Clinical trial results:
A Single-Arm, Open-Label, Phase 2 Study of Nivolumab (BMS-936558) in Subjects with Relapsed or Refractory Diffuse Large B-Cell Lymphoma (DLBCL) After Failure of Autologous Stem Cell Transplant (ASCT) or After Failure of At Least Two Prior Multi-Agent Chemotherapy Regimens in Subjects Who Are Not Candidates for ASCT

Summary

EudraCT number	2013-003621-28
Trial protocol	GB BE SE ES IT DE NL FR
Global end of trial date	08 October 2020

Results information

Result version number	v1 (current)
This version publication date	01 October 2021
First version publication date	01 October 2021

Trial information

Trial identification

Sponsor protocol code	CA209-139

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	19 February 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	08 October 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the clinical benefit of nivolumab, as measured by independent radiologic review committee (IRRC) assessed objective response rate (ORR) in subjects with Diffuse Large B-Cell Lymphoma (DLBCL) who are refractory or have relapsed following Autologous Stem Cell Transplant (ASCT) or after failure of at least two prior multi-agent chemotherapy regimens in ASCT ineligible patients.

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	05 March 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 11
Country: Number of subjects enrolled	Belgium: 6
Country: Number of subjects enrolled	Canada: 6
Country: Number of subjects enrolled	France: 11
Country: Number of subjects enrolled	Germany: 5
Country: Number of subjects enrolled	Italy: 6
Country: Number of subjects enrolled	Netherlands: 14
Country: Number of subjects enrolled	Singapore: 5
Country: Number of subjects enrolled	Spain: 5
Country: Number of subjects enrolled	Sweden: 1
Country: Number of subjects enrolled	United Kingdom: 12
Country: Number of subjects enrolled	United States: 39
Worldwide total number of subjects	121
EEA total number of subjects	48

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)	67
From 65 to 84 years	52
85 years and over	2

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

121 participants entered the treatment period.

Period 1

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

Arms

Arm title	Nivolumab 3mg/kg

Arm description:

Nivolumab 3mg/kg IV Q2W for participants who failed autologous stem cell transplant (ASCT) or who were ineligible for ASCT

Arm type	Experimental
Investigational medicinal product name	BMS-936558-01 Solution for Injection
Investigational medicinal product code	
Other name	Nivolumab
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

3 mg/Kg Q2W

Number of subjects in period 1	Nivolumab 3mg/kg
Started	121
Completed	0
Not completed	121
Participant request to discontinue treatment	2
Disease progression	104
Study drug toxicity	6
Adverse event unrelated to study drug	6
Other reasons	2
Lost to follow-up	1

Baseline characteristics

Reporting groups	
Reporting group title	Nivolumab 3mg/kg
Reporting group description:	
Nivolumab 3mg/kg IV Q2W for participants who failed autologous stem cell transplant (ASCT) or who were ineligible for ASCT	

Reporting group values	Nivolumab 3mg/kg	Total	
Number of subjects	121	121	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	67	67	
From 65-84 years	52	52	
85 years and over	2	2	
Age Continuous Units: years			
arithmetic mean	61.1		
standard deviation	± 11.96	-	
Sex: Female, Male Units:			
Female	44	44	
Male	77	77	
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	
Asian	12	12	
Native Hawaiian or Other Pacific Islander	0	0	
Black or African American	5	5	
White	102	102	
More than one race	0	0	
Unknown or Not Reported	2	2	
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	3	3	
Not Hispanic or Latino	64	64	
Unknown or Not Reported	54	54	

Subject analysis sets	
Subject analysis set title	ASCT-failed
Subject analysis set type	Full analysis
Subject analysis set description:	
Participants who failed Autologous stem cell transplant (ASCT), treated with Nivolumab 3 mg/Kg Q2W	
Subject analysis set title	ASCT-ineligible
Subject analysis set type	Full analysis
Subject analysis set description:	
Participants who were ineligible for Autologous stem cell transplant (ASCT), treated with Nivolumab 3 mg/Kg Q2W	

Reporting group values	ASCT-failed	ASCT-ineligible	
Number of subjects	87	34	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	56	11	
From 65-84 years	31	21	
85 years and over	0	2	
Age Continuous Units: years			
arithmetic mean	59.1	66.4	
standard deviation	± 10.94	± 12.98	
Sex: Female, Male Units:			
Female	31	13	
Male	56	21	
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	
Asian	11	1	
Native Hawaiian or Other Pacific Islander	0	0	
Black or African American	3	2	
White	71	31	
More than one race	0	0	
Unknown or Not Reported	2	0	
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	2	1	
Not Hispanic or Latino	44	20	
Unknown or Not Reported	41	13	

End points

End points reporting groups

Reporting group title	Nivolumab 3mg/kg
Reporting group description:	
Nivolumab 3mg/kg IV Q2W for participants who failed autologous stem cell transplant (ASCT) or who were ineligible for ASCT	
Subject analysis set title	ASCT-failed
Subject analysis set type	Full analysis
Subject analysis set description:	
Participants who failed Autologous stem cell transplant (ASCT), treated with Nivolumab 3 mg/Kg Q2W	
Subject analysis set title	ASCT-ineligible
Subject analysis set type	Full analysis
Subject analysis set description:	
Participants who were ineligible for Autologous stem cell transplant (ASCT), treated with Nivolumab 3 mg/Kg Q2W	

Primary: Objective Response Rate (ORR) per Independent Radiologic Review Committee (IRRC) assessment

End point title	Objective Response Rate (ORR) per Independent Radiologic Review Committee (IRRC) assessment[1]
End point description:	
ORR is defined as the percentage of participants with a Best Overall Response (BOR) of Complete Remission (CR) or Partial Remission (PR), according to the 2007 revised International Working Group (IWG) Criteria for Malignant Lymphoma, , based on IRRC assessment. CR= Disappearance of all evidence of disease, confirmed by PET scan; PR= Regression of measurable disease and no emergence of new sites	
End point type	Primary
End point timeframe:	
From first dose until date of documented disease progression or subsequent therapy, whichever occurs first (assesed up to April 2016, approximately 25 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: No statistical analyses were performed for this endpoint.

End point values	ASCT-failed	ASCT-ineligible		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	87	34		
Units: Percentage of participants				
number (confidence interval 95%)	10.3 (4.8 to 18.7)	2.9 (0.1 to 15.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR)

End point title	Duration of Response (DOR)
End point description:	
DOR is defined as the time from first response (Complete Response (CR) or Partial Response (PR)) to	

the date of initial objectively documented progression as determined using the 2007 revised IWG Criteria for Malignant Lymphoma, based on Independent Radiology Review Committee (IRRC) assessment, or death due to any cause, whichever occurs first. CR= Disappearance of all evidence of disease, confirmed by PET scan; PR= Regression of measurable disease and no emergence of new sites.

End point type	Secondary

End point timeframe:

From date of first response to the date of documented disease progression or death, whichever occurs first (up to approximately 18 months)

End point values	ASCT-failed	ASCT-ineligible		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	9	1		
Units: Months				
median (confidence interval 95%)	11.43 (2.53 to 17.15)	8.34 (8.34 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Complete Remission Rate

End point title	Complete Remission Rate

End point description:

Complete Remission Rate is defined as the percentage of participants with a Best Overall Response (BOR) of Complete Response (CR) according to the 2007 revised IWG Criteria for Malignant Lymphoma, based on Independent Radiology Review Committee (IRRC) assessment. CR= Disappearance of all evidence of disease, confirmed by PET scan.

End point type	Secondary

End point timeframe:

From date of first dose to study completion (up to approximately 78 months)

End point values	ASCT-failed	ASCT-ineligible		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	87	34		
Units: Percent of participants				
number (confidence interval 95%)	3.4 (0.7 to 9.7)	0 (0 to 10.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Complete Remission

End point title	Duration of Complete Remission

End point description:

The duration of Complete Remission is defined as the time from first documentation of Complete Response (CR) (which is the date of first negative FDG-PET scan or the date of first documentation of no disease involvement in the bone marrow [if required], whichever occurs later) to the date of initial objectively documented progression as determined using the 2007 IWG criteria, based on Independent Radiology Review Committee (IRRC) assessment, or death due to any cause, whichever occurs first. CR= Disappearance of all evidence of disease, confirmed by PET scan.

End point type	Secondary

End point timeframe:

From time of first documentation of CR to the date of initial documented disease progression or death due to any cause, whichever occurs first (up approximately 14 months)

End point values	ASCT-failed	ASCT-ineligible		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	3	0[2]		
Units: Months				
median (full range (min-max))	99999 (99999 to 99999)	(to)		

Notes:

[2] - No subject achieved Complete Response in this cohort

Statistical analyses

No statistical analyses for this end point

Secondary: Partial Remission Rate

End point title	Partial Remission Rate

End point description:

Partial Remission rate is defined as the percentage of participants with a Best Overall Response (BOR) of Partial Response (PR) according to the 2007 revised IWG Criteria for Malignant Lymphoma, based on Independent Radiology Review Committee (IRRC) assessment. PR= Regression of measurable disease and no emergence of new sites.

End point type	Secondary

End point timeframe:

From date of first dose to study completion (up to approximately 78 months)

End point values	ASCT-failed	ASCT-ineligible		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	87	34		
Units: Percent of participants				
number (confidence interval 95%)	6.9 (2.6 to 14.4)	2.9 (0.1 to 15.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Partial Remission

End point title	Duration of Partial Remission

End point description:

Duration of Partial Remission is defined as the time from first documentation of Partial Response (PR) to the date of initial objectively documented progression as determined using the 2007 IWG criteria, based on Independent Radiology Review Committee (IRRC) assessment, or death due to any cause, whichever occurs first. PR= Regression of measurable disease and no emergence of new sites.

End point type	Secondary

End point timeframe:

From date of first documentation of PR to date of disease progression or death due to any cause, whichever occurs first (up to approximately 12 months)

End point values	ASCT-failed	ASCT-ineligible		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	6	1		
Units: Months				
median (full range (min-max))	6.64 (2.4 to 11.4)	8.34 (8.34 to 8.34)		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival

End point title	Progression Free Survival

End point description:

Progression Free Survival (PFS) is defined as the time from first dosing date to the date of the first documented progression, as determined by an Independent Radiology Review Committee (IRRC) according to the 2007 revised IWG Criteria for Malignant Lymphoma, or death due to any cause, whichever occurs first.

End point type	Secondary

End point timeframe:

From date of first dose to date of documented disease progression or death due to any cause, whichever occurs first (up to approximately 2 months)

End point values	ASCT-failed	ASCT-ineligible		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	87	34		
Units: Months				
median (confidence interval 95%)	1.87 (1.71 to 1.87)	1.41 (1.15 to 1.81)		

Statistical analyses

No statistical analyses for this end point

Secondary: Objective Response Rate (ORR) per Investigator assessment

End point title	Objective Response Rate (ORR) per Investigator assessment

End point description:

ORR is defined as the percentage of participants with a Best Overall Response (BOR) of Complete Response (CR) or Partial Response (PR), according to investigator assessment. CR= Disappearance of all evidence of disease, confirmed by PET scan; PR= Regression of measurable disease and no emergence of new sites.

End point type	Secondary

End point timeframe:

From first dose until date of documented disease progression or subsequent therapy, whichever occurs first (up to approximately 28 months)

End point values	ASCT-failed	ASCT-ineligible		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	87	34		
Units: Percent of participants				
number (confidence interval 95%)	19.5 (11.8 to 29.4)	2.9 (0.1 to 15.3)		

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 and 100 days after last dose of study therapy.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.1

Reporting groups

Reporting group title	ASCT Ineligible

Reporting group description:

Subjects who failed at least two prior multi-agent chemotherapy regimens were administered with Nivolumab 3 mg/kg solution IV every 2 weeks until progression or unacceptable toxicity.

Reporting group title	ASCT Failed

Reporting group description:

Subjects who failed Autologous Stem Cell Transplant (ASCT) were administered with Nivolumab 3 mg/kg solution intravenously (IV) every 2 weeks until progression or unacceptable toxicity.

Serious adverse events	ASCT Ineligible	ASCT Failed	
Total subjects affected by serious adverse events			
subjects affected / exposed	27 / 34 (79.41%)	56 / 87 (64.37%)	
number of deaths (all causes)	34	64	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	0 / 34 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diffuse large B-cell lymphoma			
subjects affected / exposed	5 / 34 (14.71%)	3 / 87 (3.45%)	
occurrences causally related to treatment / all	0 / 5	0 / 4	
deaths causally related to treatment / all	0 / 5	0 / 3	
Lung adenocarcinoma			
subjects affected / exposed	0 / 34 (0.00%)	1 / 87 (1.15%)	
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	10 / 34 (29.41%)	20 / 87 (22.99%)	
occurrences causally related to treatment / all	0 / 10	0 / 21	
deaths causally related to treatment / all	0 / 8	0 / 14	
Malignant pleural effusion			
subjects affected / exposed	1 / 34 (2.94%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Neoplasm malignant			
subjects affected / exposed	1 / 34 (2.94%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Neoplasm progression			
subjects affected / exposed	1 / 34 (2.94%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 34 (2.94%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 34 (2.94%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial pain			
subjects affected / exposed	0 / 34 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	1 / 34 (2.94%)	2 / 87 (2.30%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	

Localised oedema			
subjects affected / exposed	1 / 34 (2.94%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple organ dysfunction syndrome			
subjects affected / exposed	1 / 34 (2.94%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	1 / 34 (2.94%)	0 / 87 (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	2 / 34 (5.88%)	2 / 87 (2.30%)	
occurrences causally related to treatment / all	1 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Swelling face			
subjects affected / exposed	0 / 34 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute pulmonary oedema			
subjects affected / exposed	0 / 34 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Dyspnoea			
subjects affected / exposed	0 / 34 (0.00%)	2 / 87 (2.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	0 / 34 (0.00%)	2 / 87 (2.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	

Lung disorder			
subjects affected / exposed	0 / 34 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obstructive airways disorder			
subjects affected / exposed	0 / 34 (0.00%)	1 / 87 (1.15%)	
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	2 / 34 (5.88%)	2 / 87 (2.30%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	0 / 34 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	0 / 34 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stridor			
subjects affected / exposed	1 / 34 (2.94%)	0 / 87 (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	1 / 34 (2.94%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hallucination, visual			
subjects affected / exposed	1 / 34 (2.94%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			

Transaminases increased			
subjects affected / exposed	1 / 34 (2.94%)	0 / 87 (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			
Tibia fracture			
subjects affected / exposed	1 / 34 (2.94%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Arteriosclerosis coronary artery			
subjects affected / exposed	0 / 34 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	1 / 34 (2.94%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	0 / 34 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Encephalopathy			
subjects affected / exposed	1 / 34 (2.94%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	0 / 34 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
IIIrd nerve paralysis			

subjects affected / exposed	1 / 34 (2.94%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Presyncope			
subjects affected / exposed	0 / 34 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	0 / 34 (0.00%)	1 / 87 (1.15%)	
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			
Abdominal lymphadenopathy			
subjects affected / exposed	0 / 34 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			
subjects affected / exposed	0 / 34 (0.00%)	2 / 87 (2.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	3 / 34 (8.82%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	0 / 34 (0.00%)	2 / 87 (2.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	0 / 34 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			

subjects affected / exposed	0 / 34 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Eye swelling			
subjects affected / exposed	0 / 34 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uveitis			
subjects affected / exposed	1 / 34 (2.94%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 34 (5.88%)	3 / 87 (3.45%)	
occurrences causally related to treatment / all	0 / 2	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	1 / 34 (2.94%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	0 / 34 (0.00%)	3 / 87 (3.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	1 / 34 (2.94%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal perforation			
subjects affected / exposed	0 / 34 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Intestinal obstruction			

subjects affected / exposed	1 / 34 (2.94%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Melaena			
subjects affected / exposed	0 / 34 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal perforation			
subjects affected / exposed	0 / 34 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	0 / 34 (0.00%)	2 / 87 (2.30%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	1 / 34 (2.94%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hyperbilirubinaemia			
subjects affected / exposed	0 / 34 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 34 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash erythematous			
subjects affected / exposed	0 / 34 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash maculo-papular			

subjects affected / exposed	1 / 34 (2.94%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 34 (2.94%)	4 / 87 (4.60%)	
occurrences causally related to treatment / all	0 / 1	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal impairment			
subjects affected / exposed	0 / 34 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract obstruction			
subjects affected / exposed	0 / 34 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 34 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone lesion			
subjects affected / exposed	0 / 34 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Morphoea			
subjects affected / exposed	0 / 34 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neck pain			
subjects affected / exposed	0 / 34 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Infections and infestations			
Cellulitis			
subjects affected / exposed	1 / 34 (2.94%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile infection			
subjects affected / exposed	0 / 34 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	1 / 34 (2.94%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Kidney infection			
subjects affected / exposed	1 / 34 (2.94%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic sepsis			
subjects affected / exposed	0 / 34 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			
subjects affected / exposed	0 / 34 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pneumonia			
subjects affected / exposed	0 / 34 (0.00%)	7 / 87 (8.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia bacterial			
subjects affected / exposed	0 / 34 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			

subjects affected / exposed	1 / 34 (2.94%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Septic shock			
subjects affected / exposed	1 / 34 (2.94%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinusitis			
subjects affected / exposed	0 / 34 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tonsillitis			
subjects affected / exposed	0 / 34 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 34 (2.94%)	0 / 87 (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			
Dehydration			
subjects affected / exposed	0 / 34 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Failure to thrive			
subjects affected / exposed	0 / 34 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hypercalcaemia			
subjects affected / exposed	3 / 34 (8.82%)	3 / 87 (3.45%)	
occurrences causally related to treatment / all	1 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperuricaemia			

subjects affected / exposed	0 / 34 (0.00%)	2 / 87 (2.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	0 / 34 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour lysis syndrome			
subjects affected / exposed	1 / 34 (2.94%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	ASCT Ineligible	ASCT Failed	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	31 / 34 (91.18%)	83 / 87 (95.40%)	
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	4 / 34 (11.76%)	4 / 87 (4.60%)	
occurrences (all)	9	5	
Blood creatinine increased			
subjects affected / exposed	3 / 34 (8.82%)	10 / 87 (11.49%)	
occurrences (all)	5	14	
Alanine aminotransferase increased			
subjects affected / exposed	3 / 34 (8.82%)	3 / 87 (3.45%)	
occurrences (all)	7	6	
Blood alkaline phosphatase increased			
subjects affected / exposed	3 / 34 (8.82%)	2 / 87 (2.30%)	
occurrences (all)	8	2	
Blood bilirubin increased			
subjects affected / exposed	3 / 34 (8.82%)	0 / 87 (0.00%)	
occurrences (all)	4	0	
Lymphocyte count decreased			

subjects affected / exposed	2 / 34 (5.88%)	3 / 87 (3.45%)	
occurrences (all)	2	6	
Lipase increased			
subjects affected / exposed	0 / 34 (0.00%)	6 / 87 (6.90%)	
occurrences (all)	0	16	
Platelet count decreased			
subjects affected / exposed	3 / 34 (8.82%)	2 / 87 (2.30%)	
occurrences (all)	5	4	
Weight decreased			
subjects affected / exposed	0 / 34 (0.00%)	5 / 87 (5.75%)	
occurrences (all)	0	5	
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 34 (8.82%)	11 / 87 (12.64%)	
occurrences (all)	3	14	
Dizziness			
subjects affected / exposed	1 / 34 (2.94%)	5 / 87 (5.75%)	
occurrences (all)	1	5	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	7 / 34 (20.59%)	25 / 87 (28.74%)	
occurrences (all)	19	57	
Neutropenia			
subjects affected / exposed	4 / 34 (11.76%)	13 / 87 (14.94%)	
occurrences (all)	13	22	
Thrombocytopenia			
subjects affected / exposed	5 / 34 (14.71%)	15 / 87 (17.24%)	
occurrences (all)	22	37	
Leukopenia			
subjects affected / exposed	2 / 34 (5.88%)	1 / 87 (1.15%)	
occurrences (all)	5	1	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	2 / 34 (5.88%)	6 / 87 (6.90%)	
occurrences (all)	2	7	
Fatigue			

subjects affected / exposed	13 / 34 (38.24%)	36 / 87 (41.38%)	
occurrences (all)	15	53	
Oedema peripheral			
subjects affected / exposed	7 / 34 (20.59%)	10 / 87 (11.49%)	
occurrences (all)	10	13	
Pyrexia			
subjects affected / exposed	7 / 34 (20.59%)	22 / 87 (25.29%)	
occurrences (all)	7	28	
Influenza like illness			
subjects affected / exposed	0 / 34 (0.00%)	6 / 87 (6.90%)	
occurrences (all)	0	6	
Mucosal inflammation			
subjects affected / exposed	0 / 34 (0.00%)	5 / 87 (5.75%)	
occurrences (all)	0	5	
Pain			
subjects affected / exposed	3 / 34 (8.82%)	3 / 87 (3.45%)	
occurrences (all)	3	3	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	7 / 34 (20.59%)	10 / 87 (11.49%)	
occurrences (all)	8	18	
Constipation			
subjects affected / exposed	8 / 34 (23.53%)	19 / 87 (21.84%)	
occurrences (all)	11	21	
Diarrhoea			
subjects affected / exposed	2 / 34 (5.88%)	23 / 87 (26.44%)	
occurrences (all)	4	30	
Dry mouth			
subjects affected / exposed	2 / 34 (5.88%)	5 / 87 (5.75%)	
occurrences (all)	2	5	
Nausea			
subjects affected / exposed	13 / 34 (38.24%)	28 / 87 (32.18%)	
occurrences (all)	18	36	
Stomatitis			
subjects affected / exposed	1 / 34 (2.94%)	6 / 87 (6.90%)	
occurrences (all)	1	6	

Vomiting			
subjects affected / exposed	3 / 34 (8.82%)	20 / 87 (22.99%)	
occurrences (all)	4	26	
Abdominal discomfort			
subjects affected / exposed	0 / 34 (0.00%)	5 / 87 (5.75%)	
occurrences (all)	0	5	
Dysphagia			
subjects affected / exposed	2 / 34 (5.88%)	2 / 87 (2.30%)	
occurrences (all)	4	2	
Abdominal distension			
subjects affected / exposed	2 / 34 (5.88%)	1 / 87 (1.15%)	
occurrences (all)	2	1	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 34 (2.94%)	21 / 87 (24.14%)	
occurrences (all)	1	30	
Dyspnoea			
subjects affected / exposed	2 / 34 (5.88%)	17 / 87 (19.54%)	
occurrences (all)	3	21	
Dyspnoea exertional			
subjects affected / exposed	2 / 34 (5.88%)	4 / 87 (4.60%)	
occurrences (all)	2	4	
Pleural effusion			
subjects affected / exposed	2 / 34 (5.88%)	2 / 87 (2.30%)	
occurrences (all)	2	2	
Skin and subcutaneous tissue disorders			
Night sweats			
subjects affected / exposed	2 / 34 (5.88%)	6 / 87 (6.90%)	
occurrences (all)	2	7	
Pruritus			
subjects affected / exposed	4 / 34 (11.76%)	5 / 87 (5.75%)	
occurrences (all)	4	7	
Rash			
subjects affected / exposed	2 / 34 (5.88%)	14 / 87 (16.09%)	
occurrences (all)	3	18	
Psychiatric disorders			

Anxiety			
subjects affected / exposed	1 / 34 (2.94%)	8 / 87 (9.20%)	
occurrences (all)	1	9	
Insomnia			
subjects affected / exposed	1 / 34 (2.94%)	10 / 87 (11.49%)	
occurrences (all)	1	10	
Confusional state			
subjects affected / exposed	2 / 34 (5.88%)	2 / 87 (2.30%)	
occurrences (all)	2	2	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	6 / 34 (17.65%)	13 / 87 (14.94%)	
occurrences (all)	6	19	
Back pain			
subjects affected / exposed	4 / 34 (11.76%)	9 / 87 (10.34%)	
occurrences (all)	6	12	
Pain in extremity			
subjects affected / exposed	4 / 34 (11.76%)	9 / 87 (10.34%)	
occurrences (all)	4	10	
Musculoskeletal chest pain			
subjects affected / exposed	0 / 34 (0.00%)	5 / 87 (5.75%)	
occurrences (all)	0	5	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	0 / 34 (0.00%)	7 / 87 (8.05%)	
occurrences (all)	0	10	
Upper respiratory tract infection			
subjects affected / exposed	0 / 34 (0.00%)	9 / 87 (10.34%)	
occurrences (all)	0	10	
Urinary tract infection			
subjects affected / exposed	2 / 34 (5.88%)	4 / 87 (4.60%)	
occurrences (all)	2	4	
Metabolism and nutrition disorders			
Hypercalcaemia			
subjects affected / exposed	3 / 34 (8.82%)	6 / 87 (6.90%)	
occurrences (all)	3	11	

Decreased appetite			
subjects affected / exposed	5 / 34 (14.71%)	18 / 87 (20.69%)	
occurrences (all)	5	19	
Hyperglycaemia			
subjects affected / exposed	3 / 34 (8.82%)	6 / 87 (6.90%)	
occurrences (all)	9	21	
Hypokalaemia			
subjects affected / exposed	3 / 34 (8.82%)	7 / 87 (8.05%)	
occurrences (all)	9	14	
Hypomagnesaemia			
subjects affected / exposed	1 / 34 (2.94%)	7 / 87 (8.05%)	
occurrences (all)	1	10	
Hypoalbuminaemia			
subjects affected / exposed	3 / 34 (8.82%)	3 / 87 (3.45%)	
occurrences (all)	7	4	
Dehydration			
subjects affected / exposed	2 / 34 (5.88%)	4 / 87 (4.60%)	
occurrences (all)	2	4	
Hyponatraemia			
subjects affected / exposed	3 / 34 (8.82%)	2 / 87 (2.30%)	
occurrences (all)	7	4	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 July 2016	Safety management algorithms updated

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported