Clinical trial results:
A Phase II Study of Pembrolizumab (MK-3475) in Subjects with Relapsed or Refractory Primary Mediastinal Large B-cell Lymphoma (rrPMBCL) or Relapsed or Refractory Richter Syndrome (rrRS)

Summary

EudraCT number	2015-002406-37
Trial protocol	SE PL ES FR
Global end of trial date	23 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	3475-170

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02576990
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Merck Sharp & Dohme Corp.
Sponsor organisation address	2000 Galloping Hill Road, Kenilworth, NJ, United States, 07033
Public contact	Clinical Trials Disclosure, Merck Sharp & Dohme Corp., ClinicalTrialsDisclosure@merck.com
Scientific contact	Clinical Trials Disclosure, Merck Sharp & Dohme Corp., ClinicalTrialsDisclosure@merck.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	23 October 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	28 May 2019
Global end of trial reached?	Yes
Global end of trial date	23 October 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This study is being done to estimate the objective response rate (ORR) of pembrolizumab (MK-3475) by blinded independent central review (BICR) according to the International Working Group (IWG) response criteria, with special considerations for Richter Syndrome (RS) (relapsed or refractory RS (rrRS) participants only). The primary study hypothesis is that intravenous (IV) administration of single agent pembrolizumab to the relapsed or refractory primary mediastinal large B-cell lymphoma (rrPMBCL) cohort will result in an Objective Response Rate (ORR) of greater than 15% using the International Working Group (IWG) response criteria (Cheson, 2007) by independent central review (ICR).

Protection of trial subjects:

This study was conducted in conformance with Good Clinical Practice standards and applicable country and/or local statutes and regulations regarding ethical committee review, informed consent, and the protection of human subjects participating in biomedical research.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	02 December 2015
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy
Long term follow-up duration	24 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 2
Country: Number of subjects enrolled	Brazil: 3
Country: Number of subjects enrolled	Chile: 3
Country: Number of subjects enrolled	France: 16
Country: Number of subjects enrolled	Germany: 2
Country: Number of subjects enrolled	Italy: 13
Country: Number of subjects enrolled	Poland: 2
Country: Number of subjects enrolled	Russian Federation: 11
Country: Number of subjects enrolled	Spain: 2
Country: Number of subjects enrolled	Sweden: 3
Country: Number of subjects enrolled	Switzerland: 2
Country: Number of subjects enrolled	Turkey: 6
Country: Number of subjects enrolled	United States: 15

Worldwide total number of subjects	80
EEA total number of subjects	38

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)	62
From 65 to 84 years	18
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Of the 80 participants allocated in the study, 76 participants received at least one dose of study treatment.

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	Pembrolizumab: rrPMBCL

Arm description:

Participants with rrPMBCL receive pembrolizumab 200 mg every 3 weeks (Q3W), intravenous infusion (IV) on Day 1 of each 3-week cycle for up to 35 administrations (approximately 2 years).

Arm type	Experimental
Investigational medicinal product name	Pembrolizumab
Investigational medicinal product code	
Other name	MK-3475 KEYTRUDA® SCH 900475
Pharmaceutical forms	Powder for solution for injection/infusion, Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

200 mg of pembrolizumab Q3W, IV on Day 1 of each 3-week cycle for up to a maximum of 35 administrations (approximately 2 years).

Arm title	Pembrolizumab: rrRS

Arm description:

Participants with rrRS receive pembrolizumab 200 mg Q3W, IV on Day 1 of each 3-week cycle for up to 35 administrations (approximately 2 years).

Arm type	Experimental
Investigational medicinal product name	Pembrolizumab
Investigational medicinal product code	
Other name	MK-3475 KEYTRUDA® SCH 900475
Pharmaceutical forms	Powder for solution for injection/infusion, Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

200 mg of pembrolizumab Q3W, IV on Day 1 of each 3-week cycle for up to a maximum of 35 administrations (approximately 2 years).

Number of subjects in period 1	Pembrolizumab: rrPMBCL	Pembrolizumab: rrRS
Started	56	24
Treated	53	23
Completed	0	0
Not completed	56	24
Adverse event, serious fatal	29	18
Sponsor's decision	24	4
Physician decision	1	-
Consent withdrawn by subject	-	2
Screen failure	2	-

Baseline characteristics

Reporting groups	
Reporting group title	Pembrolizumab: rrPMBCL
Reporting group description:	
Participants with rrPMBCL receive pembrolizumab 200 mg every 3 weeks (Q3W), intravenous infusion (IV) on Day 1 of each 3-week cycle for up to 35 administrations (approximately 2 years).	
Reporting group title	Pembrolizumab: rrRS
Reporting group description:	
Participants with rrRS receive pembrolizumab 200 mg Q3W, IV on Day 1 of each 3-week cycle for up to 35 administrations (approximately 2 years).	

Reporting group values	Pembrolizumab: rrPMBCL	Pembrolizumab: rrRS	Total
Number of subjects	56	24	80
Age categorical Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			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)			0
From 65-84 years			0
85 years and over			0
Age Continuous Units: Years			
arithmetic mean	35.0	67.2	
standard deviation	± 10.4	± 11.0	-
Sex: Female, Male Units: Participants			
Female	30	7	37
Male	26	17	43
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	1	0	1
White	51	24	75
More than one race	0	0	0
Unknown or Not Reported	4	0	4
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	4	1	5
Not Hispanic or Latino	37	21	58
Unknown or Not Reported	15	2	17

End points

End points reporting groups

Reporting group title	Pembrolizumab: rrPMBCL
Reporting group description:	
Participants with rrPMBCL receive pembrolizumab 200 mg every 3 weeks (Q3W), intravenous infusion (IV) on Day 1 of each 3-week cycle for up to 35 administrations (approximately 2 years).	
Reporting group title	Pembrolizumab: rrRS
Reporting group description:	
Participants with rrRS receive pembrolizumab 200 mg Q3W, IV on Day 1 of each 3-week cycle for up to 35 administrations (approximately 2 years).	

Primary: Objective Response Rate (ORR) Based on International Working Group (IWG) Response Assessment Criteria per Independent Central Review (ICR)

End point title	Objective Response Rate (ORR) Based on International Working Group (IWG) Response Assessment Criteria per Independent Central Review (ICR)[1]

End point description:

The ORR was assessed by ICR utilizing IWG response assessment criteria per Cheson 2007 of pembrolizumab in participants with rrPMBCL. For participants with rrRS, IWG criteria with special considerations for RS was used for progression. The ORR was defined as percentage of participants who had a response (complete response, CR or partial response, PR) prior to disease progression. CR is the disappearance of all evidence of disease & PR is the regression of measurable disease & no new sites. Participants with missing data were considered non-responders. In rrPMBCL cohort, an exact binomial test was conducted versus a fixed historical control rate. For rrPMBCL cohort, ORR was estimated and 95% 2-sided exact confidence interval (CI) using Clopper-Pearson method whereas rrRS cohort was estimated with 90% 2-sided CI. The analysis population included all participants who received at least one dose of study medication (pembrolizumab).

End point type	Primary

End point timeframe:

Up to approximately 27 months (Database Cutoff: 28MAY2019)

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: No statistical comparisons were planned for this endpoint for database cutoff date 28May2019.

End point values	Pembrolizumab : rrPMBCL	Pembrolizumab : rrRS		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53	23		
Units: Percentage of participants				
number (confidence interval 95%)	45.3 (31.6 to 59.6)	13.0 (3.7 to 30.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: ORR Based on IWG Response Assessment Criteria by Investigator Assessment

End point title	ORR Based on IWG Response Assessment Criteria by Investigator Assessment

End point description:

The ORR was assessed by Investigator assessment utilizing the IWG response assessment criteria per Cheson 2007 of pembrolizumab in participants with rrPMBCL. For participants with rrRS, IWG criteria with special considerations for RS was used for progression. The ORR was defined as the percentage of participants who had a response (CR or PR) prior to disease progression. CR is the disappearance of all evidence of disease and PR is the regression of measurable disease and no new sites. Participants with missing data were considered non-responders. In the rrPMBCL cohort, an exact binomial test was conducted versus a fixed historical control rate. The analysis population included all participants who received at least one dose of study medication (pembrolizumab).

End point type	Secondary

End point timeframe:

Up to approximately 27 months (Database Cutoff Date: 28MAY2019)

End point values	Pembrolizumab : rrPMBCL	Pembrolizumab : rrRS		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53	23		
Units: Percentage of participants				
number (confidence interval 90%)	41.5 (30.0 to 53.7)	4.3 (0.2 to 19.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival (PFS) Based on IWG Response Assessment Criteria by ICR

End point title	Progression Free Survival (PFS) Based on IWG Response Assessment Criteria by ICR

End point description:

PFS was defined as the time from first dose to the first documented progressive disease (PD) or death due to any cause, whichever occurs first. PD is the appearance of any new lesion or increase by ≥ 50% of previously involved site from nadir. Calculated from the product-limit (Kaplan-Meier) method for censored data. The analysis population included all participants who received at least one dose of study medication (pembrolizumab).

End point type	Secondary

End point timeframe:

Up to approximately 27 months (Database Cutoff Date: 28MAY2019)

End point values	Pembrolizumab : rrPMBCL	Pembrolizumab : rrRS		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53	23		
Units: Months				
median (confidence interval 95%)	5.5 (2.8 to 15.1)	1.6 (1.0 to 2.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival (PFS) Based on IWG Response Assessment Criteria by Investigator Assessment

End point title	Progression Free Survival (PFS) Based on IWG Response Assessment Criteria by Investigator Assessment

End point description:

PFS was defined as the time from the first dose to the first documented PD or death due to any cause, whichever occurs first. PD is the appearance of any new lesion or increase by ≥ 50% of previously involved site from nadir. Calculated from the product-limit (Kaplan-Meier) method for censored data. The analysis population included all participants who received at least one dose of study medication (pembrolizumab).

End point type	Secondary

End point timeframe:

Up to approximately 27 months (Database Cutoff Date: 28MAY2019)

End point values	Pembrolizumab : rrPMBCL	Pembrolizumab : rrRS		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53	23		
Units: Months				
median (confidence interval 95%)	4.3 (2.8 to 13.8)	1.8 (1.0 to 2.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR) Based on IWG Response Assessment Criteria by ICR in Participants with Responses

End point title	Duration of Response (DOR) Based on IWG Response Assessment Criteria by ICR in Participants with Responses

End point description:

DOR was defined, only for subgroup of participants who achieved a CR or PR by ICR, as time from start of first documentation of objective tumor response (CR or PR) to first documentation of PD or death due to any cause, whichever comes first. CR is disappearance of all evidence of disease & PR is regression of measurable disease & no new sites. PD is appearance any new lesion or increase by ≥50% of previously involved site from nadir. The analysis consisted of Kaplan-Meier estimates. DOR data was censored on date of last disease assessment documenting absence of PD for participants who did not have tumor progression & were still on study at time of an analysis, were given antitumor treatment other than study treatment, or were removed from study prior to documentation of tumor progression. 9999 indicates median or limit was not reached. The analysis population included all participants who received at least one dose of study drug & who achieved a CR or PR.

End point type	Secondary

End point timeframe:

Up to approximately 27 months (Database Cutoff Date: 28MAY2019)

End point values	Pembrolizumab : rrPMBCL	Pembrolizumab : rrRS		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	3		
Units: Months				
median (confidence interval 95%)	9999 (25.2 to 9999)	4.5 (2.7 to 6.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR) Based on IWG Response Assessment Criteria by Investigator Assessment in Participants with Responses

End point title	Duration of Response (DOR) Based on IWG Response Assessment Criteria by Investigator Assessment in Participants with Responses

End point description:

DOR was defined, only for subgroup of participants who achieved a CR or PR by investigator assessment, as time from start of first documentation of objective tumor response (CR or PR) to first documentation of PD or death due to any cause, whichever comes first. CR is disappearance of all evidence of disease & PR is regression of measurable disease & no new sites. PD is appearance any new lesion or increase by ≥ 50% of previously involved site from nadir. The analysis consisted of Kaplan-Meier estimates. DOR data was censored on date of last disease assessment documenting absence of PD for participants who did not have tumor progression & were still on study at time of an analysis, were given antitumor treatment other than study treatment, or were removed from study prior to documentation of tumor progression. 9999 indicates median or limit was not reached. The analysis population included all participants who received at least one dose of study drug & who achieved a CR or PR.

End point type	Secondary

End point timeframe:

Up to approximately 27 months (Database Cutoff Date: 28MAY2019)

End point values	Pembrolizumab : rrPMBCL	Pembrolizumab : rrRS		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	1		
Units: Months				
median (confidence interval 95%)	9999 (25.2 to 9999)	9999 (9999 to 9999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Control Rate (DCR) Based on IWG Response Assessment Criteria by ICR

End point title	Disease Control Rate (DCR) Based on IWG Response Assessment Criteria by ICR

End point description:

DCR was defined as the percentage of participants in the analysis population who have achieved a CR, PR or stable disease (SD) response prior to PD. CR is the disappearance of all evidence of disease and PR is the regression of measurable disease and no new sites. SD is the failure to attain CR or PR or PD. PD is the appearance any new lesion or increase by ≥ 50% of previously involved site from nadir. Participants with missing data were considered non-responders. The analysis population included all participants who received at least one dose of study medication (pembrolizumab).

End point type	Secondary

End point timeframe:

Up to approximately 27 months (Database Cutoff Date: 28MAY2019)

End point values	Pembrolizumab : rrPMBCL	Pembrolizumab : rrRS		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53	23		
Units: Percentage of participants				
number (confidence interval 90%)	54.7 (42.6 to 66.5)	17.4 (6.2 to 35.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Control Rate (DCR) Based on IWG Response Assessment Criteria by Investigator Assessment

End point title	Disease Control Rate (DCR) Based on IWG Response Assessment Criteria by Investigator Assessment

End point description:

DCR was defined as the percentage of participants in the analysis population who have achieved a CR, PR or SD response prior to PD. CR is the disappearance of all evidence of disease and PR is the regression of measurable disease and no new sites. SD is the failure to attain CR or PR or PD. PD is the appearance any new lesion or increase by ≥ 50% of previously involved site from nadir. Participants with missing data were considered non-responders. The analysis population included all participants who received at least one dose of study medication (pembrolizumab).

End point type	Secondary

End point timeframe:

Up to approximately 27 months (Database Cutoff Date: 28MAY2019)

End point values	Pembrolizumab : rrPMBCL	Pembrolizumab : rrRS		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53	23		
Units: Percentage of participants				
number (confidence interval 90%)	52.8 (40.7 to 64.7)	26.1 (12.0 to 45.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

OS was defined as the time from the first dose to death due to any cause. OS is presented from product limit (Kaplan-Meier) method for censored data (censored at the last assessment). 9999 indicates limit was not reached. The analysis population included all participants who received at least one dose of study medication (pembrolizumab).

End point type	Secondary

End point timeframe:

Up to approximately 27 months (Database Cutoff Date: 28MAY2019)

End point values	Pembrolizumab : rrPMBCL	Pembrolizumab : rrRS		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53	23		
Units: Months				
median (confidence interval 95%)	22.3 (7.3 to 9999)	3.8 (1.8 to 18.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Who Experienced an Adverse Event (AE)

End point title	Number of Participants Who Experienced an Adverse Event (AE)

End point description:

An adverse event (AE) is defined as any unfavorable and unintended sign including an abnormal laboratory finding, symptom or disease associated with the use of a medical treatment or procedure, regardless of whether it is considered related to the medical treatment or procedure, that occurs during the course of the study. The number of participants who experienced an AE were reported. The analysis population included all participants who received at least one dose of study medication (pembrolizumab).

End point type	Secondary

End point timeframe:

Up to approximately 30 months (Up to 90 days after last dose of study treatment) (Database Cutoff

End point values	Pembrolizumab : rrPMBCL	Pembrolizumab : rrRS		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53	23		
Units: Participants	50	23		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Who Discontinued Study Drug Due to an AE

End point title	Number of Participants Who Discontinued Study Drug Due to an AE

End point description:

An AE is defined as any unfavorable and unintended sign including an abnormal laboratory finding, symptom or disease associated with the use of a medical treatment or procedure, regardless of whether it is considered related to the medical treatment or procedure, that occurs during the course of the study. The number of participants who discontinued study drug due to an AE were reported. The analysis population included all participants who received at least one dose of study medication (pembrolizumab).

End point type	Secondary

End point timeframe:

Up to approximately 27 months (Database Cutoff Date: 28MAY2019)

End point values	Pembrolizumab : rrPMBCL	Pembrolizumab : rrRS		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53	23		
Units: Participants	6	4		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Serious adverse events (AEs), non-serious AEs and all-cause mortality was collected up to approximately 56 months through end of trial (EOT) data cut-off date 23 Oct 2020.

Adverse event reporting additional description:

All-cause mortality was reported on all allocated participants. Serious and non-serious AEs were reported among participants who received at least one dose of study treatment. MedDRA preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to study drug were excluded.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.1

Reporting groups

Reporting group title	Pembrolizumab: rrRS

Reporting group description:

Participants with rrRS receive pembrolizumab 200 mg Q3W, IV on Day 1 of each 3-week cycle for up to 35 administrations (approximately 2 years).

Reporting group title	Pembrolizumab: rrPMBCL

Reporting group description:

Participants with rrPMBCL receive pembrolizumab 200 mg every 3 weeks (Q3W), intravenous infusion (IV) on Day 1 of each 3-week cycle for up to 35 administrations (approximately 2 years).

Serious adverse events	Pembrolizumab: rrRS	Pembrolizumab: rrPMBCL	
Total subjects affected by serious adverse events			
subjects affected / exposed	15 / 23 (65.22%)	14 / 53 (26.42%)	
number of deaths (all causes)	19	30	
number of deaths resulting from adverse events	0	0	
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 23 (4.35%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous thrombosis			
subjects affected / exposed	0 / 23 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Death			

subjects affected / exposed	1 / 23 (4.35%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
General physical health deterioration			
subjects affected / exposed	1 / 23 (4.35%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	0 / 23 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 23 (0.00%)	1 / 53 (1.89%)	
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	1 / 23 (4.35%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	1 / 23 (4.35%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	1 / 23 (4.35%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 23 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Hepatic enzyme increased			
subjects affected / exposed	0 / 23 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Subdural haematoma			
subjects affected / exposed	1 / 23 (4.35%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac disorders			
Cardiac tamponade			
subjects affected / exposed	0 / 23 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Myocardial infarction			
subjects affected / exposed	0 / 23 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pericardial effusion			
subjects affected / exposed	0 / 23 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericarditis			
subjects affected / exposed	0 / 23 (0.00%)	1 / 53 (1.89%)	
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 / 23 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia			
subjects affected / exposed	0 / 23 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Blood and lymphatic system disorders			
Autoimmune haemolytic anaemia			
subjects affected / exposed	1 / 23 (4.35%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	3 / 23 (13.04%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	1 / 4	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	1 / 23 (4.35%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	1 / 23 (4.35%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 23 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric perforation			
subjects affected / exposed	0 / 23 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 23 (4.35%)	0 / 53 (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	1 / 23 (4.35%)	0 / 53 (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	1 / 23 (4.35%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract obstruction			
subjects affected / exposed	1 / 23 (4.35%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Hypercalcaemia of malignancy			
subjects affected / exposed	1 / 23 (4.35%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hyperthyroidism			
subjects affected / exposed	1 / 23 (4.35%)	0 / 53 (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			
Aspergillus infection			
subjects affected / exposed	0 / 23 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Clostridium difficile infection			
subjects affected / exposed	0 / 23 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	1 / 23 (4.35%)	0 / 53 (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 / 23 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 23 (4.35%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	1 / 23 (4.35%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Staphylococcal infection			
subjects affected / exposed	1 / 23 (4.35%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal sepsis			
subjects affected / exposed	1 / 23 (4.35%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hypercalcaemia			
subjects affected / exposed	2 / 23 (8.70%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	

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

Non-serious adverse events	Pembrolizumab: rrRS	Pembrolizumab: rrPMBCL	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	23 / 23 (100.00%)	46 / 53 (86.79%)	
Investigations			
Aspartate aminotransferase increased			

subjects affected / exposed	2 / 23 (8.70%)	1 / 53 (1.89%)	
occurrences (all)	2	2	
Blood alkaline phosphatase increased			
subjects affected / exposed	2 / 23 (8.70%)	1 / 53 (1.89%)	
occurrences (all)	2	1	
Blood creatinine increased			
subjects affected / exposed	3 / 23 (13.04%)	0 / 53 (0.00%)	
occurrences (all)	3	0	
Blood bilirubin increased			
subjects affected / exposed	2 / 23 (8.70%)	0 / 53 (0.00%)	
occurrences (all)	2	0	
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 23 (0.00%)	3 / 53 (5.66%)	
occurrences (all)	0	3	
Headache			
subjects affected / exposed	1 / 23 (4.35%)	6 / 53 (11.32%)	
occurrences (all)	1	11	
Hypoaesthesia			
subjects affected / exposed	2 / 23 (8.70%)	0 / 53 (0.00%)	
occurrences (all)	2	0	
Neuropathy peripheral			
subjects affected / exposed	2 / 23 (8.70%)	1 / 53 (1.89%)	
occurrences (all)	2	1	
Somnolence			
subjects affected / exposed	2 / 23 (8.70%)	2 / 53 (3.77%)	
occurrences (all)	2	3	
Blood and lymphatic system disorders			
Leukopenia			
subjects affected / exposed	2 / 23 (8.70%)	4 / 53 (7.55%)	
occurrences (all)	2	5	
Anaemia			
subjects affected / exposed	7 / 23 (30.43%)	6 / 53 (11.32%)	
occurrences (all)	9	6	
Lymph node pain			

subjects affected / exposed	2 / 23 (8.70%)	0 / 53 (0.00%)	
occurrences (all)	2	0	
Thrombocytopenia			
subjects affected / exposed	3 / 23 (13.04%)	2 / 53 (3.77%)	
occurrences (all)	3	3	
Neutropenia			
subjects affected / exposed	2 / 23 (8.70%)	15 / 53 (28.30%)	
occurrences (all)	2	29	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 23 (0.00%)	4 / 53 (7.55%)	
occurrences (all)	0	4	
Asthenia			
subjects affected / exposed	2 / 23 (8.70%)	7 / 53 (13.21%)	
occurrences (all)	2	10	
Fatigue			
subjects affected / exposed	8 / 23 (34.78%)	6 / 53 (11.32%)	
occurrences (all)	8	7	
Chills			
subjects affected / exposed	3 / 23 (13.04%)	0 / 53 (0.00%)	
occurrences (all)	3	0	
Pyrexia			
subjects affected / exposed	3 / 23 (13.04%)	15 / 53 (28.30%)	
occurrences (all)	4	25	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	3 / 23 (13.04%)	5 / 53 (9.43%)	
occurrences (all)	3	5	
Constipation			
subjects affected / exposed	3 / 23 (13.04%)	4 / 53 (7.55%)	
occurrences (all)	3	4	
Diarrhoea			
subjects affected / exposed	5 / 23 (21.74%)	7 / 53 (13.21%)	
occurrences (all)	5	9	
Nausea			

subjects affected / exposed	6 / 23 (26.09%)	6 / 53 (11.32%)	
occurrences (all)	7	8	
Stomatitis			
subjects affected / exposed	2 / 23 (8.70%)	0 / 53 (0.00%)	
occurrences (all)	2	0	
Vomiting			
subjects affected / exposed	2 / 23 (8.70%)	5 / 53 (9.43%)	
occurrences (all)	2	5	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	2 / 23 (8.70%)	10 / 53 (18.87%)	
occurrences (all)	2	11	
Cough			
subjects affected / exposed	2 / 23 (8.70%)	10 / 53 (18.87%)	
occurrences (all)	2	15	
Oropharyngeal pain			
subjects affected / exposed	0 / 23 (0.00%)	3 / 53 (5.66%)	
occurrences (all)	0	4	
Productive cough			
subjects affected / exposed	0 / 23 (0.00%)	4 / 53 (7.55%)	
occurrences (all)	0	4	
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	0 / 23 (0.00%)	3 / 53 (5.66%)	
occurrences (all)	0	3	
Pruritus			
subjects affected / exposed	1 / 23 (4.35%)	4 / 53 (7.55%)	
occurrences (all)	1	6	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	2 / 23 (8.70%)	1 / 53 (1.89%)	
occurrences (all)	2	1	
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	2 / 23 (8.70%)	4 / 53 (7.55%)	
occurrences (all)	2	4	

Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 23 (0.00%)	6 / 53 (11.32%)	
occurrences (all)	0	7	
Myalgia			
subjects affected / exposed	0 / 23 (0.00%)	3 / 53 (5.66%)	
occurrences (all)	0	4	
Back pain			
subjects affected / exposed	2 / 23 (8.70%)	5 / 53 (9.43%)	
occurrences (all)	2	5	
Pain in extremity			
subjects affected / exposed	1 / 23 (4.35%)	3 / 53 (5.66%)	
occurrences (all)	1	3	
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 23 (0.00%)	3 / 53 (5.66%)	
occurrences (all)	0	3	
Herpes zoster			
subjects affected / exposed	1 / 23 (4.35%)	3 / 53 (5.66%)	
occurrences (all)	1	3	
Nasopharyngitis			
subjects affected / exposed	0 / 23 (0.00%)	8 / 53 (15.09%)	
occurrences (all)	0	10	
Pharyngitis			
subjects affected / exposed	0 / 23 (0.00%)	3 / 53 (5.66%)	
occurrences (all)	0	3	
Upper respiratory tract infection			
subjects affected / exposed	0 / 23 (0.00%)	4 / 53 (7.55%)	
occurrences (all)	0	5	
Rhinitis			
subjects affected / exposed	0 / 23 (0.00%)	5 / 53 (9.43%)	
occurrences (all)	0	6	
Urinary tract infection			
subjects affected / exposed	2 / 23 (8.70%)	1 / 53 (1.89%)	
occurrences (all)	2	1	
Vulvovaginal mycotic infection			

subjects affected / exposed	0 / 23 (0.00%)	4 / 53 (7.55%)	
occurrences (all)	0	5	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	3 / 23 (13.04%)	2 / 53 (3.77%)	
occurrences (all)	3	2	
Hyperglycaemia			
subjects affected / exposed	4 / 23 (17.39%)	4 / 53 (7.55%)	
occurrences (all)	4	5	
Hyperkalaemia			
subjects affected / exposed	3 / 23 (13.04%)	0 / 53 (0.00%)	
occurrences (all)	3	0	
Hypokalaemia			
subjects affected / exposed	2 / 23 (8.70%)	2 / 53 (3.77%)	
occurrences (all)	2	2	
Hyponatraemia			
subjects affected / exposed	2 / 23 (8.70%)	2 / 53 (3.77%)	
occurrences (all)	2	2	
Hypophosphataemia			
subjects affected / exposed	2 / 23 (8.70%)	1 / 53 (1.89%)	
occurrences (all)	2	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 July 2016	Major change of Amendment (AM) 1 included adding Richter syndrome cohort of participants.
22 February 2017	Major change of AM2 included adding inclusion criteria updates for future biomedical research and for Richter syndrome participants.
02 October 2017	Major changes of AM3 was to add interim analysis for rrPMBCL cohort of participants, adding formal hypothesis testing for primary objective and adding additional long term follow-up of participants who underwent allogenic stem cell transplant.
18 December 2017	Major change of AM4 was to expand the dose modification and toxicity management guidelines table to cover supportive care, monitoring, and follow up.
20 February 2018	Major change of AM5 was to add the efficacy update for participants with rrPMBCL to be conducted at 9 months after the last subject initiated treatment and 12 months after the last participant initiated treatment.
07 August 2020	Major change of AM6 was to allow ending of the trial.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported