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris	Additional description: Relatedness has not been included in the report Fatalities number not included in the report		
subjects affected / exposed	0 / 215 (0.00%)	1 / 219 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation	Additional description: Relatedness has not been included in the report Fatalities number not included in the report		
subjects affected / exposed	1 / 215 (0.47%)	1 / 219 (0.46%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bundle branch block right	Additional description: Relatedness has not been included in the report Fatalities number not included in the report		
subjects affected / exposed	0 / 215 (0.00%)	1 / 219 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure	Additional description: Relatedness has not been included in the report Fatalities number not included in the report		

subjects affected / exposed	2 / 215 (0.93%)	1 / 219 (0.46%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease	Additional description: Relatedness has not been included in the report Fatalities number not included in the report		
subjects affected / exposed	0 / 215 (0.00%)	1 / 219 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left ventricular dysfunction	Additional description: Relatedness has not been included in the report Fatalities number not included in the report		
subjects affected / exposed	1 / 215 (0.47%)	0 / 219 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction	Additional description: Relatedness has not been included in the report Fatalities number not included in the report		
subjects affected / exposed	2 / 215 (0.93%)	0 / 219 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial ischaemia	Additional description: Relatedness has not been included in the report Fatalities number not included in the report		
subjects affected / exposed	1 / 215 (0.47%)	1 / 219 (0.46%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Right ventricular failure	Additional description: Relatedness has not been included in the report Fatalities number not included in the report		
subjects affected / exposed	0 / 215 (0.00%)	1 / 219 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular extrasystoles	Additional description: Relatedness has not been included in the report Fatalities number not included in the report		
subjects affected / exposed	1 / 215 (0.47%)	0 / 219 (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			
Cerebrovascular accident	Additional description: Relatedness has not been included in the report Fatalities number not included in the report		
subjects affected / exposed	1 / 215 (0.47%)	2 / 219 (0.91%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Encephalopathy	Additional description: Relatedness has not been included in the report Fatalities number not included in the report		
subjects affected / exposed	1 / 215 (0.47%)	0 / 219 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache	Additional description: Relatedness has not been included in the report Fatalities number not included in the report		
subjects affected / exposed	1 / 215 (0.47%)	0 / 219 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lethargy	Additional description: Relatedness has not been included in the report Fatalities number not included in the report		
subjects affected / exposed	1 / 215 (0.47%)	0 / 219 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukoencephalopathy	Additional description: Relatedness has not been included in the report Fatalities number not included in the report		
subjects affected / exposed	0 / 215 (0.00%)	1 / 219 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Loss of consciousness	Additional description: Relatedness has not been included in the report Fatalities number not included in the report		
subjects affected / exposed	1 / 215 (0.47%)	0 / 219 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Presyncope	Additional description: Relatedness has not been included in the report Fatalities number not included in the report		
subjects affected / exposed	2 / 215 (0.93%)	1 / 219 (0.46%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure	Additional description: Relatedness has not been included in the report Fatalities number not included in the report		
subjects affected / exposed	0 / 215 (0.00%)	1 / 219 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope	Additional description: Relatedness has not been included in the report Fatalities number not included in the report		

subjects affected / exposed	1 / 215 (0.47%)	1 / 219 (0.46%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack	Additional description: Relatedness has not been included in the report Fatalities number not included in the report		
subjects affected / exposed	1 / 215 (0.47%)	0 / 219 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia	Additional description: Relatedness has not been included in the report Fatalities number not included in the report		
subjects affected / exposed	5 / 215 (2.33%)	9 / 219 (4.11%)	
occurrences causally related to treatment / all	0 / 6	0 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aplasia pure red cell	Additional description: Relatedness has not been included in the report Fatalities number not included in the report		
subjects affected / exposed	1 / 215 (0.47%)	0 / 219 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone marrow failure	Additional description: Relatedness has not been included in the report Fatalities number not included in the report		
subjects affected / exposed	1 / 215 (0.47%)	0 / 219 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia	Additional description: Relatedness has not been included in the report Fatalities number not included in the report		
subjects affected / exposed	9 / 215 (4.19%)	7 / 219 (3.20%)	
occurrences causally related to treatment / all	0 / 9	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia	Additional description: Relatedness has not been included in the report Fatalities number not included in the report		
subjects affected / exposed	1 / 215 (0.47%)	2 / 219 (0.91%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain	Additional description: Relatedness has not been included in the report Fatalities number not included in the report		

subjects affected / exposed	0 / 215 (0.00%)	4 / 219 (1.83%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation	Additional description: Relatedness has not been included in the report Fatalities number not included in the report		
subjects affected / exposed	1 / 215 (0.47%)	2 / 219 (0.91%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea	Additional description: Relatedness has not been included in the report Fatalities number not included in the report		
subjects affected / exposed	0 / 215 (0.00%)	3 / 219 (1.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer	Additional description: Relatedness has not been included in the report Fatalities number not included in the report		
subjects affected / exposed	1 / 215 (0.47%)	0 / 219 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis	Additional description: Relatedness has not been included in the report Fatalities number not included in the report		
subjects affected / exposed	1 / 215 (0.47%)	0 / 219 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea	Additional description: Relatedness has not been included in the report Fatalities number not included in the report		
subjects affected / exposed	1 / 215 (0.47%)	0 / 219 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting	Additional description: Relatedness has not been included in the report Fatalities number not included in the report		
subjects affected / exposed	1 / 215 (0.47%)	2 / 219 (0.91%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis acute	Additional description: Relatedness has not been included in the report Fatalities number not included in the report		

subjects affected / exposed	1 / 215 (0.47%)	2 / 219 (0.91%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis	Additional description: Relatedness has not been included in the report Fatalities number not included in the report		
subjects affected / exposed	1 / 215 (0.47%)	0 / 219 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic cirrhosis	Additional description: Relatedness has not been included in the report Fatalities number not included in the report		
subjects affected / exposed	0 / 215 (0.00%)	1 / 219 (0.46%)	
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			
Angioedema	Additional description: Relatedness has not been included in the report Fatalities number not included in the report		
subjects affected / exposed	1 / 215 (0.47%)	0 / 219 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dermatitis allergic	Additional description: Relatedness has not been included in the report Fatalities number not included in the report		
subjects affected / exposed	1 / 215 (0.47%)	0 / 219 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dermatitis exfoliative generalised	Additional description: Relatedness has not been included in the report Fatalities number not included in the report		
subjects affected / exposed	1 / 215 (0.47%)	0 / 219 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug eruption	Additional description: Relatedness has not been included in the report Fatalities number not included in the report		
subjects affected / exposed	2 / 215 (0.93%)	2 / 219 (0.91%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperhidrosis	Additional description: Relatedness has not been included in the report Fatalities number not included in the report		

subjects affected / exposed	0 / 215 (0.00%)	1 / 219 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lichen planus	Additional description: Relatedness has not been included in the report Fatalities number not included in the report		
subjects affected / exposed	1 / 215 (0.47%)	0 / 219 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psoriasis	Additional description: Relatedness has not been included in the report Fatalities number not included in the report		
subjects affected / exposed	1 / 215 (0.47%)	0 / 219 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash	Additional description: Relatedness has not been included in the report Fatalities number not included in the report		
subjects affected / exposed	1 / 215 (0.47%)	1 / 219 (0.46%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash maculo-papular	Additional description: Relatedness has not been included in the report Fatalities number not included in the report		
subjects affected / exposed	0 / 215 (0.00%)	4 / 219 (1.83%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin ulcer	Additional description: Relatedness has not been included in the report Fatalities number not included in the report		
subjects affected / exposed	1 / 215 (0.47%)	0 / 219 (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	Additional description: Relatedness has not been included in the report Fatalities number not included in the report		
subjects affected / exposed	3 / 215 (1.40%)	0 / 219 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal impairment	Additional description: Relatedness has not been included in the report Fatalities number not included in the report		
subjects affected / exposed	0 / 215 (0.00%)	1 / 219 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Urinary retention	Additional description: Relatedness has not been included in the report Fatalities number not included in the report		
subjects affected / exposed	1 / 215 (0.47%)	3 / 219 (1.37%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain	Additional description: Relatedness has not been included in the report Fatalities number not included in the report		
subjects affected / exposed	1 / 215 (0.47%)	2 / 219 (0.91%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal chest pain	Additional description: Relatedness has not been included in the report Fatalities number not included in the report		
subjects affected / exposed	1 / 215 (0.47%)	0 / 219 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal osteoarthritis	Additional description: Relatedness has not been included in the report Fatalities number not included in the report		
subjects affected / exposed	1 / 215 (0.47%)	0 / 219 (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			
Abdominal infection	Additional description: Relatedness has not been included in the report Fatalities number not included in the report		
subjects affected / exposed	1 / 215 (0.47%)	0 / 219 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anorectal infection	Additional description: Relatedness has not been included in the report Fatalities number not included in the report		
subjects affected / exposed	1 / 215 (0.47%)	0 / 219 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atypical pneumonia	Additional description: Relatedness has not been included in the report Fatalities number not included in the report		
subjects affected / exposed	0 / 215 (0.00%)	1 / 219 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis	Additional description: Relatedness has not been included in the report Fatalities number not included in the report		

subjects affected / exposed	1 / 215 (0.47%)	1 / 219 (0.46%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
COVID-19	Additional description: Relatedness has not been included in the report Fatalities number not included in the report	
subjects affected / exposed	1 / 215 (0.47%)	2 / 219 (0.91%)
occurrences causally related to treatment / all	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Campylobacter infection	Additional description: Relatedness has not been included in the report Fatalities number not included in the report	
subjects affected / exposed	1 / 215 (0.47%)	0 / 219 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Candida infection	Additional description: Relatedness has not been included in the report Fatalities number not included in the report	
subjects affected / exposed	0 / 215 (0.00%)	1 / 219 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Cellulitis	Additional description: Relatedness has not been included in the report Fatalities number not included in the report	
subjects affected / exposed	1 / 215 (0.47%)	1 / 219 (0.46%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Cytomegalovirus colitis	Additional description: Relatedness has not been included in the report Fatalities number not included in the report	
subjects affected / exposed	1 / 215 (0.47%)	0 / 219 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Encephalitis	Additional description: Relatedness has not been included in the report Fatalities number not included in the report	
subjects affected / exposed	1 / 215 (0.47%)	0 / 219 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Encephalitis viral	Additional description: Relatedness has not been included in the report Fatalities number not included in the report	
subjects affected / exposed	1 / 215 (0.47%)	0 / 219 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0

Escherichia infection	Additional description: Relatedness has not been included in the report Fatalities number not included in the report		
subjects affected / exposed	0 / 215 (0.00%)	1 / 219 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis viral	Additional description: Relatedness has not been included in the report Fatalities number not included in the report		
subjects affected / exposed	2 / 215 (0.93%)	0 / 219 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis B	Additional description: Relatedness has not been included in the report Fatalities number not included in the report		
subjects affected / exposed	1 / 215 (0.47%)	0 / 219 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster	Additional description: Relatedness has not been included in the report Fatalities number not included in the report		
subjects affected / exposed	0 / 215 (0.00%)	2 / 219 (0.91%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster oticus	Additional description: Relatedness has not been included in the report Fatalities number not included in the report		
subjects affected / exposed	0 / 215 (0.00%)	1 / 219 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection	Additional description: Relatedness has not been included in the report Fatalities number not included in the report		
subjects affected / exposed	7 / 215 (3.26%)	5 / 219 (2.28%)	
occurrences causally related to treatment / all	0 / 7	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infective exacerbation of bronchiectasis	Additional description: Relatedness has not been included in the report Fatalities number not included in the report		
subjects affected / exposed	1 / 215 (0.47%)	0 / 219 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine infection	Additional description: Relatedness has not been included in the report Fatalities number not included in the report		

subjects affected / exposed	1 / 215 (0.47%)	0 / 219 (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	Additional description: Relatedness has not been included in the report Fatalities number not included in the report		
subjects affected / exposed	22 / 215 (10.23%)	13 / 219 (5.94%)	
occurrences causally related to treatment / all	0 / 23	0 / 14	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic sepsis	Additional description: Relatedness has not been included in the report Fatalities number not included in the report		
subjects affected / exposed	19 / 215 (8.84%)	13 / 219 (5.94%)	
occurrences causally related to treatment / all	0 / 20	0 / 14	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oral candidiasis	Additional description: Relatedness has not been included in the report Fatalities number not included in the report		
subjects affected / exposed	0 / 215 (0.00%)	1 / 219 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumocystis jirovecii pneumonia	Additional description: Relatedness has not been included in the report Fatalities number not included in the report		
subjects affected / exposed	1 / 215 (0.47%)	0 / 219 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia	Additional description: Relatedness has not been included in the report Fatalities number not included in the report		
subjects affected / exposed	13 / 215 (6.05%)	5 / 219 (2.28%)	
occurrences causally related to treatment / all	0 / 13	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia pneumococcal	Additional description: Relatedness has not been included in the report Fatalities number not included in the report		
subjects affected / exposed	0 / 215 (0.00%)	1 / 219 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Progressive multifocal leukoencephalopathy	Additional description: Relatedness has not been included in the report Fatalities number not included in the report		
subjects affected / exposed	0 / 215 (0.00%)	1 / 219 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pulmonary sepsis	Additional description: Relatedness has not been included in the report Fatalities number not included in the report		
subjects affected / exposed	1 / 215 (0.47%)	0 / 219 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection	Additional description: Relatedness has not been included in the report Fatalities number not included in the report		
subjects affected / exposed	0 / 215 (0.00%)	2 / 219 (0.91%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Salmonellosis	Additional description: Relatedness has not been included in the report Fatalities number not included in the report		
subjects affected / exposed	0 / 215 (0.00%)	1 / 219 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis	Additional description: Relatedness has not been included in the report Fatalities number not included in the report		
subjects affected / exposed	9 / 215 (4.19%)	4 / 219 (1.83%)	
occurrences causally related to treatment / all	0 / 9	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock	Additional description: Relatedness has not been included in the report Fatalities number not included in the report		
subjects affected / exposed	0 / 215 (0.00%)	1 / 219 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection	Additional description: Relatedness has not been included in the report Fatalities number not included in the report		
subjects affected / exposed	0 / 215 (0.00%)	4 / 219 (1.83%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection	Additional description: Relatedness has not been included in the report Fatalities number not included in the report		
subjects affected / exposed	1 / 215 (0.47%)	3 / 219 (1.37%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis	Additional description: Relatedness has not been included in the report Fatalities number not included in the report		

subjects affected / exposed	1 / 215 (0.47%)	2 / 219 (0.91%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection	Additional description: Relatedness has not been included in the report Fatalities number not included in the report		
subjects affected / exposed	0 / 215 (0.00%)	2 / 219 (0.91%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral upper respiratory tract infection	Additional description: Relatedness has not been included in the report Fatalities number not included in the report		
subjects affected / exposed	1 / 215 (0.47%)	0 / 219 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection	Additional description: Relatedness has not been included in the report Fatalities number not included in the report		
subjects affected / exposed	1 / 215 (0.47%)	0 / 219 (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			
Alcohol intolerance	Additional description: Relatedness has not been included in the report Fatalities number not included in the report		
subjects affected / exposed	0 / 215 (0.00%)	1 / 219 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration	Additional description: Relatedness has not been included in the report Fatalities number not included in the report		
subjects affected / exposed	1 / 215 (0.47%)	1 / 219 (0.46%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia	Additional description: Relatedness has not been included in the report Fatalities number not included in the report		
subjects affected / exposed	0 / 215 (0.00%)	2 / 219 (0.91%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia	Additional description: Relatedness has not been included in the report Fatalities number not included in the report		
subjects affected / exposed	1 / 215 (0.47%)	2 / 219 (0.91%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Hypokalaemic syndrome	Additional description: Relatedness has not been included in the report Fatalities number not included in the report		
subjects affected / exposed	1 / 215 (0.47%)	0 / 219 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour lysis syndrome	Additional description: Relatedness has not been included in the report Fatalities number not included in the report		
subjects affected / exposed	2 / 215 (0.93%)	0 / 219 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Bendamustine	Chlorambucil	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	180 / 215 (83.72%)	184 / 219 (84.02%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other, specify			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	5 / 215 (2.33%)	6 / 219 (2.74%)	
occurrences (all)	6	6	
Vascular disorders			
Flushing			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	2 / 215 (0.93%)	2 / 219 (0.91%)	
occurrences (all)	2	2	
Haematoma			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	2 / 215 (0.93%)	0 / 219 (0.00%)	
occurrences (all)	2	0	
Hot flashes			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 215 (0.47%)	0 / 219 (0.00%)	
occurrences (all)	1	0	
Hypertension			

alternative dictionary used: CTCAE 4			
subjects affected / exposed	3 / 215 (1.40%)	5 / 219 (2.28%)	
occurrences (all)	3	5	
Hypotension			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	6 / 215 (2.79%)	9 / 219 (4.11%)	
occurrences (all)	6	9	
Phlebitis			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 215 (0.47%)	0 / 219 (0.00%)	
occurrences (all)	2	0	
Thromboembolic event			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	2 / 215 (0.93%)	2 / 219 (0.91%)	
occurrences (all)	2	4	
Vascular disorders - Other, specify			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	2 / 215 (0.93%)	1 / 219 (0.46%)	
occurrences (all)	2	1	
General disorders and administration site conditions			
Chills			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	15 / 215 (6.98%)	18 / 219 (8.22%)	
occurrences (all)	18	21	
Edema face			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	2 / 215 (0.93%)	0 / 219 (0.00%)	
occurrences (all)	2	0	
Edema limbs			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	21 / 215 (9.77%)	13 / 219 (5.94%)	
occurrences (all)	22	14	
Fatigue			
alternative dictionary used: CTCAE 4			

subjects affected / exposed	70 / 215 (32.56%)	80 / 219 (36.53%)	
occurrences (all)	91	100	
Fever			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	26 / 215 (12.09%)	10 / 219 (4.57%)	
occurrences (all)	30	14	
Flu like symptoms			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	11 / 215 (5.12%)	5 / 219 (2.28%)	
occurrences (all)	11	6	
Gait disturbance			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 215 (0.47%)	1 / 219 (0.46%)	
occurrences (all)	1	1	
General disorders and administration site conditions - Other, specify			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	17 / 215 (7.91%)	22 / 219 (10.05%)	
occurrences (all)	24	29	
Infusion related reaction			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	63 / 215 (29.30%)	65 / 219 (29.68%)	
occurrences (all)	84	101	
Infusion site extravasation			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 215 (0.47%)	0 / 219 (0.00%)	
occurrences (all)	1	0	
Injection site reaction			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 215 (0.00%)	1 / 219 (0.46%)	
occurrences (all)	0	1	
Localized edema			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 215 (0.47%)	2 / 219 (0.91%)	
occurrences (all)	1	2	

Malaise			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 215 (0.47%)	3 / 219 (1.37%)	
occurrences (all)	2	3	
Neck edema			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 215 (0.00%)	1 / 219 (0.46%)	
occurrences (all)	0	1	
Non-cardiac chest pain			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 215 (0.47%)	4 / 219 (1.83%)	
occurrences (all)	1	4	
Oedema			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	15 / 215 (6.98%)	10 / 219 (4.57%)	
occurrences (all)	17	11	
Pain			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	30 / 215 (13.95%)	17 / 219 (7.76%)	
occurrences (all)	32	29	
Immune system disorders			
Allergic reaction			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	20 / 215 (9.30%)	25 / 219 (11.42%)	
occurrences (all)	23	32	
Anaphylaxis			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 215 (0.47%)	0 / 219 (0.00%)	
occurrences (all)	1	0	
Immune system disorders - Other, specify			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	2 / 215 (0.93%)	1 / 219 (0.46%)	
occurrences (all)	2	1	
Reproductive system and breast disorders			

Genital edema			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 215 (0.47%)	0 / 219 (0.00%)	
occurrences (all)	1	0	
Reproductive system and breast disorders - Other, specify			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 215 (0.00%)	3 / 219 (1.37%)	
occurrences (all)	0	3	
Respiratory, thoracic and mediastinal disorders			
Allergic rhinitis			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 215 (0.47%)	0 / 219 (0.00%)	
occurrences (all)	1	0	
Cough			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	52 / 215 (24.19%)	34 / 219 (15.53%)	
occurrences (all)	60	45	
Dyspnea			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	25 / 215 (11.63%)	32 / 219 (14.61%)	
occurrences (all)	27	34	
Epistaxis			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	3 / 215 (1.40%)	3 / 219 (1.37%)	
occurrences (all)	3	3	
Hoarseness			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 215 (0.47%)	3 / 219 (1.37%)	
occurrences (all)	2	4	
Hypoxia			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 215 (0.00%)	1 / 219 (0.46%)	
occurrences (all)	0	1	
Laryngeal inflammation			

alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 215 (0.47%)	2 / 219 (0.91%)	
occurrences (all)	1	2	
Nasal congestion			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	2 / 215 (0.93%)	1 / 219 (0.46%)	
occurrences (all)	2	1	
Pleural effusion			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	2 / 215 (0.93%)	0 / 219 (0.00%)	
occurrences (all)	3	0	
Pneumonitis			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	2 / 215 (0.93%)	2 / 219 (0.91%)	
occurrences (all)	2	2	
Postnasal drip			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 215 (0.47%)	2 / 219 (0.91%)	
occurrences (all)	1	2	
Productive cough			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	7 / 215 (3.26%)	3 / 219 (1.37%)	
occurrences (all)	8	3	
Respiratory, thoracic and mediastinal disorders - Other, specify			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	17 / 215 (7.91%)	7 / 219 (3.20%)	
occurrences (all)	18	7	
Sinus disorder			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 215 (0.00%)	1 / 219 (0.46%)	
occurrences (all)	0	1	
Sneezing			
alternative dictionary used: CTCAE 4			

subjects affected / exposed	1 / 215 (0.47%)	0 / 219 (0.00%)	
occurrences (all)	1	0	
Sore throat			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	13 / 215 (6.05%)	12 / 219 (5.48%)	
occurrences (all)	13	15	
Voice alteration			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 215 (0.47%)	0 / 219 (0.00%)	
occurrences (all)	1	0	
Wheezing			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 215 (0.47%)	1 / 219 (0.46%)	
occurrences (all)	2	1	
Psychiatric disorders			
Anxiety			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	3 / 215 (1.40%)	4 / 219 (1.83%)	
occurrences (all)	3	6	
Confusion			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	3 / 215 (1.40%)	0 / 219 (0.00%)	
occurrences (all)	3	0	
Delirium			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 215 (0.00%)	1 / 219 (0.46%)	
occurrences (all)	0	1	
Depression			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	4 / 215 (1.86%)	4 / 219 (1.83%)	
occurrences (all)	4	4	
Hallucinations			
alternative dictionary used: CTCAE 4			

subjects affected / exposed	1 / 215 (0.47%)	2 / 219 (0.91%)	
occurrences (all)	1	2	
Insomnia			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	8 / 215 (3.72%)	11 / 219 (5.02%)	
occurrences (all)	8	15	
Libido decreased			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 215 (0.00%)	1 / 219 (0.46%)	
occurrences (all)	0	1	
Psychiatric disorders - Other, specify			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 215 (0.00%)	1 / 219 (0.46%)	
occurrences (all)	0	1	
Investigations			
Alanine aminotransferase increased			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	3 / 215 (1.40%)	2 / 219 (0.91%)	
occurrences (all)	3	3	
Alkaline phosphatase increased			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	5 / 215 (2.33%)	6 / 219 (2.74%)	
occurrences (all)	5	6	
Aspartate aminotransferase increased			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 215 (0.00%)	3 / 219 (1.37%)	
occurrences (all)	0	3	
Blood bilirubin increased			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	4 / 215 (1.86%)	2 / 219 (0.91%)	
occurrences (all)	6	2	
CPK increased			
alternative dictionary used: CTCAE 4			

subjects affected / exposed	1 / 215 (0.47%)	0 / 219 (0.00%)	
occurrences (all)	1	0	
Creatinine increased alternative dictionary used: CTCAE 4			
subjects affected / exposed	5 / 215 (2.33%)	8 / 219 (3.65%)	
occurrences (all)	8	8	
GGT increased alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 215 (0.47%)	2 / 219 (0.91%)	
occurrences (all)	1	2	
Investigations - Other, specify alternative dictionary used: CTCAE 4			
subjects affected / exposed	7 / 215 (3.26%)	4 / 219 (1.83%)	
occurrences (all)	9	4	
Lymphocyte count decreased alternative dictionary used: CTCAE 4			
subjects affected / exposed	3 / 215 (1.40%)	1 / 219 (0.46%)	
occurrences (all)	3	1	
Lymphocyte count increased alternative dictionary used: CTCAE 4			
subjects affected / exposed	6 / 215 (2.79%)	2 / 219 (0.91%)	
occurrences (all)	6	2	
Neutrophil count decreased alternative dictionary used: CTCAE 4			
subjects affected / exposed	148 / 215 (68.84%)	144 / 219 (65.75%)	
occurrences (all)	245	250	
Platelet count decreased alternative dictionary used: CTCAE 4			
subjects affected / exposed	105 / 215 (48.84%)	92 / 219 (42.01%)	
occurrences (all)	189	178	
Weight gain alternative dictionary used: CTCAE 4			
subjects affected / exposed	2 / 215 (0.93%)	0 / 219 (0.00%)	
occurrences (all)	2	0	

Weight loss			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	7 / 215 (3.26%)	5 / 219 (2.28%)	
occurrences (all)	7	5	
White blood cell decreased			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	6 / 215 (2.79%)	7 / 219 (3.20%)	
occurrences (all)	6	9	
Injury, poisoning and procedural complications			
Bruising			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	3 / 215 (1.40%)	3 / 219 (1.37%)	
occurrences (all)	3	4	
Fall			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	7 / 215 (3.26%)	4 / 219 (1.83%)	
occurrences (all)	7	5	
Fracture			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 215 (0.00%)	3 / 219 (1.37%)	
occurrences (all)	0	3	
Injury, poisoning and procedural complications - Other, specify			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	4 / 215 (1.86%)	2 / 219 (0.91%)	
occurrences (all)	4	2	
Wrist fracture			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 215 (0.00%)	1 / 219 (0.46%)	
occurrences (all)	0	1	
Cardiac disorders			
Aortic valve disease			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 215 (0.47%)	0 / 219 (0.00%)	
occurrences (all)	1	0	

Atrial fibrillation			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	4 / 215 (1.86%)	4 / 219 (1.83%)	
occurrences (all)	4	4	
Atrial flutter			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 215 (0.47%)	0 / 219 (0.00%)	
occurrences (all)	1	0	
Cardiac disorders - Other, specify			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	3 / 215 (1.40%)	8 / 219 (3.65%)	
occurrences (all)	3	8	
Chest pain - cardiac			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	3 / 215 (1.40%)	2 / 219 (0.91%)	
occurrences (all)	3	2	
Heart failure			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 215 (0.47%)	1 / 219 (0.46%)	
occurrences (all)	1	1	
Palpitations			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	3 / 215 (1.40%)	3 / 219 (1.37%)	
occurrences (all)	3	3	
Sinus bradycardia			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	2 / 215 (0.93%)	1 / 219 (0.46%)	
occurrences (all)	2	1	
Sinus tachycardia			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	2 / 215 (0.93%)	3 / 219 (1.37%)	
occurrences (all)	2	3	
Ventricular tachycardia			
alternative dictionary used: CTCAE 4			

subjects affected / exposed	1 / 215 (0.47%)	0 / 219 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Central nervous system necrosis			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 215 (0.47%)	0 / 219 (0.00%)	
occurrences (all)	1	0	
Concentration impairment			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 215 (0.47%)	1 / 219 (0.46%)	
occurrences (all)	1	1	
Dizziness			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	14 / 215 (6.51%)	14 / 219 (6.39%)	
occurrences (all)	15	14	
Dysarthria			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 215 (0.00%)	1 / 219 (0.46%)	
occurrences (all)	0	1	
Dysesthesia			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 215 (0.47%)	0 / 219 (0.00%)	
occurrences (all)	1	0	
Dysgeusia			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	7 / 215 (3.26%)	4 / 219 (1.83%)	
occurrences (all)	7	4	
Extrapyramidal disorder			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 215 (0.00%)	1 / 219 (0.46%)	
occurrences (all)	0	1	
Headache			
alternative dictionary used: CTCAE 4			

subjects affected / exposed	15 / 215 (6.98%)	13 / 219 (5.94%)	
occurrences (all)	19	19	
Lethargy			
subjects affected / exposed	13 / 215 (6.05%)	17 / 219 (7.76%)	
occurrences (all)	14	19	
Memory impairment			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 215 (0.00%)	1 / 219 (0.46%)	
occurrences (all)	0	1	
Movements involuntary			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 215 (0.00%)	1 / 219 (0.46%)	
occurrences (all)	0	1	
Nervous system disorders - Other, specify			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	6 / 215 (2.79%)	7 / 219 (3.20%)	
occurrences (all)	7	8	
Olfactory nerve disorder			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 215 (0.47%)	0 / 219 (0.00%)	
occurrences (all)	1	0	
Paresthesia			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	4 / 215 (1.86%)	2 / 219 (0.91%)	
occurrences (all)	5	2	
Peripheral motor neuropathy			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 215 (0.47%)	1 / 219 (0.46%)	
occurrences (all)	1	1	
Peripheral sensory neuropathy			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	4 / 215 (1.86%)	10 / 219 (4.57%)	
occurrences (all)	4	14	
Presyncope			

alternative dictionary used: CTCAE 4			
subjects affected / exposed	2 / 215 (0.93%)	0 / 219 (0.00%)	
occurrences (all)	2	0	
Sinus pain			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 215 (0.47%)	0 / 219 (0.00%)	
occurrences (all)	1	0	
Somnolence			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 215 (0.47%)	1 / 219 (0.46%)	
occurrences (all)	1	1	
Syncope			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 215 (0.47%)	3 / 219 (1.37%)	
occurrences (all)	1	4	
Transient ischemic attacks			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 215 (0.47%)	1 / 219 (0.46%)	
occurrences (all)	1	1	
Tremor			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	2 / 215 (0.93%)	6 / 219 (2.74%)	
occurrences (all)	2	6	
Vasovagal reaction			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 215 (0.47%)	1 / 219 (0.46%)	
occurrences (all)	1	1	
Blood and lymphatic system disorders			
Anemia			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	71 / 215 (33.02%)	58 / 219 (26.48%)	
occurrences (all)	112	85	
Blood and lymphatic system disorders - Other, specify			
alternative dictionary used: CTCAE 4			

subjects affected / exposed	13 / 215 (6.05%)	26 / 219 (11.87%)	
occurrences (all)	23	40	
Febrile neutropenia			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 215 (0.47%)	2 / 219 (0.91%)	
occurrences (all)	1	2	
Haemolysis			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 215 (0.00%)	1 / 219 (0.46%)	
occurrences (all)	0	1	
Haemolytic uremic syndrome			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 215 (0.00%)	1 / 219 (0.46%)	
occurrences (all)	0	1	
Leukocytosis			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	6 / 215 (2.79%)	2 / 219 (0.91%)	
occurrences (all)	7	2	
Lymph node pain			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 215 (0.47%)	1 / 219 (0.46%)	
occurrences (all)	1	1	
Thrombotic thrombocytopenic purpura			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	5 / 215 (2.33%)	9 / 219 (4.11%)	
occurrences (all)	8	11	
Ear and labyrinth disorders			
Ear and labyrinth disorders - Other, specify			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 215 (0.47%)	4 / 219 (1.83%)	
occurrences (all)	1	5	
Ear pain			
alternative dictionary used: CTCAE 4			

subjects affected / exposed	3 / 215 (1.40%)	4 / 219 (1.83%)	
occurrences (all)	3	4	
External ear inflammation			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 215 (0.47%)	0 / 219 (0.00%)	
occurrences (all)	1	0	
Hearing impaired			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 215 (0.00%)	3 / 219 (1.37%)	
occurrences (all)	0	3	
Vertigo			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	4 / 215 (1.86%)	1 / 219 (0.46%)	
occurrences (all)	4	1	
Vestibular disorder			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	3 / 215 (1.40%)	0 / 219 (0.00%)	
occurrences (all)	3	0	
Eye disorders			
Blurred vision			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 215 (0.47%)	3 / 219 (1.37%)	
occurrences (all)	1	3	
Cataract			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 215 (0.47%)	1 / 219 (0.46%)	
occurrences (all)	1	1	
Conjunctivitis			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	4 / 215 (1.86%)	2 / 219 (0.91%)	
occurrences (all)	4	2	
Dry eye			
alternative dictionary used: CTCAE 4			

subjects affected / exposed	1 / 215 (0.47%)	1 / 219 (0.46%)	
occurrences (all)	1	1	
Eye disorders - Other, specify			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	7 / 215 (3.26%)	4 / 219 (1.83%)	
occurrences (all)	7	4	
Eye pain			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 215 (0.00%)	1 / 219 (0.46%)	
occurrences (all)	0	1	
Eyelid function disorder			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 215 (0.00%)	1 / 219 (0.46%)	
occurrences (all)	0	1	
Flashing lights			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 215 (0.00%)	2 / 219 (0.91%)	
occurrences (all)	0	2	
Watering eyes			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 215 (0.00%)	1 / 219 (0.46%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Abdominal distension			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 215 (0.00%)	3 / 219 (1.37%)	
occurrences (all)	0	3	
Abdominal pain			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	17 / 215 (7.91%)	16 / 219 (7.31%)	
occurrences (all)	21	17	
Anal pain			
alternative dictionary used: CTCAE 4			

subjects affected / exposed	1 / 215 (0.47%)	0 / 219 (0.00%)	
occurrences (all)	1	0	
Anal ulcer			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 215 (0.47%)	0 / 219 (0.00%)	
occurrences (all)	1	0	
Bloating			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	4 / 215 (1.86%)	1 / 219 (0.46%)	
occurrences (all)	4	2	
Colitis			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 215 (0.47%)	0 / 219 (0.00%)	
occurrences (all)	1	0	
Colonic hemorrhage			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 215 (0.47%)	1 / 219 (0.46%)	
occurrences (all)	1	1	
Constipation			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	54 / 215 (25.12%)	34 / 219 (15.53%)	
occurrences (all)	75	43	
Dental caries			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 215 (0.47%)	0 / 219 (0.00%)	
occurrences (all)	1	0	
Diarrhea			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	52 / 215 (24.19%)	46 / 219 (21.00%)	
occurrences (all)	73	69	
Dry mouth			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	11 / 215 (5.12%)	5 / 219 (2.28%)	
occurrences (all)	12	6	

Dyspepsia			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 215 (0.47%)	4 / 219 (1.83%)	
occurrences (all)	1	4	
Dysphagia			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 215 (0.00%)	1 / 219 (0.46%)	
occurrences (all)	0	1	
Esophageal pain			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 215 (0.47%)	0 / 219 (0.00%)	
occurrences (all)	1	0	
Flatulence			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	2 / 215 (0.93%)	0 / 219 (0.00%)	
occurrences (all)	2	0	
Gastroesophageal reflux disease			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	3 / 215 (1.40%)	2 / 219 (0.91%)	
occurrences (all)	3	2	
Gastrointestinal disorders - Other, specify			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	15 / 215 (6.98%)	7 / 219 (3.20%)	
occurrences (all)	18	7	
Gastrointestinal pain			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 215 (0.47%)	0 / 219 (0.00%)	
occurrences (all)	1	0	
Gingival pain			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 215 (0.47%)	1 / 219 (0.46%)	
occurrences (all)	1	1	
Haemorrhoids			
alternative dictionary used: CTCAE 4			

subjects affected / exposed	2 / 215 (0.93%)	0 / 219 (0.00%)	
occurrences (all)	2	0	
Mucositis oral			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	7 / 215 (3.26%)	5 / 219 (2.28%)	
occurrences (all)	7	5	
Nausea			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	71 / 215 (33.02%)	74 / 219 (33.79%)	
occurrences (all)	95	104	
Oral dysesthesia			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 215 (0.47%)	0 / 219 (0.00%)	
occurrences (all)	1	0	
Oral pain			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	4 / 215 (1.86%)	9 / 219 (4.11%)	
occurrences (all)	4	9	
Rectal hemorrhage			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 215 (0.47%)	0 / 219 (0.00%)	
occurrences (all)	1	0	
Salivary duct inflammation			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 215 (0.00%)	1 / 219 (0.46%)	
occurrences (all)	0	1	
Stomach pain			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 215 (0.47%)	4 / 219 (1.83%)	
occurrences (all)	1	5	
Toothache			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 215 (0.00%)	3 / 219 (1.37%)	
occurrences (all)	0	3	

Vomiting			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	31 / 215 (14.42%)	39 / 219 (17.81%)	
occurrences (all)	39	50	
Hepatobiliary disorders			
Hepatic pain			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 215 (0.47%)	0 / 219 (0.00%)	
occurrences (all)	1	0	
Portal vein thrombosis			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 215 (0.47%)	0 / 219 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Alopecia			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	4 / 215 (1.86%)	9 / 219 (4.11%)	
occurrences (all)	4	11	
Body odor			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 215 (0.47%)	0 / 219 (0.00%)	
occurrences (all)	1	0	
Dry skin			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	13 / 215 (6.05%)	8 / 219 (3.65%)	
occurrences (all)	15	9	
Erythema multiforme			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	4 / 215 (1.86%)	1 / 219 (0.46%)	
occurrences (all)	4	1	
Hyperhidrosis			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	5 / 215 (2.33%)	6 / 219 (2.74%)	
occurrences (all)	5	6	
Palmar-plantar erythrodysesthesia syndrome			

alternative dictionary used: CTCAE 4			
subjects affected / exposed	3 / 215 (1.40%)	1 / 219 (0.46%)	
occurrences (all)	3	2	
Pruritus			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	24 / 215 (11.16%)	13 / 219 (5.94%)	
occurrences (all)	27	13	
Purpura			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 215 (0.00%)	1 / 219 (0.46%)	
occurrences (all)	0	1	
Rash Macular			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	4 / 215 (1.86%)	0 / 219 (0.00%)	
occurrences (all)	4	0	
Rash acneiform			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	2 / 215 (0.93%)	2 / 219 (0.91%)	
occurrences (all)	2	2	
Rash erythematous			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	5 / 215 (2.33%)	5 / 219 (2.28%)	
occurrences (all)	5	5	
Rash generalized			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	12 / 215 (5.58%)	9 / 219 (4.11%)	
occurrences (all)	15	11	
Rash maculo-papular			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	31 / 215 (14.42%)	29 / 219 (13.24%)	
occurrences (all)	35	32	
Rash pruritic			
alternative dictionary used: CTCAE 4			

subjects affected / exposed	1 / 215 (0.47%)	0 / 219 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders - Other, specify			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	41 / 215 (19.07%)	34 / 219 (15.53%)	
occurrences (all)	61	56	
Skin ulceration			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	2 / 215 (0.93%)	3 / 219 (1.37%)	
occurrences (all)	2	3	
Urticaria			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	2 / 215 (0.93%)	6 / 219 (2.74%)	
occurrences (all)	2	6	
Renal and urinary disorders			
Acute kidney injury			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 215 (0.47%)	2 / 219 (0.91%)	
occurrences (all)	1	2	
Cystitis noninfective			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 215 (0.47%)	0 / 219 (0.00%)	
occurrences (all)	1	0	
Haematuria			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 215 (0.47%)	1 / 219 (0.46%)	
occurrences (all)	1	1	
Renal and urinary disorders - Other, specify			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 215 (0.47%)	0 / 219 (0.00%)	
occurrences (all)	1	0	
Renal calculi			
alternative dictionary used: CTCAE 4			

subjects affected / exposed	0 / 215 (0.00%)	1 / 219 (0.46%)	
occurrences (all)	0	1	
Urinary frequency			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	5 / 215 (2.33%)	7 / 219 (3.20%)	
occurrences (all)	5	7	
Urinary retention			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 215 (0.00%)	1 / 219 (0.46%)	
occurrences (all)	0	1	
Urinary tract obstruction			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 215 (0.47%)	0 / 219 (0.00%)	
occurrences (all)	1	0	
Urinary tract pain			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 215 (0.00%)	1 / 219 (0.46%)	
occurrences (all)	0	1	
Endocrine disorders			
Endocrine disorders - Other, specify			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 215 (0.00%)	1 / 219 (0.46%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Arthralgia			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	4 / 215 (1.86%)	1 / 219 (0.46%)	
occurrences (all)	5	1	
Arthritis			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 215 (0.47%)	0 / 219 (0.00%)	
occurrences (all)	1	0	
Back pain			
alternative dictionary used: CTCAE 4			

subjects affected / exposed	15 / 215 (6.98%)	25 / 219 (11.42%)	
occurrences (all)	15	28	
Bone pain			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 215 (0.47%)	0 / 219 (0.00%)	
occurrences (all)	1	0	
Chest wall pain			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	2 / 215 (0.93%)	4 / 219 (1.83%)	
occurrences (all)	2	4	
Generalized muscle weakness			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 215 (0.00%)	2 / 219 (0.91%)	
occurrences (all)	0	2	
Joint effusion			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 215 (0.47%)	0 / 219 (0.00%)	
occurrences (all)	1	0	
Muscle weakness left-sided			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 215 (0.00%)	1 / 219 (0.46%)	
occurrences (all)	0	1	
Muscle weakness lower limb			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	2 / 215 (0.93%)	3 / 219 (1.37%)	
occurrences (all)	2	3	
Muscle weakness upper limb			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 215 (0.47%)	0 / 219 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorder - Other, specify			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	9 / 215 (4.19%)	12 / 219 (5.48%)	
occurrences (all)	11	14	

Myalgia			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	3 / 215 (1.40%)	1 / 219 (0.46%)	
occurrences (all)	3	1	
Neck pain			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	2 / 215 (0.93%)	3 / 219 (1.37%)	
occurrences (all)	2	3	
Pain in extremity			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	5 / 215 (2.33%)	5 / 219 (2.28%)	
occurrences (all)	6	5	
Infections and infestations			
Bladder infection			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 215 (0.47%)	0 / 219 (0.00%)	
occurrences (all)	1	0	
Bronchial infection			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	6 / 215 (2.79%)	11 / 219 (5.02%)	
occurrences (all)	6	13	
Device related infection			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 215 (0.47%)	0 / 219 (0.00%)	
occurrences (all)	1	0	
Eye infection			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	4 / 215 (1.86%)	3 / 219 (1.37%)	
occurrences (all)	5	3	
Hepatic infection			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 215 (0.47%)	0 / 219 (0.00%)	
occurrences (all)	1	0	
Infections and infestations - Other, specify			
alternative dictionary used: CTCAE			

4				
subjects affected / exposed	29 / 215 (13.49%)	29 / 219 (13.24%)		
occurrences (all)	32	37		
Lip infection				
alternative dictionary used: CTCAE 4				
subjects affected / exposed	1 / 215 (0.47%)	0 / 219 (0.00%)		
occurrences (all)	1	0		
Lung infection				
alternative dictionary used: CTCAE 4				
subjects affected / exposed	8 / 215 (3.72%)	13 / 219 (5.94%)		
occurrences (all)	10	13		
Mucosal infection				
alternative dictionary used: CTCAE 4				
subjects affected / exposed	1 / 215 (0.47%)	2 / 219 (0.91%)		
occurrences (all)	2	2		
Otitis media				
alternative dictionary used: CTCAE 4				
subjects affected / exposed	1 / 215 (0.47%)	0 / 219 (0.00%)		
occurrences (all)	1	0		
Papulopustular rash				
alternative dictionary used: CTCAE 4				
subjects affected / exposed	2 / 215 (0.93%)	0 / 219 (0.00%)		
occurrences (all)	2	0		
Penile infection				
alternative dictionary used: CTCAE 4				
subjects affected / exposed	1 / 215 (0.47%)	0 / 219 (0.00%)		
occurrences (all)	1	0		
Pharyngitis				
alternative dictionary used: CTCAE 4				
subjects affected / exposed	1 / 215 (0.47%)	2 / 219 (0.91%)		
occurrences (all)	1	2		
Phlebitis infective				
alternative dictionary used: CTCAE 4				

subjects affected / exposed	0 / 215 (0.00%)	1 / 219 (0.46%)	
occurrences (all)	0	1	
Rash pustular			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 215 (0.00%)	2 / 219 (0.91%)	
occurrences (all)	0	2	
Rhinitis infective			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 215 (0.47%)	1 / 219 (0.46%)	
occurrences (all)	1	1	
Sepsis			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 215 (0.00%)	1 / 219 (0.46%)	
occurrences (all)	0	1	
Sinusitis			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 215 (0.47%)	2 / 219 (0.91%)	
occurrences (all)	3	2	
Skin infection			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	7 / 215 (3.26%)	7 / 219 (3.20%)	
occurrences (all)	7	7	
Soft tissue infection			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	2 / 215 (0.93%)	0 / 219 (0.00%)	
occurrences (all)	2	0	
Tooth infection			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	2 / 215 (0.93%)	2 / 219 (0.91%)	
occurrences (all)	2	2	
Upper respiratory infection			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	13 / 215 (6.05%)	11 / 219 (5.02%)	
occurrences (all)	14	12	

Urinary tract infection			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	7 / 215 (3.26%)	11 / 219 (5.02%)	
occurrences (all)	9	16	
Vaginal infection			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	2 / 215 (0.93%)	1 / 219 (0.46%)	
occurrences (all)	2	1	
Vulval infection			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 215 (0.47%)	1 / 219 (0.46%)	
occurrences (all)	1	1	
Metabolism and nutrition disorders			
Anorexia			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	25 / 215 (11.63%)	14 / 219 (6.39%)	
occurrences (all)	26	16	
Hypercalcemia			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 215 (0.47%)	0 / 219 (0.00%)	
occurrences (all)	1	0	
Hyperglycemia			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	3 / 215 (1.40%)	7 / 219 (3.20%)	
occurrences (all)	5	16	
Hyperkalemia			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	4 / 215 (1.86%)	5 / 219 (2.28%)	
occurrences (all)	4	5	
Hypernatremia			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 215 (0.00%)	1 / 219 (0.46%)	
occurrences (all)	0	1	
Hyperuricemia			
alternative dictionary used: CTCAE 4			

subjects affected / exposed	1 / 215 (0.47%)	6 / 219 (2.74%)	
occurrences (all)	1	8	
Hypoalbuminemia			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	3 / 215 (1.40%)	0 / 219 (0.00%)	
occurrences (all)	7	0	
Hypocalcemia			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	5 / 215 (2.33%)	2 / 219 (0.91%)	
occurrences (all)	5	2	
Hypoglycemia			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	2 / 215 (0.93%)	0 / 219 (0.00%)	
occurrences (all)	2	0	
Hypokalemia			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	4 / 215 (1.86%)	5 / 219 (2.28%)	
occurrences (all)	5	7	
Hypomagnesemia			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	2 / 215 (0.93%)	1 / 219 (0.46%)	
occurrences (all)	2	2	
Hyponatremia			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	3 / 215 (1.40%)	5 / 219 (2.28%)	
occurrences (all)	8	8	
Hypophosphatemia			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 215 (0.47%)	0 / 219 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders - Other, specify			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	4 / 215 (1.86%)	2 / 219 (0.91%)	
occurrences (all)	6	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 September 2011	Amended version submitted in response to grounds for non-acceptance from MHRA. Main changes from Version 1: Date: 28.06.2011: Changes and clarification to Exclusion criteria Yellow fever vaccine and hypersensitivity to the active substance and its excipients have been added as exclusion criterion. In addition a note of justification for the lower neutrophil and platelet exclusion criteria which are contradictory to the Bendamustine SmPC has been included. Addition of justification for the Ofatumumab in study rationale The rationale for the dosage of ofatumumab in the trial population has now been explicitly stated within the study rationale. (section 2.2) Addition of specific surveillance activities during the study The requirement for surveillance of patients for suicidality (MS patients only), bowel obstruction and PML before and during treatment have been addressed throughout the protocol.
05 October 2011	Main changes from Version 2: Date: 06.09.2011: Changes to Sample Collection Requirements for Central Pathological Review (CPR) - Volume of blood for CPR has been increased from 5ml to 6ml due to the lack of a suitable 5ml collection tube. - Addition of a blood sample for CPR at 2 months post treatment - Inclusion of option to retain bone marrow trephine samples for future research should the patients give their consent. Changes to Study Schedule - Inclusion of standard sodium, total protein and gamma-GT biochemistry tests at all visits where safety samples are collected. - Height and weight to be performed initially at screening rather baseline for the purposes of ordering drug supply immediately following randomisation. - Monitoring for suicidality, bowel obstruction and PML has been redefined as a toxicity rather than a physical examination assessment. Changes to Pharmacovigilance Reporting Procedure Pharmacovigilance reporting procedures were revised to reflect the introduction of remote data entry for PV reporting within the LCTC to replace the previous system of faxing hard copy forms.

11 June 2012	Main changes from Version 3: Date: 05/10/2011: Changes to Eligibility - Inclusion of patients with SLL. - Addition of clarification regarding which prior CLL therapies are excluded. - Addition of clarification and further guidance regarding patients with seropositivity for HBV. Changes to Study Schedule - CIRS: Additional guidance added regarded scoring of haematopoietic category. - Removal of baseline weight measurement. - Clarification regarding follow up assessments to be performed by patient's post-disease progression. - Removal of chloride and haptoglobin from the list of required laboratory tests. - Format changes to study schedule table to clarify post-PD follow up for overall survival assessments and to also separate out the clinical assessments from the lab assessments. Trial Treatment - Inclusion of wording allowing a delay in the commencement of chlorambucil/bendamustine until day 2 if practical reasons preclude commencement on day 1 of the treatment cycle. - Addition of geriatric assessments 2 months post treatment. - Addition of EORTC QLQ-CLL16 questionnaire every 3 months for duration of trial. - Inclusion of guidance regarding dose reduction of allopurinol for renal impairment. - Inclusion of wording allowing sites to use alternative glucocorticoid, antiemetic and hyperuricemia prophylaxis in accordance with local practice. - Inclusion of wording allowing the omission of baseline, 2 months post treatment and progression bone marrow samples under specific circumstances at the discretion of the chief investigator. Other - Change of Manufacturer name for free Ofatumumab and Bendamustine supply. - Addition of wording regarding acknowledgement of receipt of SAEs. - Administrative and typographical changes.
29 January 2013	Main changes from Version 4: Date: 11/06/2012: Eligibility Criteria - Additional of inclusion criterion 1e in line with NCI/IWCLL 2008 criteria. This was omitted from previous version protocols in error. - Change to inclusion criteria 1a and 1d, in line with NCI/IWCLL 2008 criteria - Inclusion of patients who have received prior localised radiotherapy for CLL (inclusion criteria #2). Sampling: - Revision of sampling schedule for Biobank samples - changed to visit-led rather than time-led schedule with first post treatment samples collected 6 months post treatment end. - Extension of MRD blood sampling (4ml) out to every 3 months in follow up from 9 months post treatment end until end of trial, progression or commencement of second line therapy. - Removal of bicarbonate, gamma GT and from the biochemistry profile as these are deemed non-essential for safety purposes. - Inclusion of paraprotein screen as part of immunoglobulin tests at baseline only. - Addition of clarification regarding the provision of archived diagnostic material from those patients who have already had bone marrow samples taken prior to trial entry (and who do not wish to undergo repeat sampling for trial purposes) and the wish to retain part of this material for research purposes providing that the patient and local Trust consents. - Addition of clarification regarding collection of sequential biobanking samples until 100 complete patient sets are received. Also updates to Quality of Life Questionnaires, Treatment and Safety sections

17 July 2013	Main changes from version: 5 Date: 29/01/2013: Exclusion Criteria: - Addition of exclusion criteria points 7 to 13 in line with Gilead's protocol. - Change in exclusion criteria 8 from ongoing drug induced pneumonitis to history drug of pneumonitis - Exclusion criteria 16 updated to include hypersensitivity to idelalisib. - Change in exclusion criteria 6 from bilirubin more than twice the ULN to more than 1.5 the ULN Study Schematic: - Updated to include unacceptable toxicity Intervention: - Additional double blinded randomisation using a factorial design to include idelalisib / placebo. Rationale: - Update to rationale section to include data on idelalisib and to support the new trial design. Objectives: - Update to objectives to include idelalisib - Addition of objective to investigate the effect of adding idelalisib to ofatumumab-containing chemo-immunotherapy. Potential Risks and Benefits: - Addition of side effects associated with idelalisib. - Addition of the benefits associated with adding idelalisib. Enrolment & randomisation: - Addition of information allowing eligibility assessments that have been performed over the 42 day window at the discretion of the Chief Investigator. Trial Treatment: - Additional treatment arm idelalisib/placebo, patients will now be allocated to one of the four treatment arms: - Arm A + idelalisib - Arm A + placebo - Arm B + idelalisib - Arm B + placebo - Update to the treatment overview section, now separated into induction and maintenance phase. - Addition of guidance for patients treated as per protocol v.5. - Guidance provided on the sequencing of study drugs. - Addition of information on how idelalisisb / placebo will be assigned using an IWRS. - Addition of information on the formation of idelalisib and placebo Also update to Assessment & Procedures section
18 December 2015	Recrtuiment size reduced from 670 to 600 - Recruitment extended until April 2017 - Overall study extended until April 2020 - Contact details updated

24 February 2016	Urgent Safety Measure changes: - Omission of idelalisib from cycle 1. - Commencement of idelalisib at attenuated dose (100 mg bd) from cycle 2 with escalation to full dose (150 mg bd) in subsequent cycles if there are no ongoing grade ≥2 toxicities attributed to idelalisib/placebo. - Inclusion of a full blood count in the day 15 safety assessments that are required for cycles 1-3. - Extension of the day 15 safety assessments beyond cycle 3 if the final dose of idelalisib/placebo has not been reached or if the previous day 15 assessment showed grade ≥3 toxicity. - Routine G-CSF support for each subsequent cycle of the induction phase in the event of: 1. Grade ≥3 infection or febrile neutropenia 2. Grade ≥3 neutropenia when the next cycle is due 3. Grade 4 neutropenia occurring at any time during the treatment cycle - Routine antimicrobial prophylaxis with co-trimoxazole for all patients. - *** Subject to tolerance, co-trimoxazole (or equivalent) should be administered during the induction phase and for the first 12 weeks of the maintenance/follow up phase. Thereafter, co-trimoxazole (or equivalent) may be discontinued if the patient has not experienced grade 3-4 neutropenia or infection for a period of 12 weeks. Additonal changes: - Clarity on the follow up assessments for patients not entering the maintenance phase. - Time point references changed from months to weeks throughout for study assessments
15 April 2016	All references to idelalisib/placebo treatment removed, background and references to effects of idelalisib removed and schedule of assessments amended accordingly - Patient recruitment target reduced from 600 to 504. - Annual CT scans no longer necessary. - Day 15 assessments required during cycle 1 for all patients (not during cycles 2 and 3). - Co-trimoxazole and G-CSF treatment requirements updated and clarified. - References to maintenance treatment removed as idelalisib/placebo no longer applicable. - References to 'induction treatment' replaced by 'treatment' as there is no 'maintenance phase'.
01 September 2016	Corrected section 8.1 'Schedule of Assessments': 1) Toxicity assessment removed from 'Screening' column as already included in 'Baseline' column. 2) 'Interim Assessments' column header corrected to state correct timing of interim assessments – this was incorrectly entered in the last version of the protocol – as such, no new assessments have been added and the ones that were missing have been re-added. 3) 'Interim Assessments' column corrected to include demographics, physical examination, WHO performance status, serum immunoglobulins and removed serum biochemistry. These changes were incorrectly made in the last version of the protocol and as such, no new assessments have been added. 'Post-treatment' column corrected to include CLL-related symptoms and physical examination - These changes were incorrectly made in the last version of the protocol and as such, no new assessments have been added. - Concomitant medication information no longer required after the formal response assessment at week 12 for all patients. Section 7.2.10 and section 20.7 of appendix M updated accordingly (in addition to Schedule of Assessments) (except for SAE reports). - Section 10.5 – Generic bendamustine may be used for patients (previously this had been Levact only). The RSI used for this study will remain as Levact. - References to GSK replaced with Novartis throughout. - 8.1.4: Reworded section on planned assessments during the follow up phase for clarity. No new assessments added. Separated patients who have received 2 cycles of treatment or more and patients who have not received 2 cycles of treatment, using headers and how they are to be managed. - GP letter updated to remove references to idelalisib/placebo and CYP3A inducers and CYP3A substrates (as treatment no longer offered on this study following the previous substantial amendment). - Patient contact card updated to remove references to idelalisib/placebo

31 May 2017	Increased recruitment target to 565 - Extended end date of recruitment to 30/04/2018 (study to end 30/04/2021) - Statistics section updated - Re-included physical examination and CLL related symptoms in the schedule of assessments table as omitted in error and re-included reminder that interim response assessments are to be performed within 7 days of the next treatment cycle - Removed reference to ofatumumab being supplied free of charge as this may change prior to the end of the recruitment period - Expanded window for collection of MRD and Biobank samples - Updated TSC membership - Removed reference to reporting SAEs online - Removed ofatumumab IB section reference of IB for RSI information
09 October 2017	- Minor protocol clarifications added/changes/corrections made to reflect already approved changes (RSI details, SAE reporting methods, translational sample window in schedule of assessments tables, references to REC)
03 April 2018	Minor protocol update regarding the methods of statistical analysis. This related to the patients treated with idelalisib. (Section 9.4 Sample Size)
18 February 2020	Removal of 'Appendix M' - this appendix covered the treatment and follow-up schedule for patients randomised to the Protocol v5 or earlier i.e. pre-idelalisib treatment (O+B vs. O+Chl). - Trial Centre personnel updates and alteration to addresses, namely the address trial samples should be sent to. - Rebranding of LCTU to LCTC. The Liverpool Cancer Trials Unit has merged with the Medicines for Children Clinical Trials Research Centre. As a collective, we are now the Liverpool Clinical Trials Centre. - Clarification of length of follow-up sections 8.1.5 (Translational) and 8.1.7 Assessments for patients who are withdrawn from trial treatment. the Protocol stipulated that patients would remain on study until the last patient had completed 3 years of follow-up. However, this is Statistical term whereby 'follow-up' is considered to be a patient's entire length of participation in the study. The last patient was randomised in April 2018; the trial is due to end is April 2021, meaning for this patient, participation in the follow-up phase itself will be a maximum of 2 years.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
14 March 2016	Recruitment was closed for 4 months from mid-March 2016 to mid-July 2016 due to safety concerns which led to the withdrawal of idealisib.	14 July 2016

Notes:

Limitations and caveats

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

Secondary outcomes, Quality of Life, Analysis of Frailty and Co-Morbidity and Predictive Value of Biomarkers, are not included in this summary of results but results are provided in the attached report.

Notes: