Clinical trial results:
A randomized, double-blind, placebo-controlled, phase 3 study of brentuximab vedotin and CHP (A+CHP) versus CHOP in the frontline treatment of patients with CD30-positive mature T-cell lymphomas

Summary

EudraCT number	2012-002751-42
Trial protocol	GB CZ DE ES DK IT HU
Global end of trial date	02 October 2020

Results information

Result version number	v1 (current)
This version publication date	07 October 2021
First version publication date	07 October 2021

Trial information

Trial identification

Sponsor protocol code	SGN35-014

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01777152
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Seagen Inc.
Sponsor organisation address	21823 30th Drive S.E., Bothell, United States, 98021
Public contact	Chief Medical Officer, Seagen Inc., 1 8554732436, medinfo@seagen.com
Scientific contact	Chief Medical Officer, Seagen Inc., 1 8554732436, medinfo@seagen.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	11 February 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	02 October 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the progression-free survival (PFS) as determined by an independent review facility (IRF) between the 2 treatment arms

Protection of trial subjects:

This study was conducted in accordance with applicable Food and Drug Administration (FDA) regulations/guidelines set forth in 21 CFR Parts 11, 50, 54, 56, and 312 and with International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines. Essential documents are retained in accordance with ICH GCP.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	24 January 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 127
Country: Number of subjects enrolled	Japan: 43
Country: Number of subjects enrolled	Korea, Republic of: 40
Country: Number of subjects enrolled	Italy: 37
Country: Number of subjects enrolled	France: 36
Country: Number of subjects enrolled	Germany: 27
Country: Number of subjects enrolled	Spain: 26
Country: Number of subjects enrolled	Czechia: 22
Country: Number of subjects enrolled	United Kingdom: 21
Country: Number of subjects enrolled	Australia: 14
Country: Number of subjects enrolled	Denmark: 14
Country: Number of subjects enrolled	Israel: 12
Country: Number of subjects enrolled	Hungary: 9
Country: Number of subjects enrolled	Taiwan: 9
Country: Number of subjects enrolled	Poland: 7
Country: Number of subjects enrolled	Canada: 6
Country: Number of subjects enrolled	Romania: 2
Worldwide total number of subjects	452
EEA total number of subjects	180

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	313
From 65 to 84 years	138
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

Jan2013-Nov2016

Pre-assignment

Screening details:

Participants were screened for eligibility prior to enrollment.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	A+CHP

Arm description:

brentuximab vedotin, cyclophosphamide, doxorubicin, and prednisone brentuximab vedotin: 1.8 mg/kg every 3 weeks by IV infusion for 6-8 cycles doxorubicin: 50 mg/m2 every 3 weeks by IV infusion for 6-8 cycles prednisone: 100 mg on Days 1 to 5 of each 3-week cycle, orally for 6-8 cycles cyclophosphamide: 750 mg/m2 every 3 weeks by IV infusion for 6-8 cycles

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

Dosage and administration details:

Brentuximab vedotin (SGN-35, ADCETRIS) 1.8 mg/kg administered IV on Day 1 of each cycle for up to 6 to 8 cycles.

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

Dosage and administration details:

Cyclophosphamide 750 mg/m2 administered IV on Day 1 of each cycle for up to 6 to 8 cycles.

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

Dosage and administration details:

Doxorubicin 50 mg/m2 administered IV on Day 1 of each cycle for up to 6 to 8 cycles.

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

Dosage and administration details:

Prednisone 100 mg daily administered orally on Days 1-5 of each cycle for up to 6 to 8 cycles.

Arm title	CHOP

Arm description:

cyclophosphamide, doxorubicin, vincristine, and prednisone doxorubicin: 50 mg/m2 every 3 weeks by IV infusion for 6-8 cycles prednisone: 100 mg on Days 1 to 5 of each 3-week cycle, orally for 6-8 cycles vincristine: 1.4 mg/m2 (maximum 2 mg) every 3 weeks by IV infusion for 6-8 cycles cyclophosphamide: 750 mg/m2 every 3 weeks by IV infusion for 6-8 cycles

Arm type	Active comparator
Investigational medicinal product name	Prednisone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Prednisone 100 mg daily administered orally on Days 1-5 of each cycle for up to 6 to 8 cycles.

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

Dosage and administration details:

Cyclophosphamide 750 mg/m2 administered IV on Day 1 of each cycle for up to 6 to 8 cycles.

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

Dosage and administration details:

Doxorubicin 50 mg/m2 administered IV on Day 1 of each cycle for up to 6 to 8 cycles.

Number of subjects in period 1	A+CHP	CHOP
Started	226	226
Completed	131	116
Not completed	95	110
Adverse event, serious fatal	68	89
Consent withdrawn by subject	22	16
Change of diagnosis	1	-
Lost to follow-up	3	5
Not eligible, no study drug received	1	-

Baseline characteristics

Reporting groups	
Reporting group title	A+CHP
Reporting group description:	
brentuximab vedotin, cyclophosphamide, doxorubicin, and prednisone brentuximab vedotin: 1.8 mg/kg every 3 weeks by IV infusion for 6-8 cycles doxorubicin: 50 mg/m2 every 3 weeks by IV infusion for 6-8 cycles prednisone: 100 mg on Days 1 to 5 of each 3-week cycle, orally for 6-8 cycles cyclophosphamide: 750 mg/m2 every 3 weeks by IV infusion for 6-8 cycles	
Reporting group title	CHOP
Reporting group description:	
cyclophosphamide, doxorubicin, vincristine, and prednisone doxorubicin: 50 mg/m2 every 3 weeks by IV infusion for 6-8 cycles prednisone: 100 mg on Days 1 to 5 of each 3-week cycle, orally for 6-8 cycles vincristine: 1.4 mg/m2 (maximum 2 mg) every 3 weeks by IV infusion for 6-8 cycles cyclophosphamide: 750 mg/m2 every 3 weeks by IV infusion for 6-8 cycles	

Reporting group values	A+CHP	CHOP	Total
Number of subjects	226	226	452
Age Categorical Units: Subjects			
<=18 years	0	0	0
Between 18 and 65 years	157	156	313
>=65 years	69	70	139
Age Continuous Units: years			
median	58	58	
full range (min-max)	18 to 85	18 to 83	-
Sex: Female, Male Units: Subjects			
Female	93	75	168
Male	133	151	284
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	10	4	14
Not Hispanic or Latino	186	193	379
Unknown or Not Reported	30	29	59
Race/Ethnicity, Customized Units: Subjects			
Asian	45	54	99
Black or African American	12	6	18
Native Hawaiian or Other Pacific Islander	1	0	1
White	139	142	281
Other	3	2	5
Unknown	26	22	48
Eastern Cooperative Oncology Group (ECOG) Performance Status			
0=Normal activity; 1=Symptoms but ambulatory; 2=In bed <50% of the time; 3= In bed >50% of the time; 4=100% bedridden; 5=Dead. One participant (ECOG=0) was assessed after start of treatment.			
Units: Subjects			
Grade 0	85	93	178

Grade 1	90	86	176
Grade 2	51	47	98

End points

End points reporting groups

Reporting group title	A+CHP

Reporting group description:

brentuximab vedotin, cyclophosphamide, doxorubicin, and prednisone brentuximab vedotin: 1.8 mg/kg every 3 weeks by IV infusion for 6-8 cycles doxorubicin: 50 mg/m2 every 3 weeks by IV infusion for 6-8 cycles prednisone: 100 mg on Days 1 to 5 of each 3-week cycle, orally for 6-8 cycles cyclophosphamide: 750 mg/m2 every 3 weeks by IV infusion for 6-8 cycles

Reporting group title	CHOP

Reporting group description:

cyclophosphamide, doxorubicin, vincristine, and prednisone doxorubicin: 50 mg/m2 every 3 weeks by IV infusion for 6-8 cycles prednisone: 100 mg on Days 1 to 5 of each 3-week cycle, orally for 6-8 cycles vincristine: 1.4 mg/m2 (maximum 2 mg) every 3 weeks by IV infusion for 6-8 cycles cyclophosphamide: 750 mg/m2 every 3 weeks by IV infusion for 6-8 cycles

Primary: Progression-free survival per independent review facility (IRF)

End point title	Progression-free survival per independent review facility (IRF)

End point description:

The time from the date of randomization to the date of first documentation of progressive disease (PD), death due to any cause, or receipt of subsequent anticancer chemotherapy to treat residual or progressive disease whichever occurred first.

End point type	Primary

End point timeframe:

Up to 60 months

End point values	A+CHP	CHOP		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	226[1]	226[2]		
Units: months				
median (inter-quartile range (Q1-Q3))	48.20 (8.87 to 999)	20.80 (4.70 to 999)		

Notes:

[1] - 999 = Not Available (follow up is not long enough to assess an upper bound)

[2] - 999 = Not Available (follow up is not long enough to assess an upper bound)

Statistical analyses

Statistical analysis title	Progression-free survival per IRF

Statistical analysis description:

The primary analysis of PFS used a stratified log-rank test at a two-sided alpha level of 0.025. A stratified Cox regression of PFS was used to estimate the hazard ratio of the A+CHP arm to the CHOP arm. A hazard ratio <1 indicates that the duration of PFS is prolonged for patients on the A+CHP arm compared with patients on the CHOP arm. Confidence intervals (CIs) were calculated at a two-sided 95% level.

Comparison groups	A+CHP v CHOP

Number of subjects included in analysis	452
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.011
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.71
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.54
upper limit	0.93

Secondary: Progression-free survival per IRF in patients with systemic anaplastic large cell lymphoma (sALCL)

End point title	Progression-free survival per IRF in patients with systemic anaplastic large cell lymphoma (sALCL)

End point description:

The time from the date of randomization to the date of first documentation of progressive disease (PD), death due to any cause, or receipt of subsequent anticancer chemotherapy to treat residual or progressive disease whichever occurred first.

End point type	Secondary

End point timeframe:

Up to 60 months

End point values	A+CHP	CHOP		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	162[3]	154[4]		
Units: months				
median (inter-quartile range (Q1-Q3))	55.66 (15.61 to 999)	32.03 (4.57 to 999)		

Notes:

[3] - 999 = Not Available (follow up is not long enough to assess an upper bound)

[4] - 999 = Not Available (follow up is not long enough to assess an upper bound)

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of adverse events (AEs)

End point title	Incidence of adverse events (AEs)

End point description:

Any untoward medical occurrence in a clinical investigational participant administered a medicinal product which does not necessarily have a causal relationship with this treatment.

End point type	Secondary

End point timeframe:

Up to 8.28 months

End point values	A+CHP	CHOP		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	223	226		
Units: Number of Participants				
Any treatment-emergent AE	221	221		
Blinded study treatment-related AE	201	193		
CHP treatment-related AE	198	205		
Any serious adverse event (SAE)	87	87		
Blinded study treatment-related SAE	58	45		
CHP treatment-related SAE	62	53		
Treatment discontinuations (TDs) due to AE	14	15		
TDs due to blinded study treatment-related AE	10	10		
TDs due to CHP treatment-related AE	8	7		

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of laboratory abnormalities

End point title	Incidence of laboratory abnormalities
End point description:	
Number of participants who experienced a Grade 3 or higher laboratory toxicity.	
End point type	Secondary
End point timeframe:	
Up to 8.28 months	

End point values	A+CHP	CHOP		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	223	226		
Units: Number of Participants				
Any Chemistry Test	25	23		
Alanine Aminotransferase High	3	1		
Albumin Low	2	3		
Alkaline Phosphatase High	1	0		
Calcium Low	1	1		
Glucose High	8	6		
Phosphate Low	4	3		
Potassium High	0	2		
Potassium Low	3	2		
Sodium High	1	0		

Sodium Low	4	6		
Urate High	5	2		
Any Hematology Test	68	78		
Absolute Neutrophil Count Low	17	19		
Hemoglobin High	1	0		
Hemoglobin Low	9	13		
Leukocytes Low	12	21		
Lymphocytes High	0	1		
Lymphocytes Low	52	61		
Neutrophils Low	17	19		
Platelets Low	1	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Complete Remission (CR) Rate Per IRF at End of Treatment (EOT)

End point title	Complete Remission (CR) Rate Per IRF at End of Treatment (EOT)

End point description:

The proportion of participants with CR per IRF following the completion of study treatment (at end of treatment or at the first assessment after the last dose of study treatment and prior to long-term follow-up) according to the Revised Response Criteria for Malignant Lymphoma.

End point type	Secondary

End point timeframe:

Up to 8.34 months

End point values	A+CHP	CHOP		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	226	226		
Units: Number of Participants	153	126		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival (OS)

End point title	Overall survival (OS)

End point description:

The time from randomization to death due to any cause.

End point type	Secondary

End point timeframe:

Until death or study closure, up to 7 years post-treatment. Median OS follow-up time of 66.76 months

End point values	A+CHP	CHOP		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	226[5]	226[6]		
Units: Months				
median (full range (min-max))	.9999999999 (0.0 to 86.5)	.9999999999 (0.1 to 90.0)		

Notes:

[5] - .9999999999 = The median OS was not reached in either treatment arm.

[6] - .9999999999 = The median OS was not reached in either treatment arm.

Statistical analyses

No statistical analyses for this end point

Secondary: Objective response rate (ORR) per IRF at end of treatment

End point title	Objective response rate (ORR) per IRF at end of treatment

End point description:

The proportion of participants with CR or partial response (PR) per IRF following the completion of study treatment (at end of treatment or the first assessment after the last dose of study treatment and prior to long-term follow-up) according to the Revised Response Criteria for Malignant Lymphoma.

End point type	Secondary

End point timeframe:

Up to 8.34 months

End point values	A+CHP	CHOP		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	226	226		
Units: Number of Participants	188	163		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Non-serious AEs followed up to 8 months. Serious AEs followed up to 90 months

Adverse event reporting additional description:

Safety Analysis Population: Includes all randomized participants who received at least one dose of study treatment.

Investigator and study personnel report all adverse events (AEs) and serious adverse events (SAEs) whether elicited during patient questioning, discovered during physical examination, laboratory testing and/or other means.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups

Reporting group title	CHOP

Reporting group description:

cyclophosphamide, doxorubicin, vincristine, and prednisone doxorubicin: 50 mg/m2 every 3 weeks by IV infusion for 6-8 cycles prednisone: 100 mg on Days 1 to 5 of each 3-week cycle, orally for 6-8 cycles vincristine: 1.4 mg/m2 (maximum 2 mg) every 3 weeks by IV infusion for 6-8 cycles cyclophosphamide: 750 mg/m2 every 3 weeks by IV infusion for 6-8 cycles

Reporting group title	A+CHP

Reporting group description:

brentuximab vedotin, cyclophosphamide, doxorubicin, and prednisone brentuximab vedotin: 1.8 mg/kg every 3 weeks by IV infusion for 6-8 cycles doxorubicin: 50 mg/m2 every 3 weeks by IV infusion for 6-8 cycles prednisone: 100 mg on Days 1 to 5 of each 3-week cycle, orally for 6-8 cycles cyclophosphamide: 750 mg/m2 every 3 weeks by IV infusion for 6-8 cycles

Serious adverse events	CHOP	A+CHP	
Total subjects affected by serious adverse events			
subjects affected / exposed	90 / 226 (39.82%)	89 / 223 (39.91%)	
number of deaths (all causes)	89	67	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Peripheral T-cell lymphoma unspecified			
subjects affected / exposed	0 / 226 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Papillary thyroid cancer			
subjects affected / exposed	0 / 226 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Tumour haemorrhage			
subjects affected / exposed	0 / 226 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaplastic large cell lymphoma T- and null-cell types			
subjects affected / exposed	11 / 226 (4.87%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	0 / 13	0 / 0	
deaths causally related to treatment / all	0 / 8	0 / 0	
Cancer pain			
subjects affected / exposed	1 / 226 (0.44%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to central nervous system			
subjects affected / exposed	2 / 226 (0.88%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Transitional cell carcinoma			
subjects affected / exposed	1 / 226 (0.44%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour associated fever			
subjects affected / exposed	1 / 226 (0.44%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cutaneous T-cell lymphoma			
subjects affected / exposed	1 / 226 (0.44%)	2 / 223 (0.90%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myelodysplastic syndrome			
subjects affected / exposed	1 / 226 (0.44%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasm malignant			

subjects affected / exposed	0 / 226 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
T-cell type acute leukaemia			
subjects affected / exposed	1 / 226 (0.44%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	2 / 226 (0.88%)	3 / 223 (1.35%)	
occurrences causally related to treatment / all	0 / 2	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolism			
subjects affected / exposed	0 / 226 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	1 / 226 (0.44%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombophlebitis superficial			
subjects affected / exposed	1 / 226 (0.44%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orthostatic hypotension			
subjects affected / exposed	1 / 226 (0.44%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	8 / 226 (3.54%)	9 / 223 (4.04%)	
occurrences causally related to treatment / all	3 / 9	3 / 16	
deaths causally related to treatment / all	0 / 0	0 / 0	

Asthenia			
subjects affected / exposed	0 / 226 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Extravasation			
subjects affected / exposed	0 / 226 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperthermia			
subjects affected / exposed	0 / 226 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucosal inflammation			
subjects affected / exposed	1 / 226 (0.44%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	0 / 226 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	1 / 226 (0.44%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Multiple organ dysfunction syndrome			
subjects affected / exposed	3 / 226 (1.33%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	2 / 2	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pneumonitis			
subjects affected / exposed	0 / 226 (0.00%)	5 / 223 (2.24%)	
occurrences causally related to treatment / all	0 / 0	3 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	

Respiratory failure			
subjects affected / exposed	2 / 226 (0.88%)	3 / 223 (1.35%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	6 / 226 (2.65%)	2 / 223 (0.90%)	
occurrences causally related to treatment / all	1 / 6	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory failure			
subjects affected / exposed	0 / 226 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cough			
subjects affected / exposed	0 / 226 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	0 / 226 (0.00%)	2 / 223 (0.90%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	0 / 226 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	0 / 226 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	0 / 226 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Pulmonary cavitation			

subjects affected / exposed	0 / 226 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Acute respiratory distress syndrome			
subjects affected / exposed	1 / 226 (0.44%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Mental status changes			
subjects affected / exposed	0 / 226 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Confusional state			
subjects affected / exposed	1 / 226 (0.44%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Device issue			
subjects affected / exposed	1 / 226 (0.44%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Weight decreased			
subjects affected / exposed	0 / 226 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CSF volume decreased			
subjects affected / exposed	1 / 226 (0.44%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Splenic rupture			

subjects affected / exposed	0 / 226 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	1 / 226 (0.44%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal compression fracture			
subjects affected / exposed	1 / 226 (0.44%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 226 (0.44%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	1 / 226 (0.44%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	1 / 1	0 / 1	
Sinus tachycardia			
subjects affected / exposed	0 / 226 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	0 / 226 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia			
subjects affected / exposed	2 / 226 (0.88%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular fibrillation			

subjects affected / exposed	0 / 226 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Arrhythmia			
subjects affected / exposed	1 / 226 (0.44%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac failure acute			
subjects affected / exposed	1 / 226 (0.44%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiogenic shock			
subjects affected / exposed	0 / 226 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Nervous system disorders			
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 226 (0.00%)	2 / 223 (0.90%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	0 / 226 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	0 / 226 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral motor neuropathy			
subjects affected / exposed	0 / 226 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			

subjects affected / exposed	1 / 226 (0.44%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	0 / 226 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Autonomic neuropathy			
subjects affected / exposed	1 / 226 (0.44%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral infarction			
subjects affected / exposed	1 / 226 (0.44%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydrocephalus			
subjects affected / exposed	1 / 226 (0.44%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Paraesthesia			
subjects affected / exposed	1 / 226 (0.44%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	26 / 226 (11.50%)	32 / 223 (14.35%)	
occurrences causally related to treatment / all	33 / 38	34 / 42	
deaths causally related to treatment / all	1 / 1	0 / 0	
Neutropenia			
subjects affected / exposed	6 / 226 (2.65%)	8 / 223 (3.59%)	
occurrences causally related to treatment / all	4 / 8	13 / 16	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			

subjects affected / exposed	1 / 226 (0.44%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	3 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			
subjects affected / exposed	3 / 226 (1.33%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	1 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphopenia			
subjects affected / exposed	0 / 226 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphadenopathy			
subjects affected / exposed	0 / 226 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	1 / 226 (0.44%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	1 / 226 (0.44%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Retinal vein occlusion			
subjects affected / exposed	1 / 226 (0.44%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	3 / 226 (1.33%)	4 / 223 (1.79%)	
occurrences causally related to treatment / all	0 / 3	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			

subjects affected / exposed	1 / 226 (0.44%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	1 / 226 (0.44%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer haemorrhage			
subjects affected / exposed	0 / 226 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenitis haemorrhagic			
subjects affected / exposed	0 / 226 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis			
subjects affected / exposed	1 / 226 (0.44%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia strangulated			
subjects affected / exposed	0 / 226 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal perforation			
subjects affected / exposed	0 / 226 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	4 / 226 (1.77%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	3 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			

subjects affected / exposed	0 / 226 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	3 / 226 (1.33%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	2 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	1 / 226 (0.44%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer			
subjects affected / exposed	1 / 226 (0.44%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematemesis			
subjects affected / exposed	1 / 226 (0.44%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	1 / 226 (0.44%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower gastrointestinal haemorrhage			
subjects affected / exposed	1 / 226 (0.44%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Odynophagia			
subjects affected / exposed	1 / 226 (0.44%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophagitis			

subjects affected / exposed	1 / 226 (0.44%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	1 / 226 (0.44%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			
subjects affected / exposed	2 / 226 (0.88%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subileus			
subjects affected / exposed	1 / 226 (0.44%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ulcerative gastritis			
subjects affected / exposed	1 / 226 (0.44%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatic function abnormal			
subjects affected / exposed	0 / 226 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangitis			
subjects affected / exposed	1 / 226 (0.44%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 226 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash maculo-papular			

subjects affected / exposed	0 / 226 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blister			
subjects affected / exposed	1 / 226 (0.44%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 226 (0.00%)	3 / 223 (1.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 1	
Haematuria			
subjects affected / exposed	1 / 226 (0.44%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	1 / 226 (0.44%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	0 / 226 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oliguria			
subjects affected / exposed	1 / 226 (0.44%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Bone pain			
subjects affected / exposed	0 / 226 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pain in extremity			
subjects affected / exposed	0 / 226 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular weakness			
subjects affected / exposed	1 / 226 (0.44%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vertebral column mass			
subjects affected / exposed	1 / 226 (0.44%)	0 / 223 (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			
Pneumonia			
subjects affected / exposed	3 / 226 (1.33%)	11 / 223 (4.93%)	
occurrences causally related to treatment / all	4 / 4	10 / 14	
deaths causally related to treatment / all	0 / 0	1 / 1	
Sepsis			
subjects affected / exposed	4 / 226 (1.77%)	5 / 223 (2.24%)	
occurrences causally related to treatment / all	5 / 6	4 / 5	
deaths causally related to treatment / all	2 / 2	1 / 1	
Cellulitis			
subjects affected / exposed	0 / 226 (0.00%)	2 / 223 (0.90%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	0 / 226 (0.00%)	2 / 223 (0.90%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	0 / 226 (0.00%)	2 / 223 (0.90%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			

subjects affected / exposed	0 / 226 (0.00%)	2 / 223 (0.90%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic infection			
subjects affected / exposed	1 / 226 (0.44%)	2 / 223 (0.90%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumocystis jirovecii pneumonia			
subjects affected / exposed	0 / 226 (0.00%)	2 / 223 (0.90%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	0 / 226 (0.00%)	2 / 223 (0.90%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess soft tissue			
subjects affected / exposed	0 / 226 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal fistula infection			
subjects affected / exposed	0 / 226 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial pyelonephritis			
subjects affected / exposed	0 / 226 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial sepsis			
subjects affected / exposed	0 / 226 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopulmonary aspergillosis			

subjects affected / exposed	0 / 226 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheter site cellulitis			
subjects affected / exposed	0 / 226 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile infection			
subjects affected / exposed	0 / 226 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus infection			
subjects affected / exposed	0 / 226 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis infectious			
subjects affected / exposed	0 / 226 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epstein-Barr virus infection			
subjects affected / exposed	0 / 226 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
H1N1 influenza			
subjects affected / exposed	0 / 226 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	1 / 226 (0.44%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injection site infection			

subjects affected / exposed	0 / 226 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymph gland infection			
subjects affected / exposed	0 / 226 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Otitis externa			
subjects affected / exposed	0 / 226 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Perirectal abscess			
subjects affected / exposed	0 / 226 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory syncytial virus infection			
subjects affected / exposed	0 / 226 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	2 / 226 (0.88%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	3 / 3	1 / 1	
deaths causally related to treatment / all	1 / 1	0 / 0	
Soft tissue infection			
subjects affected / exposed	1 / 226 (0.44%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal infection			
subjects affected / exposed	2 / 226 (0.88%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			

subjects affected / exposed	1 / 226 (0.44%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia sepsis			
subjects affected / exposed	2 / 226 (0.88%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Groin abscess			
subjects affected / exposed	1 / 226 (0.44%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngitis			
subjects affected / exposed	1 / 226 (0.44%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic sepsis			
subjects affected / exposed	3 / 226 (1.33%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin infection			
subjects affected / exposed	2 / 226 (0.88%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal sepsis			
subjects affected / exposed	1 / 226 (0.44%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Streptococcal sepsis			
subjects affected / exposed	1 / 226 (0.44%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral upper respiratory tract infection			

subjects affected / exposed	1 / 226 (0.44%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic foot infection			
subjects affected / exposed	0 / 226 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Tumour lysis syndrome			
subjects affected / exposed	0 / 226 (0.00%)	3 / 223 (1.35%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	3 / 226 (1.33%)	2 / 223 (0.90%)	
occurrences causally related to treatment / all	1 / 3	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Decreased appetite			
subjects affected / exposed	0 / 226 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fluid overload			
subjects affected / exposed	0 / 226 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	0 / 226 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperuricaemia			
subjects affected / exposed	1 / 226 (0.44%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			

subjects affected / exposed	1 / 226 (0.44%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Type 2 diabetes mellitus			
subjects affected / exposed	1 / 226 (0.44%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	CHOP	A+CHP	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	218 / 226 (96.46%)	220 / 223 (98.65%)	
Vascular disorders			
Hypotension			
subjects affected / exposed	14 / 226 (6.19%)	15 / 223 (6.73%)	
occurrences (all)	16	17	
Hypertension			
subjects affected / exposed	68 / 226 (30.09%)	71 / 223 (31.84%)	
occurrences (all)	75	76	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	80 / 226 (35.40%)	83 / 223 (37.22%)	
occurrences (all)	142	135	
Pyrexia			
subjects affected / exposed	74 / 226 (32.74%)	86 / 223 (38.57%)	
occurrences (all)	109	134	
Asthenia			
subjects affected / exposed	20 / 226 (8.85%)	35 / 223 (15.70%)	
occurrences (all)	27	45	
Oedema peripheral			
subjects affected / exposed	36 / 226 (15.93%)	40 / 223 (17.94%)	
occurrences (all)	48	53	
Mucosal inflammation			

subjects affected / exposed	14 / 226 (6.19%)	15 / 223 (6.73%)	
occurrences (all)	17	17	
Chest pain			
subjects affected / exposed	8 / 226 (3.54%)	14 / 223 (6.28%)	
occurrences (all)	8	15	
Malaise			
subjects affected / exposed	12 / 226 (5.31%)	8 / 223 (3.59%)	
occurrences (all)	26	8	
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	14 / 226 (6.19%)	9 / 223 (4.04%)	
occurrences (all)	16	9	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	33 / 226 (14.60%)	39 / 223 (17.49%)	
occurrences (all)	60	54	
Oropharyngeal pain			
subjects affected / exposed	19 / 226 (8.41%)	21 / 223 (9.42%)	
occurrences (all)	23	23	
Cough			
subjects affected / exposed	44 / 226 (19.47%)	37 / 223 (16.59%)	
occurrences (all)	45	53	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	49 / 226 (21.68%)	52 / 223 (23.32%)	
occurrences (all)	54	62	
Anxiety			
subjects affected / exposed	13 / 226 (5.75%)	30 / 223 (13.45%)	
occurrences (all)	14	34	
Depression			
subjects affected / exposed	15 / 226 (6.64%)	16 / 223 (7.17%)	
occurrences (all)	15	16	
Investigations			
Weight decreased			
subjects affected / exposed	43 / 226 (19.03%)	54 / 223 (24.22%)	
occurrences (all)	48	62	

Alanine aminotransferase increased			
subjects affected / exposed	0 / 226 (0.00%)	11 / 223 (4.93%)	
occurrences (all)	0	13	
Nervous system disorders			
Peripheral sensory neuropathy			
subjects affected / exposed	108 / 226 (47.79%)	112 / 223 (50.22%)	
occurrences (all)	152	179	
Headache			
subjects affected / exposed	36 / 226 (15.93%)	37 / 223 (16.59%)	
occurrences (all)	52	48	
Dizziness			
subjects affected / exposed	24 / 226 (10.62%)	32 / 223 (14.35%)	
occurrences (all)	38	52	
Dysgeusia			
subjects affected / exposed	15 / 226 (6.64%)	13 / 223 (5.83%)	
occurrences (all)	19	14	
Paraesthesia			
subjects affected / exposed	19 / 226 (8.41%)	13 / 223 (5.83%)	
occurrences (all)	25	14	
Peripheral motor neuropathy			
subjects affected / exposed	18 / 226 (7.96%)	8 / 223 (3.59%)	
occurrences (all)	23	15	
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	81 / 226 (35.84%)	87 / 223 (39.01%)	
occurrences (all)	203	285	
Anaemia			
subjects affected / exposed	49 / 226 (21.68%)	64 / 223 (28.70%)	
occurrences (all)	163	218	
Leukopenia			
subjects affected / exposed	13 / 226 (5.75%)	18 / 223 (8.07%)	
occurrences (all)	76	63	
Febrile neutropenia			
subjects affected / exposed	9 / 226 (3.98%)	16 / 223 (7.17%)	
occurrences (all)	12	36	
Thrombocytopenia			

subjects affected / exposed	14 / 226 (6.19%)	21 / 223 (9.42%)	
occurrences (all)	42	77	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	91 / 226 (40.27%)	114 / 223 (51.12%)	
occurrences (all)	172	228	
Diarrhoea			
subjects affected / exposed	55 / 226 (24.34%)	93 / 223 (41.70%)	
occurrences (all)	71	174	
Constipation			
subjects affected / exposed	94 / 226 (41.59%)	98 / 223 (43.95%)	
occurrences (all)	124	145	
Vomiting			
subjects affected / exposed	37 / 226 (16.37%)	60 / 223 (26.91%)	
occurrences (all)	58	92	
Stomatitis			
subjects affected / exposed	27 / 226 (11.95%)	28 / 223 (12.56%)	
occurrences (all)	42	41	
Abdominal pain upper			
subjects affected / exposed	10 / 226 (4.42%)	23 / 223 (10.31%)	
occurrences (all)	11	26	
Dyspepsia			
subjects affected / exposed	12 / 226 (5.31%)	17 / 223 (7.62%)	
occurrences (all)	12	21	
Abdominal pain			
subjects affected / exposed	22 / 226 (9.73%)	26 / 223 (11.66%)	
occurrences (all)	26	39	
Gastrooesophageal reflux disease			
subjects affected / exposed	16 / 226 (7.08%)	22 / 223 (9.87%)	
occurrences (all)	16	23	
Haemorrhoids			
subjects affected / exposed	12 / 226 (5.31%)	8 / 223 (3.59%)	
occurrences (all)	12	10	
Skin and subcutaneous tissue disorders			
Alopecia			

subjects affected / exposed	56 / 226 (24.78%)	58 / 223 (26.01%)	
occurrences (all)	61	66	
Rash			
subjects affected / exposed	21 / 226 (9.29%)	27 / 223 (12.11%)	
occurrences (all)	25	37	
Night sweats			
subjects affected / exposed	63 / 226 (27.88%)	46 / 223 (20.63%)	
occurrences (all)	68	56	
Pruritus			
subjects affected / exposed	15 / 226 (6.64%)	22 / 223 (9.87%)	
occurrences (all)	16	28	
Dry skin			
subjects affected / exposed	17 / 226 (7.52%)	10 / 223 (4.48%)	
occurrences (all)	18	10	
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	11 / 226 (4.87%)	12 / 223 (5.38%)	
occurrences (all)	11	12	
Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	21 / 226 (9.29%)	27 / 223 (12.11%)	
occurrences (all)	38	45	
Arthralgia			
subjects affected / exposed	20 / 226 (8.85%)	31 / 223 (13.90%)	
occurrences (all)	28	49	
Back pain			
subjects affected / exposed	43 / 226 (19.03%)	44 / 223 (19.73%)	
occurrences (all)	49	47	
Pain in extremity			
subjects affected / exposed	21 / 226 (9.29%)	23 / 223 (10.31%)	
occurrences (all)	24	25	
Bone pain			
subjects affected / exposed	12 / 226 (5.31%)	15 / 223 (6.73%)	
occurrences (all)	15	18	
Neck pain			

subjects affected / exposed	8 / 226 (3.54%)	11 / 223 (4.93%)	
occurrences (all)	9	12	
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	12 / 226 (5.31%)	18 / 223 (8.07%)	
occurrences (all)	13	19	
Nasopharyngitis			
subjects affected / exposed	12 / 226 (5.31%)	10 / 223 (4.48%)	
occurrences (all)	13	12	
Urinary tract infection			
subjects affected / exposed	9 / 226 (3.98%)	12 / 223 (5.38%)	
occurrences (all)	9	12	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	47 / 226 (20.80%)	53 / 223 (23.77%)	
occurrences (all)	54	74	
Hypokalaemia			
subjects affected / exposed	24 / 226 (10.62%)	29 / 223 (13.00%)	
occurrences (all)	52	55	
Diabetes mellitus			
subjects affected / exposed	13 / 226 (5.75%)	14 / 223 (6.28%)	
occurrences (all)	13	14	
Hypercholesterolaemia			
subjects affected / exposed	12 / 226 (5.31%)	10 / 223 (4.48%)	
occurrences (all)	12	10	
Hyperlipidaemia			
subjects affected / exposed	13 / 226 (5.75%)	9 / 223 (4.04%)	
occurrences (all)	13	9	
Hyperglycaemia			
subjects affected / exposed	9 / 226 (3.98%)	11 / 223 (4.93%)	
occurrences (all)	14	21	
Hyperuricaemia			
subjects affected / exposed	9 / 226 (3.98%)	11 / 223 (4.93%)	
occurrences (all)	9	12	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 September 2012	Excludes subjects with known HIV or hepatitis B or suspected hepatitis C infection. Included ECG or MUGA scan to screening procedures. Removes a planned interim analysis.
31 January 2013	Excludes subjects with the demyelinating form of Charcot-Marie-Tooth syndrome, subjects previously treated with complete cumulative doses of doxorubicin or other anthracyclines, and subjects with known urinary outflow obstruction. Update to baseline laboratory inclusion criteria. Increases the period of time following the end of treatment that contraception must be used. Adds Objective Response Rate as a secondary endpoint.
05 March 2015	Increases the planned enrollment from 300 to 450 subjects.
15 March 2018	Clarification to timing of final primary analysis.
18 December 2018	Administrative clarifications and organizational changes.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported