Clinical trial results:
A Randomized, Open Label, Phase 2 Study of Rituximab and Bendamustine With or Without Brentuximab Vedotin for Relapsed or Refractory CD30-Positive Diffuse Large B-Cell Lymphoma

Summary

EudraCT number	2015-001671-51
Trial protocol	GB CZ FR ES PL
Global end of trial date	30 September 2017

Results information

Result version number	v1 (current)
This version publication date	03 October 2018
First version publication date	03 October 2018

Trial information

Trial identification

Sponsor protocol code	SGN35-023

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02594163
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Seattle Genetics, Inc.
Sponsor organisation address	21823 30th Dr, Bothell, United States, 98021
Public contact	Chief Medical Officer, Seattle Genetics, Inc., 1 8554732436, medinfo@seagen.com
Scientific contact	Chief Medical Officer, Seattle Genetics, Inc., 1 8554732436, medinfo@seagen.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	01 August 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 September 2017
Global end of trial reached?	Yes
Global end of trial date	30 September 2017
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

This is a randomized, open-label, multicenter, Phase 2 clinical trial designed to evaluate the efficacy and safety of brentuximab vedotin in combination with rituximab and bendamustine for the treatment of patients with relapsed or refractory CD30-positive diffuse large B-cell lymphoma (DLBCL) after failure of second-line salvage therapy or as second-line treatment in patients ineligible for autologous stem cell transplant (ASCT). Patients will be randomized in a 1:1 manner to receive rituximab plus bendamustine with or without brentuximab vedotin. Patients who respond to combination treatment containing brentuximab vedotin and do not experience excessive toxicity may receive additional single-agent brentuximab vedotin following combination treatment, for up to an additional 10 cycles (up to 16 total cycles of treatment).

Protection of trial subjects:

The protocol for this study was designed in accordance with the general ethical principles outlined in the Declaration of Helsinki. The conduct of all aspects of the study, including methods for obtaining informed consent, were also in accordance with principles enunciated in the declaration, the International Council for Harmonisation (ICH) Good Clinical Practices (GCP), and applicable Food and Drug Administration (FDA) regulations/guidelines set forth in Title 21 CFR Parts 11, 50, 56, and 312. The consent form approved by each IRB/IEC included all elements required by the applicable regional laws and regulations, including a statement that Seattle Genetics, Inc. and authorities had access to patient records. Consent was obtained from all patients before any protocol-required procedures were performed, including any procedure not part of normal patient care.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	14 September 2015
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	Poland: 1
Country: Number of subjects enrolled	United Kingdom: 5
Country: Number of subjects enrolled	Czech Republic: 1
Country: Number of subjects enrolled	France: 6
Country: Number of subjects enrolled	Italy: 7
Country: Number of subjects enrolled	United States: 5
Worldwide total number of subjects	25
EEA total number of subjects	20

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)	10
From 65 to 84 years	14
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

First patient began treatment on 09 Mar 2016; the last patient began treatment on 11 May 2017.

Pre-assignment

Screening details:

The population to be studied includes patients with relapsed or refractory CD30-positive diffuse large B-cell lymphoma.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Rituximab, Bendamustine Control

Arm description:

Subjects randomized to the control arm will receive IV infusions of rituximab on day 1 or day 2 and bendamustine on both days 1 and 2 of each 21 day cycle.

Rituximab

Bendamustine

Arm type	Active comparator
Investigational medicinal product name	Rituximab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

375 mg/m2 IV infusion (per institutional standard of care) on Day 2 (+1) of each 21-day cycle

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

Dosage and administration details:

90 mg/m2 IV infusion on Day 1 AND Day 2 (+1) of each 21-day cycle

Arm title	Brentuximab Vedotin plus Rituximab plus Bendamustine

Arm description:

Subjects randomized to the brentuximab vedotin arm will receive IV infusions of brentuximab vedotin followed by bendamustine on day 1, and rituximab followed by bendamustine on day 2 of each 21 day cycle.

Brentuximab Vedotin

Rituximab

Bendamustine

Arm type	Experimental

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

Dosage and administration details:

375 mg/m2 IV infusion (per institutional standard of care) on Day 2 (+1) of each 21-day cycle

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

Dosage and administration details:

90 mg/m2 IV infusion on Day 1 AND Day 2 (+1) of each 21-day cycle

Investigational medicinal product name	Brentuximab vedotin
Investigational medicinal product code	
Other name	Adcetris
Pharmaceutical forms	Powder for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

1.8 mg/kg IV infusion on Day 1 of each 21-day cycle

Number of subjects in period 1	Rituximab, Bendamustine Control	Brentuximab Vedotin plus Rituximab plus Bendamustine
Started	12	13
Completed	1	1
Not completed	11	12
Withdrawl by Subject	-	1
Physician decision	-	1
Adverse Event	-	1
Death	2	5
Progressive Disease	2	-
Lost to follow-up	1	-
Study Termination by Sponsor	6	4

Baseline characteristics

Reporting groups	
Reporting group title	Rituximab, Bendamustine Control

Reporting group description:

Subjects randomized to the control arm will receive IV infusions of rituximab on day 1 or day 2 and bendamustine on both days 1 and 2 of each 21 day cycle.

Rituximab

Bendamustine

Reporting group title	Brentuximab Vedotin plus Rituximab plus Bendamustine

Reporting group description:

Subjects randomized to the brentuximab vedotin arm will receive IV infusions of brentuximab vedotin followed by bendamustine on day 1, and rituximab followed by bendamustine on day 2 of each 21 day cycle.

Brentuximab Vedotin

Rituximab

Bendamustine

Reporting group values	Rituximab, Bendamustine Control	Brentuximab Vedotin plus Rituximab plus Bendamustine	Total
Number of subjects	12	13	25
Age categorical Units: Subjects			
Adults (18-64 years)	6	4	10
From 65-84 years	5	9	14
85 years and over	1	0	1
Age continuous Units: years			
median	64.5	68	
full range (min-max)	47 to 85	40 to 79	-
Gender categorical Units: Subjects			
Female	8	6	14
Male	4	7	11
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	2	1	3
Not Hispanic or Latino	7	10	17
Unknown or Not Reported	3	2	5
Race (NIH/OMB) Units: Subjects			
White	9	11	20
Unknown or Not Reported	3	2	5
Eastern Cooperative Oncology Group (ECOG) Performance Status			
0=Normal activity; 1=Symptoms but ambulatory; 2=In bed <50% of the time; 3= In bed >50% of the time; 4=100% bedridden; 5=Dead			
Units: Subjects			

0: Normal Activity	7	6	13
1: Symptoms but ambulatory	5	4	9
2: In bed less than 50% of the time	0	3	3

End points

End points reporting groups

Reporting group title	Rituximab, Bendamustine Control

Reporting group description:

Subjects randomized to the control arm will receive IV infusions of rituximab on day 1 or day 2 and bendamustine on both days 1 and 2 of each 21 day cycle.

Rituximab

Bendamustine

Reporting group title	Brentuximab Vedotin plus Rituximab plus Bendamustine

Reporting group description:

Subjects randomized to the brentuximab vedotin arm will receive IV infusions of brentuximab vedotin followed by bendamustine on day 1, and rituximab followed by bendamustine on day 2 of each 21 day cycle.

Brentuximab Vedotin

Rituximab

Bendamustine

Primary: Objective Response Rate (ORR)

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

End point description:

ORR is defined as the percentage of patients who achieve a Complete Response (CR) (including Complete Metabolic Response (CMR)) or Partial Response (PR) (including Partial Metabolic Response (PMR)) as best response to combination therapy on study

End point type	Primary

End point timeframe:

Approximately 1 year

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: Due to the small number of patients recruited in the study there will be no formal assessment of the primary endpoint. The observed ORR (a best response of CR/CMR, PR/PMR) is presented by treatment arm for the ITT population along with the corresponding exact 90% and 95% confidence intervals (CIs) using the exact binomial method (i.e., Clopper-Pearson method).

End point values	Rituximab, Bendamustine Control	Brentuximab Vedotin plus Rituximab plus Bendamustine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	13		
Units: percentage of participants				
number (confidence interval 95%)	91.7 (61.5 to 99.8)	61.5 (31.6 to 86.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free Survival (PFS)

End point title	Progression-free Survival (PFS)

End point description:

PFS is defined as the time from randomization to disease progression/relapse, receipt of subsequent lymphoma chemotherapy other than the components of the study treatment regimen, or death from any cause, whichever occurs first.

End point type	Secondary

End point timeframe:

Up to 11.8 months

End point values	Rituximab, Bendamustine Control	Brentuximab Vedotin plus Rituximab plus Bendamustine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	13		
Units: months				
median (full range (min-max))	4.9 (1.6 to 11.8)	3.7 (0.8 to 11.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Complete Remission (CR) Rate

End point title	Complete Remission (CR) Rate

End point description:

CRR is the proportion of patients who achieve a Complete Response (CR) (including Complete Metabolic Response (CMR)) as best response to combination therapy on study.

End point type	Secondary

End point timeframe:

Approximately 1 year

End point values	Rituximab, Bendamustine Control	Brentuximab Vedotin plus Rituximab plus Bendamustine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	13		
Units: participants	8	7		

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 observation of response to disease progression/relapse, receipt of subsequent lymphoma chemotherapy other than the components of the study treatment regimen, or death from any cause, whichever occurs first.

End point type	Secondary

End point timeframe:

Up to 10.5 months

End point values	Rituximab, Bendamustine Control	Brentuximab Vedotin plus Rituximab plus Bendamustine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	8		
Units: months				
median (full range (min-max))	3.7 (0.0 to 10.5)	4.1 (0.0 to 10.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

OS is defined as the time randomization to death from any cause.

End point type	Secondary

End point timeframe:

Up to 1.5 years

End point values	Rituximab, Bendamustine Control	Brentuximab Vedotin plus Rituximab plus Bendamustine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	13		
Units: months				
median (full range (min-max))	14.3 (3.9 to 18)	6.5 (1.9 to 11.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number and Severity of Adverse Events (AEs)

End point title	Number and Severity of Adverse Events (AEs)

End point description:

All AEs are included in the summaries, unless treatment-emergent is specified.

End point type	Secondary

End point timeframe:

Approximately 1 year

End point values	Rituximab, Bendamustine Control	Brentuximab Vedotin plus Rituximab plus Bendamustine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	13		
Units: events				
Treatment-Emergent Adverse Event	11	13		
Treatment-Related Adverse Event	10	13		
Brentuximab Vedotin-Related Adverse Event	0	11		
Rituximab-Related Adverse Event	6	10		
Bendamustine-Related Adverse Event	10	13		
Adverse Event with Outcome of Death	0	1		
Serious Adverse Event	3	8		
Treatment-Related Serious Adverse Event	3	3		
Adverse Event Leading to Dose Delay	3	0		
Adverse Event Leading to Treatment Discontinuation	1	5		
Grade 3-5 Treatment-Emergent Adverse Event	4	11		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Approximately 1 year

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	Rituximab, Bendamustine Control

Reporting group description:

Subjects randomized to the control arm will receive IV infusions of rituximab on day 1 or day 2 and bendamustine on both days 1 and 2 of each 21 day cycle.

Rituximab

Bendamustine

Reporting group title	Brentuximab Vedotin

Reporting group description:

Subjects randomized to the brentuximab vedotin arm will receive IV infusions of brentuximab vedotin followed by bendamustine on day 1, and rituximab followed by bendamustine on day 2 of each 21 day cycle.

Brentuximab Vedotin

Rituximab

Bendamustine

Serious adverse events	Rituximab, Bendamustine Control	Brentuximab Vedotin	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 12 (25.00%)	8 / 13 (61.54%)	
number of deaths (all causes)	2	5	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			
subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	
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	0 / 12 (0.00%)	1 / 13 (7.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	

Diffuse large B-cell lymphoma refractory			
subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to peritoneum			
subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood creatinine increased			
subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutrophil count decreased			
subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelet count decreased			
subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
White blood cell count decreased			
subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Transient ischaemic attack			
subjects affected / exposed	1 / 12 (8.33%)	0 / 13 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			

subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 13 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Histiocytosis haematophagic			
subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	
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			
Pyrexia			
subjects affected / exposed	1 / 12 (8.33%)	1 / 13 (7.69%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthenia			
subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	1 / 12 (8.33%)	0 / 13 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			

Abdominal pain			
subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	
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			
Hypoxia			
subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Sepsis			
subjects affected / exposed	0 / 12 (0.00%)	2 / 13 (15.38%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Kidney infection			
subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphangitis			
subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pneumonia			
subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia viral			
subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	
occurrences causally related to treatment / all	0 / 0	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	Rituximab, Bendamustine Control	Brentuximab Vedotin	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	11 / 12 (91.67%)	13 / 13 (100.00%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Diffuse large B-cell lymphoma refractory			
subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	5	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	2 / 12 (16.67%)	3 / 13 (23.08%)	
occurrences (all)	6	3	
Fatigue			
subjects affected / exposed	2 / 12 (16.67%)	3 / 13 (23.08%)	
occurrences (all)	2	6	
Pyrexia			
subjects affected / exposed	1 / 12 (8.33%)	4 / 13 (30.77%)	
occurrences (all)	4	5	
Chills			

subjects affected / exposed	2 / 12 (16.67%)	0 / 13 (0.00%)	
occurrences (all)	3	0	
Device malfunction			
subjects affected / exposed	1 / 12 (8.33%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Pain			
subjects affected / exposed	1 / 12 (8.33%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Performance status decreased			
subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 12 (16.67%)	3 / 13 (23.08%)	
occurrences (all)	3	3	
Dyspnoea			
subjects affected / exposed	2 / 12 (16.67%)	1 / 13 (7.69%)	
occurrences (all)	3	2	
Hypoxia			
subjects affected / exposed	0 / 12 (0.00%)	2 / 13 (15.38%)	
occurrences (all)	0	3	
Pleural effusion			
subjects affected / exposed	0 / 12 (0.00%)	2 / 13 (15.38%)	
occurrences (all)	0	2	
Hiccups			
subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Nasal congestion			
subjects affected / exposed	1 / 12 (8.33%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Pneumomediastinum			
subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Pneumonitis			

subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Respiratory failure			
subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Investigations			
Neutrophil count decreased			
subjects affected / exposed	1 / 12 (8.33%)	2 / 13 (15.38%)	
occurrences (all)	1	6	
Platelet count decreased			
subjects affected / exposed	1 / 12 (8.33%)	1 / 13 (7.69%)	
occurrences (all)	7	8	
White blood cell count decreased			
subjects affected / exposed	0 / 12 (0.00%)	2 / 13 (15.38%)	
occurrences (all)	0	8	
Alanine aminotransferase increased			
subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Amylase increased			
subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Blood lactate dehydrogenase increased			
subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Blood phosphorus decreased			
subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	2	
Lipase increased			

subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Lymphocyte count decreased			
subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	6	
Weight decreased			
subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Lumbar vertebral fracture			
subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Cardiac disorders			
Sinus tachycardia			
subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 12 (8.33%)	2 / 13 (15.38%)	
occurrences (all)	1	2	
Paraesthesia			
subjects affected / exposed	0 / 12 (0.00%)	3 / 13 (23.08%)	
occurrences (all)	0	3	
Neuropathy peripheral			
subjects affected / exposed	0 / 12 (0.00%)	2 / 13 (15.38%)	
occurrences (all)	0	2	
Syncope			
subjects affected / exposed	0 / 12 (0.00%)	2 / 13 (15.38%)	
occurrences (all)	0	3	
Dysaesthesia			
subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Dysgeusia			

subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Dyskinesia			
subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 12 (25.00%)	2 / 13 (15.38%)	
occurrences (all)	3	2	
Neutropenia			
subjects affected / exposed	3 / 12 (25.00%)	1 / 13 (7.69%)	
occurrences (all)	9	5	
Thrombocytopenia			
subjects affected / exposed	2 / 12 (16.67%)	0 / 13 (0.00%)	
occurrences (all)	2	0	
Pancytopenia			
subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	2	
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Vertigo			
subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Eye disorders			
Eye pain			
subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	2 / 12 (16.67%)	6 / 13 (46.15%)	
occurrences (all)	2	9	
Nausea			
subjects affected / exposed	3 / 12 (25.00%)	5 / 13 (38.46%)	
occurrences (all)	3	7	
Vomiting			

subjects affected / exposed	1 / 12 (8.33%)	5 / 13 (38.46%)	
occurrences (all)	1	5	
Abdominal pain			
subjects affected / exposed	0 / 12 (0.00%)	4 / 13 (30.77%)	
occurrences (all)	0	4	
Dyspepsia			
subjects affected / exposed	1 / 12 (8.33%)	2 / 13 (15.38%)	
occurrences (all)	1	2	
Constipation			
subjects affected / exposed	1 / 12 (8.33%)	1 / 13 (7.69%)	
occurrences (all)	1	1	
Stomatitis			
subjects affected / exposed	1 / 12 (8.33%)	1 / 13 (7.69%)	
occurrences (all)	1	1	
Abdominal distension			
subjects affected / exposed	1 / 12 (8.33%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Abdominal pain upper			
subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Gastritis			
subjects affected / exposed	1 / 12 (8.33%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Dermatitis exfoliative			
subjects affected / exposed	1 / 12 (8.33%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Dry skin			
subjects affected / exposed	1 / 12 (8.33%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Eczema			
subjects affected / exposed	1 / 12 (8.33%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Generalised erythema			
subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	

Pruritus			
subjects affected / exposed	1 / 12 (8.33%)	0 / 13 (0.00%)	
occurrences (all)	2	0	
Rash			
subjects affected / exposed	1 / 12 (8.33%)	0 / 13 (0.00%)	
occurrences (all)	2	0	
Urticaria			
subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	0 / 12 (0.00%)	2 / 13 (15.38%)	
occurrences (all)	0	2	
Urinary retention			
subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 12 (0.00%)	2 / 13 (15.38%)	
occurrences (all)	0	2	
Bone pain			
subjects affected / exposed	1 / 12 (8.33%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Groin pain			
subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Musculoskeletal pain			
subjects affected / exposed	1 / 12 (8.33%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	1 / 12 (8.33%)	1 / 13 (7.69%)	
occurrences (all)	2	1	
Bronchitis			
subjects affected / exposed	1 / 12 (8.33%)	0 / 13 (0.00%)	
occurrences (all)	1	0	

Cystitis			
subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Oral candidiasis			
subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Oral fungal infection			
subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Pneumonia viral			
subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Rhinovirus infection			
subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Urinary tract infection			
subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 12 (8.33%)	3 / 13 (23.08%)	
occurrences (all)	1	3	
Hypokalaemia			
subjects affected / exposed	0 / 12 (0.00%)	4 / 13 (30.77%)	
occurrences (all)	0	9	
Hypocalcaemia			
subjects affected / exposed	0 / 12 (0.00%)	2 / 13 (15.38%)	
occurrences (all)	0	3	
Dehydration			
subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	2	
Failure to thrive			
subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Fluid retention			

subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	2	
Hypoalbuminaemia			
subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	4	
Hyponatraemia			
subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	2	
Hypophosphataemia			
subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	3	
Vitamin D deficiency			
subjects affected / exposed	0 / 12 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 June 2015	The protocol was updated to add the EudraCT number to the cover page.
10 November 2015	The protocol was amended for the following reasons: • To provide additional detail in the study objective and endpoints. • To exclude patients unable to give consent by removing the option for a legally acceptable representative to consent. • Revise the entry criteria to: o Increase the required platelet count for study entry to ≥75,000/µL o Require females of childbearing potential and males who have partners of childbearing potential to use 2 effective contraceptive methods and to specify which methods are considered effective o Exclude subjects with major surgery less than 30 days prior to first dose of study drug , live vaccines within 1 month of first dose of study drug, current severe immunodeficiency, history of recurring or chronic infections or with underlying conditions which may further predispose patients to serious infection, or concomitant use of bleomycin. • Require study discontinuation in the case of pregnancy. o Require pretreatment assessment for hepatitis B. o Require electrocardiogram assessment at each cycle. o Require pregnancy testing (for women of childbearing potential only) at each cycle and require that pregnancy testing be by serum β-hCG • Clearly specify the requirement for physical examinations and require physical examination to include neurological examination at all time points where physical examination is required, including where it is required as part of the lymphoma assessment. • To clarify that sampling for brentuximab and MMAE exposure was only required for subjects on the treatment arm (brentuximab vedotin) and to extend this sampling to all combination treatment cycles (up to Cycle 6). • To limit ATA sampling to the treatment arm (brentuximab vedotin). • Clarify that safety reporting is required in all regions of study conducted as required by local and international standards. • To update the reference to the NCCN guideline for the prevention and treatment of cancer-related infections.
19 February 2016	The protocol was amended to • Clarify that the objectives of the study were to investigate the effects of study treatment both in patients with DLCBL and those with follicular NHL grade 3b • Allow a second dose reduction of bendamustine (to 50 mg/m2) • Recommend prophylactic growth factor support and clarified that transfusions and intrathecal prophylactic treatment for cerebral/meningeal disease are permitted • Correct an error regarding timing of posttreatment assessments: The timing of all posttreatment assessments is relative to Cycle 1 Day 1 (not the end of treatment) • Add an additional safety assessment visit during the second week of Cycles 1 and 2 • To change the definition of PFS and OS to begin at randomization (rather than date of first treatment) and to include subsequent treatment for lymphoma (other than post-treatment consolidative radiotherapy, post-treatment chemotherapy for the purpose of mobilizing peripheral blood stem cells, and consolidative autologous or allogeneic SCT) as an event in the progression analyses to reflect current statistical planning • Remove the requirement that biopsy samples be obtained within than 1 year before screening • Clarify that tumor samples are only to be collected from archival samples; no tumor biopsies are required to be performed for this study • Make minor editorial and formatting changes throughout the protocol

13 July 2016	The protocol was amended to • Reflect that Teva Pharmaceuticals is discontinuing distribution of the bendamustine hydrochloride liquid formulation TREANDA, which was being used at all US sites in this study. Investigators may continue to dispense TREANDA until its expiration date, as described in previous versions of the protocol and in the pharmacy manual. When acquiring new supplies, sites are to acquire bendamustine hydrochloride lyophilized powder. • Allow the assessment of CD30 for eligibility assessment to be performed either by local or central laboratory • Clarify that a new biopsy may be required for subjects with relapsed disease if one has not been obtained since relapse • To correct an inconsistency between the schedule of follow-up assessments and the text description of follow-up events • Make minor editorial and formatting changes throughout the protocol

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported