Clinical trial results:
A Phase 2, Open-label, Single-arm, Two-cohort Study of Nivolumab in Relapsed/Refractory Primary Central Nervous System Lymphoma (PCNSL) or Relapsed/Refractory Primary Testicular Lymphoma (PTL)

Summary

EudraCT number	2016-000894-19
Trial protocol	HU FR DE IT
Global end of trial date	24 November 2020

Results information

Result version number	v1 (current)
This version publication date	13 December 2021
First version publication date	13 December 2021

Trial information

Trial identification

Sponsor protocol code	CA209-647

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Bristol-Myers Squibb
Sponsor organisation address	Chaussée de la Hulpe 185, Brussels, Belgium, 1170
Public contact	EU Study Start-Up Unit, Bristol-Myers Squibb International Corporation, Clinical.Trials@bms.com
Scientific contact	Bristol-Myers Squibb Study Director, Bristol-Myers Squibb, Clinical.Trials@bms.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	29 January 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	24 November 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Investigate clinically meaningful efficacy treatment with Nivolumab in subjects with relapsed/refractory PCNSL or PTL

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization Good Clinical Practice Guidelines. All the local regulatory requirements pertinent to safety of trial participants were followed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	21 October 2016
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	Canada: 2
Country: Number of subjects enrolled	France: 7
Country: Number of subjects enrolled	Germany: 6
Country: Number of subjects enrolled	Hong Kong: 1
Country: Number of subjects enrolled	Hungary: 3
Country: Number of subjects enrolled	Israel: 2
Country: Number of subjects enrolled	Italy: 8
Country: Number of subjects enrolled	Japan: 9
Country: Number of subjects enrolled	Russian Federation: 1
Country: Number of subjects enrolled	Singapore: 1
Country: Number of subjects enrolled	United States: 26
Worldwide total number of subjects	66
EEA total number of subjects	24

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)	24
From 65 to 84 years	42
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

47 PCNSL participants treated. 19 PTL participants treated.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	PCNSL cohort

Arm description:

Nivolumab dosed to participants with relapsed/refractory Primary Central Nervous System Lymphoma (PCNSL). Nivolumab 240 mg was given every 2 weeks for 8 cycles. Beginning with Cycle 9, nivolumab 480 mg was given every 4 weeks for a total therapy duration of 2 years, or until progressive disease, unacceptable toxicity, or withdrawal of consent. Nivolumab was administered as a 30-minute infusion.

Arm type	Experimental
Investigational medicinal product name	Nivolumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Nivolumab at a dose of 240 mg as a 30-minute infusion on Day 1 of each treatment cycle for 8 cycle. Beginning with Cycle 9, Nivolumab at a dose of 480 mg as a 30-minute infusion every 4 weeks

Arm title	PTL cohort

Arm description:

Nivolumab dosed to participants with relapsed/refractory Primary Testicular Lymphoma (PTL). Nivolumab 240 mg was given every 2 weeks for 8 cycles. Beginning with Cycle 9, nivolumab 480 mg was given every 4 weeks for a total therapy duration of 2 years, or until progressive disease, unacceptable toxicity, or withdrawal of consent. Nivolumab was administered as a 30-minute infusion.

Arm type	Experimental
Investigational medicinal product name	Nivolumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Nivolumab at a dose of 240 mg as a 30-minute infusion on Day 1 of each treatment cycle for 8 cycle. Beginning with Cycle 9, Nivolumab at a dose of 480 mg as a 30-minute infusion every 4 weeks

Number of subjects in period 1	PCNSL cohort	PTL cohort
Started	47	19
Completed	0	0
Not completed	47	19
Adverse event, serious fatal	1	-
Completed treatment	-	2
Disease progression	34	13
Participant withdrew consent	1	1
Study drug toxicity	4	1
Maximum clinical benefit	1	-
Adverse event unrelated to study drug	6	2

Baseline characteristics

Reporting groups	
Reporting group title	PCNSL cohort
Reporting group description:	
Nivolumab dosed to participants with relapsed/refractory Primary Central Nervous System Lymphoma (PCNSL). Nivolumab 240 mg was given every 2 weeks for 8 cycles. Beginning with Cycle 9, nivolumab 480 mg was given every 4 weeks for a total therapy duration of 2 years, or until progressive disease, unacceptable toxicity, or withdrawal of consent. Nivolumab was administered as a 30-minute infusion.	
Reporting group title	PTL cohort
Reporting group description:	
Nivolumab dosed to participants with relapsed/refractory Primary Testicular Lymphoma (PTL). Nivolumab 240 mg was given every 2 weeks for 8 cycles. Beginning with Cycle 9, nivolumab 480 mg was given every 4 weeks for a total therapy duration of 2 years, or until progressive disease, unacceptable toxicity, or withdrawal of consent. Nivolumab was administered as a 30-minute infusion.	

Reporting group values	PCNSL cohort	PTL cohort	Total
Number of subjects	47	19	66
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	18	6	24
From 65-84 years	29	13	42
85 years and over	0	0	0
Age Continuous Units: Years			
arithmetic mean	65.9	66.7	
standard deviation	± 10.1	± 8.6	-
Sex: Female, Male Units: Participants			
Female	20	0	20
Male	27	19	46
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	10	5	15
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	0	0
White	37	12	49
More than one race	0	0	0
Unknown or Not Reported	0	2	2
Ethnicity (NIH/OMB) Units: Subjects			

Hispanic or Latino	1	0	1
Not Hispanic or Latino	33	11	44
Unknown or Not Reported	13	8	21

End points

End points reporting groups

Reporting group title	PCNSL cohort

Reporting group description:

Nivolumab dosed to participants with relapsed/refractory Primary Central Nervous System Lymphoma (PCNSL). Nivolumab 240 mg was given every 2 weeks for 8 cycles. Beginning with Cycle 9, nivolumab 480 mg was given every 4 weeks for a total therapy duration of 2 years, or until progressive disease, unacceptable toxicity, or withdrawal of consent. Nivolumab was administered as a 30-minute infusion.

Reporting group title	PTL cohort

Reporting group description:

Nivolumab dosed to participants with relapsed/refractory Primary Testicular Lymphoma (PTL). Nivolumab 240 mg was given every 2 weeks for 8 cycles. Beginning with Cycle 9, nivolumab 480 mg was given every 4 weeks for a total therapy duration of 2 years, or until progressive disease, unacceptable toxicity, or withdrawal of consent. Nivolumab was administered as a 30-minute infusion.

Primary: BICR-Assessed Objective Response Rate (ORR)

End point title	BICR-Assessed Objective Response Rate (ORR)[1]

End point description:

Percentage of participants with a confirmed objective response rate (ORR) by blinded independent central review (BICR) assessment was analyzed and reported for both PCNSL and PTL patient populations. This endpoint is further defined as the percentage of participants with a best overall response (BOR) of complete response (CR) or partial response (PR), based on the IPCG Criteria for PCNSL and Lugano 2014 response evaluation for PTL, divided by the number of treated participants within each cohort.

End point type	Primary

End point timeframe:

Up to approximately 51 months

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only summary statistics planned for this endpoint since this is a single arm (by cohort) design.

End point values	PCNSL cohort	PTL cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	19		
Units: Percentage of participants				
number (confidence interval 95%)	6.4 (1.3 to 17.5)	26.3 (9.1 to 51.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: BICR-Assessed Progression Free Survival (PFS)

End point title	BICR-Assessed Progression Free Survival (PFS)

End point description:

Progression-free survival (PFS) is defined as the time from first dosing date to the date of the first documented progression using the IPCG Criteria for PCNSL and Lugano 2014 response evaluation for

PTL, as determined by BICR, or death due to any cause, whichever occurs first.

End point type	Secondary

End point timeframe:

Up to approximately 51 months

End point values	PCNSL cohort	PTL cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	19		
Units: Months				
median (confidence interval 95%)	1.41 (1.08 to 1.74)	1.72 (1.15 to 6.28)		

Statistical analyses

No statistical analyses for this end point

Secondary: Investigator-Assessed Objective Response Rate (ORR)

End point title	Investigator-Assessed Objective Response Rate (ORR)

End point description:

Percentage of participants with a confirmed objective response rate (ORR) by investigator assessment was analyzed and reported for both PCNSL and PTL patient populations. This endpoint is further defined as the percentage of participants with a best overall response (BOR) of complete response (CR) or partial response (PR), based on the IPCG Criteria for PCNSL and Lugano 2014 response evaluation for PTL, divided by the number of treated participants within each cohort.

End point type	Secondary

End point timeframe:

Up to approximately 51 months

End point values	PCNSL cohort	PTL cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	19		
Units: Percentage of participants				
number (confidence interval 95%)	10.6 (3.5 to 23.1)	26.3 (9.1 to 51.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Investigator-Assessed Duration of Response (DOR)

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

End point description:

Duration of response (DOR) by investigator assessment was analyzed and reported for both PCNSL and PTL patient populations. This endpoint is further defined as the time from first response (CR or PR) to the date of initial objectively documented progression as determined using the IPCG Criteria for PCNSL and Lugano 2014 response evaluation for PTL, as determined by BICR, or death due to any cause, whichever occurs first.

End point type	Secondary

End point timeframe:

Up to approximately 51 months

End point values	PCNSL cohort	PTL cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	5		
Units: Months				
median (confidence interval 95%)	1.71 (0.72 to 7.10)	20.63 (0.03 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

Overall survival (OS) was analyzed and reported for both PCNSL and PTL patient populations. OS is defined as the time from first dosing date to the date of death. For participants without documentation of death, OS will be censored on the last date the participant was known to be alive.

End point type	Secondary

End point timeframe:

Up to approximately 51 months

End point values	PCNSL cohort	PTL cohort		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	19		
Units: Months				
median (confidence interval 95%)	6.77 (3.68 to 11.99)	11.17 (2.60 to 24.41)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs collected were reported between first dose of the study treatment upto 100 days after last dose of study treatment

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.1

Reporting groups

Reporting group title	Primary central nervous system lymphoma (PCNSL) Cohort

Reporting group description:

Subjects with pathologically confirmed PCNSL were administered 240 milligram (mg) of Nivolumab as a 30-minute intravenous (IV) infusion every 2 weeks (Q2W) for a total of 8 cycles followed by 480 mg of Nivolumab every 4 weeks (Q4W) for a maximum of 2 years or until progressive disease, unacceptable toxicity, or withdrawal of consent.

Reporting group title	Primary Testicular Lymphoma (PTL) Cohort

Reporting group description:

Subjects with pathologically confirmed PTL were administered 240 mg of Nivolumab as a 30-minute IV infusion Q2W for a total of 8 cycles followed by 480 mg of Nivolumab Q4W for a maximum of 2 years or until progressive disease, unacceptable toxicity, or withdrawal of consent.

Serious adverse events	Primary central nervous system lymphoma (PCNSL) Cohort	Primary Testicular Lymphoma (PTL) Cohort	
Total subjects affected by serious adverse events			
subjects affected / exposed	33 / 47 (70.21%)	15 / 19 (78.95%)	
number of deaths (all causes)	32	13	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma of colon			
subjects affected / exposed	0 / 47 (0.00%)	1 / 19 (5.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung adenocarcinoma			
subjects affected / exposed	0 / 47 (0.00%)	1 / 19 (5.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant neoplasm progression			

subjects affected / exposed	13 / 47 (27.66%)	8 / 19 (42.11%)	
occurrences causally related to treatment / all	0 / 13	0 / 9	
deaths causally related to treatment / all	0 / 9	0 / 6	
Tumour flare			
subjects affected / exposed	2 / 47 (4.26%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour pseudoprogression			
subjects affected / exposed	1 / 47 (2.13%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 47 (2.13%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	1 / 47 (2.13%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gait disturbance			
subjects affected / exposed	1 / 47 (2.13%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	2 / 47 (4.26%)	1 / 19 (5.26%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Mucosal inflammation			
subjects affected / exposed	1 / 47 (2.13%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			

subjects affected / exposed	1 / 47 (2.13%)	1 / 19 (5.26%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden death			
subjects affected / exposed	1 / 47 (2.13%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	1 / 47 (2.13%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Confusional state			
subjects affected / exposed	2 / 47 (4.26%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental status changes			
subjects affected / exposed	1 / 47 (2.13%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Lymphocyte count decreased			
subjects affected / exposed	1 / 47 (2.13%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutrophil count decreased			
subjects affected / exposed	1 / 47 (2.13%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelet count decreased			
subjects affected / exposed	1 / 47 (2.13%)	0 / 19 (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			
Cervical vertebral fracture			
subjects affected / exposed	1 / 47 (2.13%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	2 / 47 (4.26%)	1 / 19 (5.26%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	1 / 47 (2.13%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infusion related reaction			
subjects affected / exposed	1 / 47 (2.13%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Brain oedema			
subjects affected / exposed	1 / 47 (2.13%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cognitive disorder			
subjects affected / exposed	1 / 47 (2.13%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depressed level of consciousness			
subjects affected / exposed	2 / 47 (4.26%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalopathy			
subjects affected / exposed	2 / 47 (4.26%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	

Epilepsy			
subjects affected / exposed	1 / 47 (2.13%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage intracranial			
subjects affected / exposed	3 / 47 (6.38%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Headache			
subjects affected / exposed	2 / 47 (4.26%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemianopia homonymous			
subjects affected / exposed	1 / 47 (2.13%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemiparesis			
subjects affected / exposed	1 / 47 (2.13%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemiplegia			
subjects affected / exposed	1 / 47 (2.13%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental impairment			
subjects affected / exposed	1 / 47 (2.13%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorder			
subjects affected / exposed	1 / 47 (2.13%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neurological decompensation			

subjects affected / exposed	2 / 47 (4.26%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Optic neuritis			
subjects affected / exposed	0 / 47 (0.00%)	1 / 19 (5.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	4 / 47 (8.51%)	1 / 19 (5.26%)	
occurrences causally related to treatment / all	1 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	1 / 47 (2.13%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 47 (0.00%)	1 / 19 (5.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	1 / 47 (2.13%)	1 / 19 (5.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			
subjects affected / exposed	1 / 47 (2.13%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	1 / 47 (2.13%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			

Dysphagia			
subjects affected / exposed	1 / 47 (2.13%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatitis			
subjects affected / exposed	0 / 47 (0.00%)	1 / 19 (5.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis acute			
subjects affected / exposed	1 / 47 (2.13%)	0 / 19 (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			
Erythema multiforme			
subjects affected / exposed	1 / 47 (2.13%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 47 (0.00%)	1 / 19 (5.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	1 / 47 (2.13%)	2 / 19 (10.53%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 47 (0.00%)	1 / 19 (5.26%)	
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 / 47 (2.13%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Cystitis			
subjects affected / exposed	0 / 47 (0.00%)	1 / 19 (5.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	1 / 47 (2.13%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Meningitis viral			
subjects affected / exposed	1 / 47 (2.13%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 47 (0.00%)	1 / 19 (5.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary sepsis			
subjects affected / exposed	1 / 47 (2.13%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Sepsis			
subjects affected / exposed	3 / 47 (6.38%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Septic shock			
subjects affected / exposed	1 / 47 (2.13%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Urinary tract infection			

subjects affected / exposed	1 / 47 (2.13%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular device infection			
subjects affected / exposed	0 / 47 (0.00%)	1 / 19 (5.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	2 / 47 (4.26%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Failure to thrive			
subjects affected / exposed	1 / 47 (2.13%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 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	Primary central nervous system lymphoma (PCNSL) Cohort	Primary Testicular Lymphoma (PTL) Cohort	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	40 / 47 (85.11%)	16 / 19 (84.21%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant neoplasm progression			
subjects affected / exposed	1 / 47 (2.13%)	1 / 19 (5.26%)	
occurrences (all)	1	1	
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 47 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Asthenia			

subjects affected / exposed	2 / 47 (4.26%)	2 / 19 (10.53%)	
occurrences (all)	2	2	
Fatigue			
subjects affected / exposed	12 / 47 (25.53%)	2 / 19 (10.53%)	
occurrences (all)	18	2	
Gait disturbance			
subjects affected / exposed	6 / 47 (12.77%)	1 / 19 (5.26%)	
occurrences (all)	6	1	
Mucosal inflammation			
subjects affected / exposed	2 / 47 (4.26%)	1 / 19 (5.26%)	
occurrences (all)	2	1	
Non-cardiac chest pain			
subjects affected / exposed	3 / 47 (6.38%)	1 / 19 (5.26%)	
occurrences (all)	3	1	
Oedema peripheral			
subjects affected / exposed	3 / 47 (6.38%)	2 / 19 (10.53%)	
occurrences (all)	3	2	
Pyrexia			
subjects affected / exposed	9 / 47 (19.15%)	5 / 19 (26.32%)	
occurrences (all)	14	6	
Reproductive system and breast disorders			
Testicular pain			
subjects affected / exposed	0 / 47 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Testicular swelling			
subjects affected / exposed	0 / 47 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	3 / 47 (6.38%)	1 / 19 (5.26%)	
occurrences (all)	3	1	
Cough			
subjects affected / exposed	3 / 47 (6.38%)	2 / 19 (10.53%)	
occurrences (all)	3	2	
Pleural effusion			

subjects affected / exposed	1 / 47 (2.13%)	1 / 19 (5.26%)	
occurrences (all)	1	1	
Pneumonitis			
subjects affected / exposed	1 / 47 (2.13%)	1 / 19 (5.26%)	
occurrences (all)	1	1	
Psychiatric disorders			
Agitation			
subjects affected / exposed	3 / 47 (6.38%)	0 / 19 (0.00%)	
occurrences (all)	4	0	
Anxiety			
subjects affected / exposed	4 / 47 (8.51%)	0 / 19 (0.00%)	
occurrences (all)	4	0	
Confusional state			
subjects affected / exposed	4 / 47 (8.51%)	1 / 19 (5.26%)	
occurrences (all)	7	1	
Depression			
subjects affected / exposed	3 / 47 (6.38%)	0 / 19 (0.00%)	
occurrences (all)	3	0	
Insomnia			
subjects affected / exposed	5 / 47 (10.64%)	1 / 19 (5.26%)	
occurrences (all)	8	1	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	10 / 47 (21.28%)	1 / 19 (5.26%)	
occurrences (all)	19	1	
Aspartate aminotransferase increased			
subjects affected / exposed	7 / 47 (14.89%)	1 / 19 (5.26%)	
occurrences (all)	9	1	
Blood creatinine increased			
subjects affected / exposed	3 / 47 (6.38%)	1 / 19 (5.26%)	
occurrences (all)	3	1	
Human rhinovirus test positive			
subjects affected / exposed	0 / 47 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Lipase increased			

subjects affected / exposed	3 / 47 (6.38%)	1 / 19 (5.26%)	
occurrences (all)	3	1	
Lymphocyte count decreased			
subjects affected / exposed	6 / 47 (12.77%)	0 / 19 (0.00%)	
occurrences (all)	12	0	
Neutrophil count decreased			
subjects affected / exposed	5 / 47 (10.64%)	1 / 19 (5.26%)	
occurrences (all)	8	2	
Weight decreased			
subjects affected / exposed	4 / 47 (8.51%)	0 / 19 (0.00%)	
occurrences (all)	4	0	
Platelet count decreased			
subjects affected / exposed	5 / 47 (10.64%)	1 / 19 (5.26%)	
occurrences (all)	24	3	
White blood cell count decreased			
subjects affected / exposed	3 / 47 (6.38%)	1 / 19 (5.26%)	
occurrences (all)	11	1	
Injury, poisoning and procedural complications			
Clavicle fracture			
subjects affected / exposed	0 / 47 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Ankle fracture			
subjects affected / exposed	0 / 47 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Fall			
subjects affected / exposed	9 / 47 (19.15%)	3 / 19 (15.79%)	
occurrences (all)	12	4	
Procedural pain			
subjects affected / exposed	0 / 47 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Infusion related reaction			
subjects affected / exposed	2 / 47 (4.26%)	1 / 19 (5.26%)	
occurrences (all)	2	1	
Recall phenomenon			

subjects affected / exposed	0 / 47 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Upper limb fracture			
subjects affected / exposed	0 / 47 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Cardiac disorders			
Bradycardia			
subjects affected / exposed	2 / 47 (4.26%)	1 / 19 (5.26%)	
occurrences (all)	2	1	
Tachycardia			
subjects affected / exposed	0 / 47 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Nervous system disorders			
Aphasia			
subjects affected / exposed	5 / 47 (10.64%)	0 / 19 (0.00%)	
occurrences (all)	6	0	
Ataxia			
subjects affected / exposed	4 / 47 (8.51%)	0 / 19 (0.00%)	
occurrences (all)	4	0	
Dizziness			
subjects affected / exposed	4 / 47 (8.51%)	0 / 19 (0.00%)	
occurrences (all)	4	0	
Dysaesthesia			
subjects affected / exposed	0 / 47 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Facial paresis			
subjects affected / exposed	3 / 47 (6.38%)	0 / 19 (0.00%)	
occurrences (all)	3	0	
Headache			
subjects affected / exposed	12 / 47 (25.53%)	1 / 19 (5.26%)	
occurrences (all)	19	1	
Paraesthesia			
subjects affected / exposed	3 / 47 (6.38%)	0 / 19 (0.00%)	
occurrences (all)	4	0	
Hemiparesis			

subjects affected / exposed	5 / 47 (10.64%)	0 / 19 (0.00%)	
occurrences (all)	5	0	
Seizure			
subjects affected / exposed	6 / 47 (12.77%)	0 / 19 (0.00%)	
occurrences (all)	6	0	
Somnolence			
subjects affected / exposed	3 / 47 (6.38%)	0 / 19 (0.00%)	
occurrences (all)	4	0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	13 / 47 (27.66%)	1 / 19 (5.26%)	
occurrences (all)	42	1	
Thrombocytopenia			
subjects affected / exposed	4 / 47 (8.51%)	1 / 19 (5.26%)	
occurrences (all)	23	1	
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	1 / 47 (2.13%)	1 / 19 (5.26%)	
occurrences (all)	1	1	
Vertigo			
subjects affected / exposed	3 / 47 (6.38%)	0 / 19 (0.00%)	
occurrences (all)	4	0	
Eye disorders			
Conjunctival hyperaemia			
subjects affected / exposed	0 / 47 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Dry eye			
subjects affected / exposed	0 / 47 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Eye irritation			
subjects affected / exposed	1 / 47 (2.13%)	1 / 19 (5.26%)	
occurrences (all)	1	1	
Pupils unequal			
subjects affected / exposed	0 / 47 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Glaucoma			

subjects affected / exposed	0 / 47 (0.00%)	2 / 19 (10.53%)	
occurrences (all)	0	2	
Vision blurred			
subjects affected / exposed	1 / 47 (2.13%)	1 / 19 (5.26%)	
occurrences (all)	1	1	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	8 / 47 (17.02%)	4 / 19 (21.05%)	
occurrences (all)	9	4	
Diarrhoea			
subjects affected / exposed	5 / 47 (10.64%)	2 / 19 (10.53%)	
occurrences (all)	7	2	
Dry mouth			
subjects affected / exposed	0 / 47 (0.00%)	2 / 19 (10.53%)	
occurrences (all)	0	2	
Dysphagia			
subjects affected / exposed	3 / 47 (6.38%)	0 / 19 (0.00%)	
occurrences (all)	4	0	
Haematochezia			
subjects affected / exposed	0 / 47 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Nausea			
subjects affected / exposed	6 / 47 (12.77%)	2 / 19 (10.53%)	
occurrences (all)	6	2	
Stomatitis			
subjects affected / exposed	3 / 47 (6.38%)	0 / 19 (0.00%)	
occurrences (all)	4	0	
Vomiting			
subjects affected / exposed	7 / 47 (14.89%)	0 / 19 (0.00%)	
occurrences (all)	13	0	
Hepatobiliary disorders			
Hepatic steatosis			
subjects affected / exposed	0 / 47 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Hepatitis			

subjects affected / exposed	0 / 47 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Hepatotoxicity			
subjects affected / exposed	0 / 47 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Dermal cyst			
subjects affected / exposed	0 / 47 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Eczema asteatotic			
subjects affected / exposed	0 / 47 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Hyperhidrosis			
subjects affected / exposed	0 / 47 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Pruritus			
subjects affected / exposed	7 / 47 (14.89%)	1 / 19 (5.26%)	
occurrences (all)	10	1	
Rash			
subjects affected / exposed	4 / 47 (8.51%)	2 / 19 (10.53%)	
occurrences (all)	4	2	
Rash maculo-papular			
subjects affected / exposed	1 / 47 (2.13%)	3 / 19 (15.79%)	
occurrences (all)	8	3	
Skin ulcer			
subjects affected / exposed	0 / 47 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 47 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Urinary incontinence			
subjects affected / exposed	5 / 47 (10.64%)	0 / 19 (0.00%)	
occurrences (all)	5	0	
Chronic kidney disease			

subjects affected / exposed	1 / 47 (2.13%)	1 / 19 (5.26%)	
occurrences (all)	1	1	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 47 (4.26%)	4 / 19 (21.05%)	
occurrences (all)	5	7	
Arthritis			
subjects affected / exposed	1 / 47 (2.13%)	1 / 19 (5.26%)	
occurrences (all)	1	1	
Bursitis			
subjects affected / exposed	0 / 47 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Back pain			
subjects affected / exposed	4 / 47 (8.51%)	0 / 19 (0.00%)	
occurrences (all)	7	0	
Muscular weakness			
subjects affected / exposed	4 / 47 (8.51%)	2 / 19 (10.53%)	
occurrences (all)	4	2	
Myalgia			
subjects affected / exposed	1 / 47 (2.13%)	1 / 19 (5.26%)	
occurrences (all)	1	1	
Musculoskeletal chest pain			
subjects affected / exposed	1 / 47 (2.13%)	1 / 19 (5.26%)	
occurrences (all)	1	1	
Pain in extremity			
subjects affected / exposed	3 / 47 (6.38%)	1 / 19 (5.26%)	
occurrences (all)	3	1	
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 47 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Cellulitis			
subjects affected / exposed	1 / 47 (2.13%)	1 / 19 (5.26%)	
occurrences (all)	2	1	
Clostridium difficile infection			

subjects affected / exposed	1 / 47 (2.13%)	1 / 19 (5.26%)	
occurrences (all)	1	1	
Gastroenteritis			
subjects affected / exposed	1 / 47 (2.13%)	1 / 19 (5.26%)	
occurrences (all)	1	2	
Herpes simplex			
subjects affected / exposed	0 / 47 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Influenza			
subjects affected / exposed	0 / 47 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Oral candidiasis			
subjects affected / exposed	1 / 47 (2.13%)	1 / 19 (5.26%)	
occurrences (all)	1	1	
Pneumonia			
subjects affected / exposed	2 / 47 (4.26%)	1 / 19 (5.26%)	
occurrences (all)	2	1	
Upper respiratory tract infection			
subjects affected / exposed	1 / 47 (2.13%)	1 / 19 (5.26%)	
occurrences (all)	1	1	
Urinary tract infection			
subjects affected / exposed	5 / 47 (10.64%)	0 / 19 (0.00%)	
occurrences (all)	6	0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	3 / 47 (6.38%)	0 / 19 (0.00%)	
occurrences (all)	3	0	
Decreased appetite			
subjects affected / exposed	5 / 47 (10.64%)	0 / 19 (0.00%)	
occurrences (all)	6	0	
Hyperglycaemia			
subjects affected / exposed	6 / 47 (12.77%)	1 / 19 (5.26%)	
occurrences (all)	16	1	
Hypernatraemia			
subjects affected / exposed	3 / 47 (6.38%)	1 / 19 (5.26%)	
occurrences (all)	3	1	

Hypoalbuminaemia			
subjects affected / exposed	5 / 47 (10.64%)	0 / 19 (0.00%)	
occurrences (all)	7	0	
Hypocalcaemia			
subjects affected / exposed	5 / 47 (10.64%)	0 / 19 (0.00%)	
occurrences (all)	15	0	
Hypokalaemia			
subjects affected / exposed	5 / 47 (10.64%)	1 / 19 (5.26%)	
occurrences (all)	17	1	
Hyponatraemia			
subjects affected / exposed	7 / 47 (14.89%)	0 / 19 (0.00%)	
occurrences (all)	10	0	
Hypophosphataemia			
subjects affected / exposed	4 / 47 (8.51%)	0 / 19 (0.00%)	
occurrences (all)	6	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 June 2016	Inclusion Criteria Update
07 April 2017	Eligibility Criteria Update

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported