Clinical trial results:
A pivotal study of SGN-35 in treatment of patients with relapsed or refractory Hodgkin Lymphoma (HL) who have previously received autologous stem cell transplant.

Summary

EudraCT number	2008-006034-10
Trial protocol	DE BE IT FR GB
Global end of trial date	14 May 2015

Results information

Result version number	v1 (current)
This version publication date	31 July 2016
First version publication date	31 July 2016

Trial information

Trial identification

Sponsor protocol code	SG035-0003

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00848926
WHO universal trial number (UTN)	-
Other trial identifiers	ADCETRIS: SGN-35

Notes:

Sponsors

Sponsor organisation name	Seattle Genetics, Inc.
Sponsor organisation address	21823 30th Drive SE, Bothell, United States, 98021
Public contact	Chief Medical Officer, Seattle Genetics, Inc., 855 473-2436, medinfo@seagen.com
Scientific contact	Chief Medical Officer, Seattle Genetics, Inc., 855 473-2436, 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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	25 October 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	04 August 2010
Global end of trial reached?	Yes
Global end of trial date	14 May 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine the antitumor efficacy of single-agent brentuximab vedotin (1.8 mg/kg administered intravenously every 3 weeks) as measured by the overall objective response rate in patients with relapsed or refractory Hodgkin lymphoma following autologous stem cell transplant

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 Conference on Harmonisation (ICH) Good Clinical Practices (GCP), and applicable Food and Drug Administration (FDA) regulations/guidelines set forth in Title 21 CFR Parts 11, 50, 54, 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	18 February 2009
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	France: 5
Country: Number of subjects enrolled	Italy: 3
Country: Number of subjects enrolled	Canada: 8
Country: Number of subjects enrolled	United States: 86
Worldwide total number of subjects	102
EEA total number of subjects	8

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)	1
Adults (18-64 years)	98
From 65 to 84 years	3
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Feb 2009 to Aug 2009

Pre-assignment

Screening details:

Patients must have had relapsed or refractory HL following autologous stem cell transplant.

Period 1

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

Arms

Arm title	Brentuximab vedotin

Arm description:

Brentuximab vedotin 1.8 mg/kg every 3 weeks by IV infusion

Arm type	Experimental
Investigational medicinal product name	Brentuximab vedotin
Investigational medicinal product code	
Other name	ADCETRIS, SGN-35
Pharmaceutical forms	Concentrate for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Brentuximab vedotin 1.8 mg/kg every 3 weeks by IV infusion

Number of subjects in period 1	Brentuximab vedotin
Started	102
Completed	18
Not completed	84
Physician decision	12
Consent withdrawn by subject	7
Adverse event, non-fatal	20
Progressive disease	45

Baseline characteristics

Reporting groups

Reporting group title	Treatment

Reporting group description: -

Reporting group values	Treatment	Total	
Number of subjects	102	102	
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)	1	1	
Adults (18-64 years)	98	98	
From 65-84 years	3	3	
85 years and over	0	0	
Age continuous Units: years			
median	31		
full range (min-max)	15 to 77	-	
Gender categorical Units: Subjects			
Female	54	54	
Male	48	48	
Race Units: Subjects			
Asian	7	7	
Black or African American	5	5	
White	89	89	
Unknown or Not Reported	1	1	
Eastern Cooperative Oncology Group 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			
Zero	42	42	
One	60	60	
Two to Five	0	0	

End points

End points reporting groups

Reporting group title	Brentuximab vedotin

Reporting group description:

Brentuximab vedotin 1.8 mg/kg every 3 weeks by IV infusion

Primary: Objective Response Rate by Independent Review Group

End point title	Objective Response Rate by Independent Review Group[1]

End point description:

Percentage of participants who achieved a best response of complete remission (CR, disappearance of all evidence of disease) or partial remission (PR, regression of greater than or equal to 50% of measurable disease and no new sites) per Cheson 2007 Revised Response Criteria for Malignant Lymphoma.

End point type	Primary

End point timeframe:

up to 12 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: The primary efficacy hypothesis was:
H0: ORR for SGN-35 (1.8 mg/kg) is <20%
versus
Ha: ORR for SGN-35 (1.8 mg/kg) is >=20%

End point values	Brentuximab vedotin			
Subject group type	Reporting group			
Number of subjects analysed	102[2]			
Units: Percent of participants				
number (confidence interval 95%)				
ORR by Independent Review Group	75 (64.9 to 82.6)			

Notes:

[2] - Intention to treat

Statistical analyses

No statistical analyses for this end point

Secondary: Complete Remission Rate by Independent Review Group

End point title	Complete Remission Rate by Independent Review Group

End point description:

Percentage of participants who achieved a best response of CR (disappearance of all evidence of disease) per Cheson 2007 Revised Response Criteria for Malignant Lymphoma.

End point type	Secondary

End point timeframe:

up to 12 months

End point values	Brentuximab vedotin			
Subject group type	Reporting group			
Number of subjects analysed	102[3]			
Units: Percent of participants				
number (confidence interval 95%)				
CR Rate by Independent Review Group	33 (24.3 to 43.4)			

Notes:

[3] - Intention to treat

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Objective Response by Kaplan-Meier Analysis

End point title	Duration of Objective Response by Kaplan-Meier Analysis

End point description:

Duration of objective response (CR + PR) by independent review group, defined as time of initial response until disease progression or death.

End point type	Secondary

End point timeframe:

up to approximately 4 years

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Objective Response in Participants With Complete Remission by Kaplan-Meier Analysis

End point title	Duration of Objective Response in Participants With Complete Remission by Kaplan-Meier Analysis

End point description:

Duration of response from start of first objective tumor response (CR or PR) by independent review group to disease progression or death due to any cause in participants with CR.

End point type	Secondary

End point timeframe:

up to approximately 4 years

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free Survival by Kaplan-Meier Analysis

End point title	Progression-free Survival by Kaplan-Meier Analysis

End point description:

Time from start of study treatment to disease progression per independent review group or death due to any cause.

End point type	Secondary

End point timeframe:

up to approximately 4 years

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival

End point title	Overall Survival

End point description:

Time from start of study treatment to date of death due to any cause.

End point type	Secondary

End point timeframe:

up to approximately 6 years

Statistical analyses

No statistical analyses for this end point

Secondary: Adverse Events by Severity, Seriousness, and Relationship to Treatment

End point title	Adverse Events by Severity, Seriousness, and Relationship to Treatment

End point description:

Counts of participants who had adverse events or treatment-emergent adverse events (TEAE, defined as newly occurring or worsening after first dose). Serious adverse events are reported from the time of informed consent. National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE version 3.0) were used to assess severity (1=mild, 2=moderate, 3=severe, 4=life threatening/disabling, 5=death). Relatedness to study drug was assessed by the investigator (Yes/No). Participants with multiple occurrences of an adverse event within a category are counted once within the category.

End point type	Secondary

End point timeframe:

up to 12 months

End point values	Brentuximab vedotin			
Subject group type	Reporting group			
Number of subjects analysed	102[4]			
Units: Participants				
number (not applicable)				
Any TEAE	100			
TEAE related to study drug	94			
TEAE with severity grade >/=3	56			
Serious adverse event	25			
Serious adverse event related to study drug	14			
Discontinued treatment due to adverse event	20			

Notes:

[4] - All participants who received treatment

Statistical analyses

No statistical analyses for this end point

Secondary: Hematology Laboratory Abnormalities >/= Grade 3

End point title	Hematology Laboratory Abnormalities >/= Grade 3

End point description:

Counts of study participants with post-baseline hematology laboratory abnormalities of Grade 3 or greater per NCI CTCAE version 3.0. Participants with multiple occurrences of a laboratory abnormality

within a category are counted once in that category.

End point type	Secondary

End point timeframe:

up to 12 months

End point values	Brentuximab vedotin			
Subject group type	Reporting group			
Number of subjects analysed	102[5]			
Units: Participants				
number (not applicable)				
Any >/= Grade 3 hematology laboratory abnormality	35			
Hemoglobin (low)	7			
Leukocytes (low)	6			
Lymphocytes (low)	20			
Neutrophils (low)	12			
Platelets (low)	7			

Notes:

[5] - All participants who received treatment

Statistical analyses

No statistical analyses for this end point

Secondary: Chemistry Laboratory Abnormalities >/= Grade 3

End point title	Chemistry Laboratory Abnormalities >/= Grade 3

End point description:

Counts of study participants with post-baseline chemistry laboratory abnormalities of Grade 3 or greater per NCI CTCAE version 3.0. Participants with multiple occurrences of a laboratory abnormality within a category are counted once in that category.

End point type	Secondary

End point timeframe:

up to 12 months

End point values	Brentuximab vedotin			
Subject group type	Reporting group			
Number of subjects analysed	102[6]			
Units: Participants				
number (not applicable)				
Any >/= Grade 3 chemistry laboratory abnormality	14			
Alanine aminotransferase (high)	1			
Albumin (low)	1			
Calcium (low)	1			
Glucose (high)	7			

Potassium (low)	2			
Sodium (high)	1			
Urate (high)	1			

Notes:

[6] - All participants who received treatment

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Curve

End point title	Area Under the Curve

End point description:

Area under the serum concentration-time curve from time 0 to 21 days following the first dose of brentuximab vedotin

End point type	Secondary

End point timeframe:

3 weeks

End point values	Brentuximab vedotin			
Subject group type	Reporting group			
Number of subjects analysed	102[7]			
Units: day * microgram/mL				
geometric mean (geometric coefficient of variation)	88 (± 46)			

Notes:

[7] - All participants who received treatment

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Serum Concentration

End point title	Maximum Serum Concentration

End point description:

Maximum serum concentration from 0 to 21 days following the first dose of brentuximab vedotin

End point type	Secondary

End point timeframe:

3 weeks

End point values	Brentuximab vedotin			
Subject group type	Reporting group			
Number of subjects analysed	102[8]			
Units: microgram/mL				
geometric mean (geometric coefficient of variation)	35 (± 17)			

Notes:

[8] - All participants who received treatment

Statistical analyses

No statistical analyses for this end point

Secondary: Time of Maximum Serum Concentration

End point title	Time of Maximum Serum Concentration

End point description:

Time of maximum serum concentration from 0 to 21 days following the first dose of brentuximab vedotin

End point type	Secondary

End point timeframe:

3 weeks

End point values	Brentuximab vedotin			
Subject group type	Reporting group			
Number of subjects analysed	102[9]			
Units: days				
median (full range (min-max))				
Time of Maximum Serum Concentration	0.02 (0.02 to 0.02)			

Notes:

[9] - All participants who received treatment

Statistical analyses

No statistical analyses for this end point

Other pre-specified: B Symptom Resolution

End point title	B Symptom Resolution

End point description:

Percentage of participants with lymphoma-related symptoms (B symptoms: fever, night sweats, or weight loss >10%) at baseline who achieved resolution of all B symptoms at any time during the treatment period.

End point type	Other pre-specified

End point timeframe:

up to 12 months

End point values	Brentuximab vedotin			
Subject group type	Reporting group			
Number of subjects analysed	35[10]			
Units: percent of participants				
number (confidence interval 95%)				
B Symptom Resolution	77 (59.9 to 89.6)			

Notes:

[10] - Participants with B symptoms at baseline

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Up to 12 months	
Adverse event reporting additional description:	
Treatment-emergent adverse events (TEAEs) defined as newly occurring (not present at baseline) or worsening after first dose of investigational product on Study SG035-0003	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	13

Reporting groups	
Reporting group title	Brentuximab vedotin
Reporting group description:	
Brentuximab vedotin	

Serious adverse events	Brentuximab vedotin		
Total subjects affected by serious adverse events			
subjects affected / exposed	25 / 102 (24.51%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Diffuse large b-cell lymphoma			
subjects affected / exposed	1 / 102 (0.98%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hodgkin's disease recurrent			
subjects affected / exposed	1 / 102 (0.98%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Wrist fracture			
subjects affected / exposed	1 / 102 (0.98%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			

Demyelinating polyneuropathy				
subjects affected / exposed	2 / 102 (1.96%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Diabetic coma				
subjects affected / exposed	1 / 102 (0.98%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Peripheral motor neuropathy				
subjects affected / exposed	1 / 102 (0.98%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Blood and lymphatic system disorders				
Thrombocytopenia				
subjects affected / exposed	1 / 102 (0.98%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
Pyrexia				
subjects affected / exposed	2 / 102 (1.96%)			
occurrences causally related to treatment / all	3 / 4			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Abdominal pain				
subjects affected / exposed	2 / 102 (1.96%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Abdominal pain upper				
subjects affected / exposed	1 / 102 (0.98%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Diarrhoea				

subjects affected / exposed	1 / 102 (0.98%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal haemorrhage				
subjects affected / exposed	1 / 102 (0.98%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Haematemesis				
subjects affected / exposed	1 / 102 (0.98%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Intestinal perforation				
subjects affected / exposed	1 / 102 (0.98%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nausea				
subjects affected / exposed	1 / 102 (0.98%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Haemoptysis				
subjects affected / exposed	1 / 102 (0.98%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Pleural effusion				
subjects affected / exposed	1 / 102 (0.98%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonitis				
subjects affected / exposed	2 / 102 (1.96%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Pneumothorax				

subjects affected / exposed	2 / 102 (1.96%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Pulmonary embolism			
subjects affected / exposed	2 / 102 (1.96%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Stevens-johnson syndrome			
subjects affected / exposed	1 / 102 (0.98%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Mental status changes			
subjects affected / exposed	1 / 102 (0.98%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Flank pain			
subjects affected / exposed	1 / 102 (0.98%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Muscular weakness			
subjects affected / exposed	1 / 102 (0.98%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 102 (0.98%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Candidiasis			

subjects affected / exposed	1 / 102 (0.98%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cellulitis			
subjects affected / exposed	1 / 102 (0.98%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
H1n1 influenza			
subjects affected / exposed	1 / 102 (0.98%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lung infection			
subjects affected / exposed	1 / 102 (0.98%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumocystis jiroveci pneumonia			
subjects affected / exposed	1 / 102 (0.98%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	1 / 102 (0.98%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pyelonephritis			
subjects affected / exposed	2 / 102 (1.96%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Septic shock			
subjects affected / exposed	1 / 102 (0.98%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Soft tissue infection			

subjects affected / exposed	1 / 102 (0.98%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Staphylococcal bacteraemia			
subjects affected / exposed	1 / 102 (0.98%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection staphylococcal			
subjects affected / exposed	1 / 102 (0.98%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	1 / 102 (0.98%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Brentuximab vedotin		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	97 / 102 (95.10%)		
Investigations			
Weight decreased			
subjects affected / exposed	6 / 102 (5.88%)		
occurrences (all)	6		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Hodgkin's disease recurrent			
subjects affected / exposed	6 / 102 (5.88%)		
occurrences (all)	6		
Nervous system disorders			
Dizziness			
subjects affected / exposed	11 / 102 (10.78%)		
occurrences (all)	12		
Headache			

subjects affected / exposed	19 / 102 (18.63%)		
occurrences (all)	32		
Peripheral motor neuropathy			
subjects affected / exposed	11 / 102 (10.78%)		
occurrences (all)	15		
Peripheral sensory neuropathy			
subjects affected / exposed	48 / 102 (47.06%)		
occurrences (all)	76		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	9 / 102 (8.82%)		
occurrences (all)	9		
Lymphadenopathy			
subjects affected / exposed	11 / 102 (10.78%)		
occurrences (all)	17		
Neutropenia			
subjects affected / exposed	22 / 102 (21.57%)		
occurrences (all)	40		
Thrombocytopenia			
subjects affected / exposed	7 / 102 (6.86%)		
occurrences (all)	7		
General disorders and administration site conditions			
Chills			
subjects affected / exposed	13 / 102 (12.75%)		
occurrences (all)	17		
Fatigue			
subjects affected / exposed	47 / 102 (46.08%)		
occurrences (all)	71		
Pain			
subjects affected / exposed	7 / 102 (6.86%)		
occurrences (all)	7		
Pyrexia			
subjects affected / exposed	30 / 102 (29.41%)		
occurrences (all)	49		
Gastrointestinal disorders			

Abdominal pain			
subjects affected / exposed	15 / 102 (14.71%)		
occurrences (all)	17		
Constipation			
subjects affected / exposed	16 / 102 (15.69%)		
occurrences (all)	18		
Diarrhoea			
subjects affected / exposed	37 / 102 (36.27%)		
occurrences (all)	56		
Nausea			
subjects affected / exposed	43 / 102 (42.16%)		
occurrences (all)	61		
Vomiting			
subjects affected / exposed	22 / 102 (21.57%)		
occurrences (all)	28		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	21 / 102 (20.59%)		
occurrences (all)	24		
Dyspnoea			
subjects affected / exposed	13 / 102 (12.75%)		
occurrences (all)	15		
Nasal congestion			
subjects affected / exposed	6 / 102 (5.88%)		
occurrences (all)	7		
Oropharyngeal pain			
subjects affected / exposed	11 / 102 (10.78%)		
occurrences (all)	11		
Productive cough			
subjects affected / exposed	6 / 102 (5.88%)		
occurrences (all)	6		
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	13 / 102 (12.75%)		
occurrences (all)	13		
Hyperhidrosis			

subjects affected / exposed	6 / 102 (5.88%)		
occurrences (all)	8		
Night sweats			
subjects affected / exposed	12 / 102 (11.76%)		
occurrences (all)	15		
Pruritus			
subjects affected / exposed	16 / 102 (15.69%)		
occurrences (all)	23		
Rash			
subjects affected / exposed	14 / 102 (13.73%)		
occurrences (all)	20		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	11 / 102 (10.78%)		
occurrences (all)	12		
Depression			
subjects affected / exposed	8 / 102 (7.84%)		
occurrences (all)	8		
Insomnia			
subjects affected / exposed	14 / 102 (13.73%)		
occurrences (all)	14		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	19 / 102 (18.63%)		
occurrences (all)	23		
Back pain			
subjects affected / exposed	14 / 102 (13.73%)		
occurrences (all)	16		
Bone pain			
subjects affected / exposed	8 / 102 (7.84%)		
occurrences (all)	11		
Muscle spasms			
subjects affected / exposed	9 / 102 (8.82%)		
occurrences (all)	12		
Myalgia			

subjects affected / exposed	17 / 102 (16.67%)		
occurrences (all)	19		
Neck pain			
subjects affected / exposed	6 / 102 (5.88%)		
occurrences (all)	7		
Pain in extremity			
subjects affected / exposed	10 / 102 (9.80%)		
occurrences (all)	13		
Infections and infestations			
Bronchitis			
subjects affected / exposed	8 / 102 (7.84%)		
occurrences (all)	8		
Herpes zoster			
subjects affected / exposed	7 / 102 (6.86%)		
occurrences (all)	7		
Sinusitis			
subjects affected / exposed	9 / 102 (8.82%)		
occurrences (all)	11		
Upper respiratory tract infection			
subjects affected / exposed	38 / 102 (37.25%)		
occurrences (all)	47		
Urinary tract infection			
subjects affected / exposed	6 / 102 (5.88%)		
occurrences (all)	7		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	11 / 102 (10.78%)		
occurrences (all)	12		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 November 2008	Incorporation of FDA feedback during SPA review. Clarified that for patients who had bone marrow involvement at baseline, a follow-up bone marrow aspirate and biopsy was required (within 2 weeks of documentation of response) and must be negative for assessment of a CR. If the follow-up morphology was indeterminate, the biopsy tissue must be negative by immunohistochemistry or the patient was to be assessed as a PR. Specified that patients who were later determined to have the incorrect histological cancer type upon central review were to be scored as non-responders for calculating the ORR. Revised the definition of duration of response such that all deaths occurring prior to disease progression, not just deaths due to HL, were to be considered when determining the end of the response period. Revised the analysis set definitions such that the intent-to-treat (ITT) analysis set was to include all patients enrolled in the study and was to be used for the primary efficacy analysis. Secondary analyses of all efficacy endpoints were also to be performed in the per-protocol analysis set, defined as all patients who received at least 1 dose of brentuximab vedotin and who had measurable disease at baseline, the correct histological cancer type per central pathology review, and no other major protocol deviations that could potentially affect tumor response. The safety/modified intent-to-treat (mITT) analysis set, defined as all patients who received at least 1 dose of brentuximab vedotin, was to be used for safety analyses, patient demographics and baseline disease characteristics. Provided rationale as to why no formal interim efficacy or futility analysis was planned for the study.
12 January 2009	Incorporation of further FDA feedback during SPA review. The eligibility criteria were modified as follows: The time following prior immunotherapy or radioisotopic therapy was extended to 12 weeks so that any therapeutic benefit from these therapies would be realized prior to receiving brentuximab vedotin. This ensured that patients had relapsed or refractory disease prior to enrollment in the study. A new inclusion criterion was added to define which specific evidence of relapsed or refractory HL was required at the time of study enrollment.
03 October 2011	Added a section regarding the management of suspected PML
30 January 2012	Revised the timing of assessments during the study follow-up period.
03 October 2013	Removed the requirement for CT scanning during the long-term follow-up period. CT scans were only to be done if progression suspected based on clinical signs and symptoms. Added a long term follow-up questionnaire to be taken by patients who remained in remission.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/22454421