Clinical trial results:
A randomized, double-blind, placebo-controlled Phase 3 study of SGN-35 (brentuximab vedotin) and best supportive care (BSC) versus placebo and BSC in the treatment of patients at high risk of residual Hodgkin lymphoma (HL) following autologous stem cell transplant (ASCT)

Summary

EudraCT number	2009-016947-20
Trial protocol	FR HU ES CZ GB BG IT DE
Global end of trial date	27 April 2020

Results information

Result version number	v1 (current)
This version publication date	08 May 2021
First version publication date	08 May 2021

Trial information

Trial identification

Sponsor protocol code	SGN35-005

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01100502
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	PSI CRO Hungary Pharma Support LLC
Sponsor organisation address	Bank Center, Platina Tower, Szabadság tér 7, Budapest, Hungary,
Public contact	Clinical Operations, PSI CRO Hungary Pharma Support LLC, +36 1555 6755, rabudapest@psi-cro.com
Scientific contact	Clinical Operations, PSI CRO Hungary Pharma Support LLC, +36 1555 6755, rabudapest@psi-cro.com
Sponsor organisation name	Seagen Inc.
Sponsor organisation address	21823 30th Drive SE, Bothell/WA, United States, 98021
Public contact	Chief Medical Officer, Seagen Inc., 1 855-473-2436, medinfo@seagen.com
Scientific contact	Chief Medical Officer, Seagen Inc., 1 855-473-2436, 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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	27 April 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	27 April 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to compare the progression-free survival (PFS) of brentuximab vedotin and best supportive care (BSC) versus placebo and BSC.

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	06 April 2010
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy, Regulatory reason
Long term follow-up duration	6 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 54
Country: Number of subjects enrolled	Romania: 10
Country: Number of subjects enrolled	Spain: 10
Country: Number of subjects enrolled	United Kingdom: 6
Country: Number of subjects enrolled	Bulgaria: 9
Country: Number of subjects enrolled	Czech Republic: 5
Country: Number of subjects enrolled	France: 13
Country: Number of subjects enrolled	Germany: 3
Country: Number of subjects enrolled	Hungary: 20
Country: Number of subjects enrolled	Italy: 16

Country: Number of subjects enrolled	United States: 135
Country: Number of subjects enrolled	Russian Federation: 39
Country: Number of subjects enrolled	Serbia: 9
Worldwide total number of subjects	329
EEA total number of subjects	146

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)	321
From 65 to 84 years	8
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Apr 2010 to Aug 2014

Pre-assignment

Screening details:

Patients with HL who have received ASCT in the previous 30–45 days

Period 1

Period 1 title	Treatment (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Data analyst, Carer

Arms

Are arms mutually exclusive?	No
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
Routes of administration	Intravenous use

Dosage and administration details:

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

Arm title	Placebo

Arm description:

Placebo every 3 weeks by IV infusion

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Placebo every 3 weeks by IV infusion

Number of subjects in period 1	Brentuximab vedotin	Placebo
Started	165	164
Completed	78	81
Not completed	87	83
Adverse event, serious fatal	2	-

Adverse event, non-fatal	52	10
Patient decision, non-AE	9	4
Progressive disease	24	69

Baseline characteristics

Reporting groups	
Reporting group title	Brentuximab vedotin
Reporting group description:	
Brentuximab vedotin 1.8 mg/kg every 3 weeks by IV infusion	
Reporting group title	Placebo
Reporting group description:	
Placebo every 3 weeks by IV infusion	

Reporting group values	Brentuximab vedotin	Placebo	Total
Number of subjects	165	164	329
Age categorical Units: Subjects			
Adults (18-64 years)	160	161	321
From 65-84 years	5	3	8
Age continuous Units: years			
median	33	32	
full range (min-max)	18 to 71	18 to 76	-
Gender categorical Units: Subjects			
Female	89	67	156
Male	76	97	173
Race Units: Subjects			
Asian	2	3	5
Black or African American	10	2	12
White	153	156	309
Other	0	3	3
Eastern Cooperative Oncology Group Performance Status			
Zero = Normal activity One = Symptoms but ambulatory Two = In bed < 50% of the time			
Units: Subjects			
Zero	87	97	184
One	77	67	144
Two	1	0	1
HL status after frontline therapy			
Refractory/relapsed status after the end of frontline standard chemotherapy or a combined modality treatment program.			
Units: Subjects			
Refractory	99	97	196
Relapse <12 months	53	54	107
Relapse >=12 months with extranodal disease	13	13	26
Best response to salvage therapy pre-ASCT Units: Subjects			

Complete remission	61	62	123
Partial remission	57	56	113
Stable disease	47	46	93

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	
Reporting group title	Placebo
Reporting group description:	
Placebo every 3 weeks by IV infusion	
Subject analysis set title	BV Arm - Safety Analysis Set
Subject analysis set type	Safety analysis
Subject analysis set description:	
Safety Analysis Set includes all patients who received at least 1 dose of brentuximab vedotin or only received placebo: 2 patients randomized to placebo received a single dose of brentuximab vedotin and are included in the brentuximab vedotin arm; 2 patients randomized to placebo received no study treatment and are not included in the analysis	
Subject analysis set title	Placebo Arm - Safety Analysis Set
Subject analysis set type	Safety analysis
Subject analysis set description:	
Safety Analysis Set includes all patients who received at least 1 dose of brentuximab vedotin or only received placebo: 2 patients randomized to placebo received a single dose of brentuximab vedotin and are included in the brentuximab vedotin arm; 2 patients randomized to placebo received no study treatment and are not included in the analysis	

Primary: Progression-free survival by independent review

End point title	Progression-free survival by independent review
End point description:	
Time from date of randomization to the first documentation of disease progression by independent review or to death due to any cause, whichever comes first.	
End point type	Primary
End point timeframe:	
Up to approximately 4 years	

End point values	Brentuximab vedotin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	165[1]	164[2]		
Units: Months				
median (confidence interval 95%)	42.9 (30.4 to 42.9)	24.1 (11.5 to 999)		

Notes:

[1] - Intention-to-treat

[2] - 999 = Not available (follow-up is not long enough to assess an upper bound)

Statistical analyses

Statistical analysis title	Progression-free survival by independent review

Statistical analysis description:

The primary analysis of PFS used a stratified log-rank test at a one-sided alpha level of 0.025. A stratified Cox regression model was used to estimate the HR and the corresponding 95% CI for the treatment effect. An HR <1 indicates that the duration of PFS is prolonged for patients on the

brentuximab vedotin arm compared with patients on the placebo arm. The median PFS and its two-sided 95% CI for the median was calculated using the complementary log-log transformation method (Collett 1994).

Comparison groups	Brentuximab vedotin v Placebo
Number of subjects included in analysis	329
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0013
Method	Mantel-Haenszel
Parameter estimate	Hazard ratio (HR)
Point estimate	0.571
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.404
upper limit	0.808
Variability estimate	Standard deviation

Secondary: Adverse events

End point title	Adverse events

End point description:

Counts of participants who had treatment-emergent adverse events, defined as newly occurring (not present at baseline) or worsening after first dose of study drug. Relatedness to study drug was assessed by the investigator. Serious adverse events are reported from the time of informed consent. All events are from study day 1 pre-dose to the end of the safety reporting period. 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	BV Arm - Safety Analysis Set	Placebo Arm - Safety Analysis Set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	167	160		
Units: Number of participants				
Any AE	163	142		
Treatment-related AE	147	79		
AE >=Grade 3	93	51		
Any SAE	41	20		
Any treatment-related SAE	19	7		
Discontinued treatment due to AE	54	10		

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of anti-therapeutic antibodies (ATA) to brentuximab vedotin

End point title	Incidence of anti-therapeutic antibodies (ATA) to brentuximab vedotin

End point description:

Counts of participants with anti-brentuximab vedotin antibodies at any time during treatment.

End point type	Secondary

End point timeframe:

Up to 12 months

End point values	Brentuximab vedotin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	157[3]	154[4]		
Units: Number of participants				
Baseline (BL) negative	138	142		
- BL negative, negative post-BL	92	104		
- BL negative, transiently positive post-BL	36	27		
- BL negative, persistently positive post-BL	10	11		
Baseline (BL) positive	19	12		
- BL positive, negative post-BL	7	0		
- BL positive, transiently positive post-BL	9	5		
- BL positive, persistently positive post-BL	3	7		

Notes:

[3] - ATA-evaluable patients (i.e., patients with a baseline and at least one postbaseline sample)

[4] - ATA-evaluable patients (i.e., patients with a baseline and at least one postbaseline sample)

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival

End point title	Overall Survival

End point description:

Time from date of randomization to date of death due to any cause.

Due to patients lost to follow up, patient withdrawal of consent and post ASCT therapies; there were less deaths on study than anticipated. Therefore, median OS was not reached. '999' is listed in lieu of "NA" due to requirement for numerical entry.

Full Observed Range:
Brentuximab Vedotin Arm: 1.31 to 117.88 months
Placebo Arm: 0.03 to 119.23 months

End point type	Secondary

End point timeframe:

Up to approximately 10 years

End point values	Brentuximab vedotin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	165	164		
Units: months	999	999		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Non-serious adverse events were followed for up to 15 months. Serious adverse event data were collected for up to approximately 10 years (116 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 SGN35-005

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups

Reporting group title	Placebo

Reporting group description:

placebo every 3 weeks by IV infusion

Reporting group title	Brentuximab Vedotin

Reporting group description:

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

Serious adverse events	Placebo	Brentuximab Vedotin	
Total subjects affected by serious adverse events			
subjects affected / exposed	21 / 160 (13.13%)	43 / 167 (25.75%)	
number of deaths (all causes)	2	4	
number of deaths resulting from adverse events	1	2	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bladder cancer			
subjects affected / exposed	0 / 160 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
Acute myeloid leukaemia			
subjects affected / exposed	1 / 160 (0.63%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Mantle cell lymphoma			
subjects affected / exposed	1 / 160 (0.63%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Myelodysplastic syndrome			
subjects affected / exposed	1 / 160 (0.63%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	2 / 2	2 / 2	
deaths causally related to treatment / all	1 / 1	1 / 1	
Anogenital warts			
subjects affected / exposed	0 / 160 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain neoplasm			
subjects affected / exposed	0 / 160 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Metastases to spine			
subjects affected / exposed	1 / 160 (0.63%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Pelvic venous thrombosis			
subjects affected / exposed	0 / 160 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	0 / 160 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 160 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	5 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disease progression			
subjects affected / exposed	0 / 160 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pyrexia			
subjects affected / exposed	2 / 160 (1.25%)	6 / 167 (3.59%)	
occurrences causally related to treatment / all	0 / 5	6 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	1 / 160 (0.63%)	2 / 167 (1.20%)	
occurrences causally related to treatment / all	0 / 4	3 / 5	
deaths causally related to treatment / all	0 / 1	1 / 2	
Asthma			
subjects affected / exposed	1 / 160 (0.63%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchospasm			
subjects affected / exposed	0 / 160 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Idiopathic pneumonia syndrome			
subjects affected / exposed	1 / 160 (0.63%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infiltration			
subjects affected / exposed	1 / 160 (0.63%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	0 / 160 (0.00%)	2 / 167 (1.20%)	
occurrences causally related to treatment / all	0 / 0	2 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	0 / 160 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pulmonary toxicity			
subjects affected / exposed	0 / 160 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 160 (0.63%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
subjects affected / exposed	0 / 160 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression suicidal			
subjects affected / exposed	1 / 160 (0.63%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicidal ideation			
subjects affected / exposed	0 / 160 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood bilirubin increased			
subjects affected / exposed	1 / 160 (0.63%)	0 / 167 (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			
Radiation myelopathy			
subjects affected / exposed	0 / 160 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Bradycardia			

subjects affected / exposed	0 / 160 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	0 / 160 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	0 / 160 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial effusion			
subjects affected / exposed	1 / 160 (0.63%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus tachycardia			
subjects affected / exposed	0 / 160 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Basilar migraine			
subjects affected / exposed	0 / 160 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Posterior reversible encephalopathy syndrome			
subjects affected / exposed	0 / 160 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	0 / 160 (0.00%)	2 / 167 (1.20%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuralgia			

subjects affected / exposed	0 / 160 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral motor neuropathy			
subjects affected / exposed	0 / 160 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 160 (0.00%)	3 / 167 (1.80%)	
occurrences causally related to treatment / all	0 / 0	13 / 13	
deaths causally related to treatment / all	0 / 0	0 / 0	
Presyncope			
subjects affected / exposed	0 / 160 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	0 / 160 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Bone marrow failure			
subjects affected / exposed	1 / 160 (0.63%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	1 / 160 (0.63%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	2 / 160 (1.25%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	9 / 9	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			

Abdominal pain			
subjects affected / exposed	1 / 160 (0.63%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	0 / 160 (0.00%)	2 / 167 (1.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	1 / 160 (0.63%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epigastric discomfort			
subjects affected / exposed	0 / 160 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erosive duodenitis			
subjects affected / exposed	0 / 160 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 160 (0.63%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	1 / 160 (0.63%)	4 / 167 (2.40%)	
occurrences causally related to treatment / all	0 / 2	3 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	0 / 160 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			

subjects affected / exposed	1 / 160 (0.63%)	5 / 167 (2.99%)	
occurrences causally related to treatment / all	0 / 2	4 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatotoxicity			
subjects affected / exposed	1 / 160 (0.63%)	3 / 167 (1.80%)	
occurrences causally related to treatment / all	0 / 4	0 / 12	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	0 / 160 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash			
subjects affected / exposed	0 / 160 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dermatitis allergic			
subjects affected / exposed	0 / 160 (0.00%)	2 / 167 (1.20%)	
occurrences causally related to treatment / all	0 / 0	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Bone pain			
subjects affected / exposed	1 / 160 (0.63%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Acute hepatitis b			
subjects affected / exposed	0 / 160 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Complicated appendicitis			

subjects affected / exposed	0 / 160 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic candidiasis			
subjects affected / exposed	0 / 160 (0.00%)	1 / 167 (0.60%)	
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 / 160 (0.63%)	2 / 167 (1.20%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumocystis jirovecii pneumonia			
subjects affected / exposed	0 / 160 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	4 / 160 (2.50%)	7 / 167 (4.19%)	
occurrences causally related to treatment / all	0 / 7	4 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	1 / 160 (0.63%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinusitis			
subjects affected / exposed	1 / 160 (0.63%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	1 / 160 (0.63%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyperglycaemia			

subjects affected / exposed	0 / 160 (0.00%)	1 / 167 (0.60%)	
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	Placebo	Brentuximab Vedotin	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	127 / 160 (79.38%)	151 / 167 (90.42%)	
Vascular disorders			
Hypotension			
subjects affected / exposed	4 / 160 (2.50%)	9 / 167 (5.39%)	
occurrences (all)	7	10	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	7 / 160 (4.38%)	13 / 167 (7.78%)	
occurrences (all)	10	13	
Chills			
subjects affected / exposed	8 / 160 (5.00%)	17 / 167 (10.18%)	
occurrences (all)	8	21	
Fatigue			
subjects affected / exposed	29 / 160 (18.13%)	40 / 167 (23.95%)	
occurrences (all)	34	68	
Non-cardiac chest pain			
subjects affected / exposed	9 / 160 (5.63%)	6 / 167 (3.59%)	
occurrences (all)	10	8	
Oedema peripheral			
subjects affected / exposed	10 / 160 (6.25%)	8 / 167 (4.79%)	
occurrences (all)	14	12	
Pain			
subjects affected / exposed	5 / 160 (3.13%)	11 / 167 (6.59%)	
occurrences (all)	5	19	
Pyrexia			
subjects affected / exposed	23 / 160 (14.38%)	27 / 167 (16.17%)	
occurrences (all)	37	49	
Respiratory, thoracic and mediastinal			

disorders			
Cough			
subjects affected / exposed	26 / 160 (16.25%)	35 / 167 (20.96%)	
occurrences (all)	33	43	
Dyspnoea			
subjects affected / exposed	10 / 160 (6.25%)	21 / 167 (12.57%)	
occurrences (all)	11	34	
Oropharyngeal pain			
subjects affected / exposed	8 / 160 (5.00%)	8 / 167 (4.79%)	
occurrences (all)	10	9	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	13 / 160 (8.13%)	14 / 167 (8.38%)	
occurrences (all)	14	15	
Insomnia			
subjects affected / exposed	5 / 160 (3.13%)	14 / 167 (8.38%)	
occurrences (all)	5	15	
Investigations			
Weight decreased			
subjects affected / exposed	9 / 160 (5.63%)	31 / 167 (18.56%)	
occurrences (all)	10	64	
Weight increased			
subjects affected / exposed	14 / 160 (8.75%)	5 / 167 (2.99%)	
occurrences (all)	28	5	
Cardiac disorders			
Sinus tachycardia			
subjects affected / exposed	3 / 160 (1.88%)	9 / 167 (5.39%)	
occurrences (all)	3	10	
Nervous system disorders			
Headache			
subjects affected / exposed	13 / 160 (8.13%)	19 / 167 (11.38%)	
occurrences (all)	18	31	
Paraesthesia			
subjects affected / exposed	2 / 160 (1.25%)	16 / 167 (9.58%)	
occurrences (all)	2	33	
Peripheral motor neuropathy			

subjects affected / exposed	3 / 160 (1.88%)	37 / 167 (22.16%)	
occurrences (all)	3	39	
Peripheral sensory neuropathy			
subjects affected / exposed	25 / 160 (15.63%)	92 / 167 (55.09%)	
occurrences (all)	32	220	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	4 / 160 (2.50%)	14 / 167 (8.38%)	
occurrences (all)	11	36	
Leukopenia			
subjects affected / exposed	3 / 160 (1.88%)	9 / 167 (5.39%)	
occurrences (all)	7	18	
Neutropenia			
subjects affected / exposed	18 / 160 (11.25%)	58 / 167 (34.73%)	
occurrences (all)	36	163	
Thrombocytopenia			
subjects affected / exposed	3 / 160 (1.88%)	12 / 167 (7.19%)	
occurrences (all)	7	39	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	5 / 160 (3.13%)	20 / 167 (11.98%)	
occurrences (all)	7	30	
Constipation			
subjects affected / exposed	5 / 160 (3.13%)	20 / 167 (11.98%)	
occurrences (all)	5	27	
Diarrhoea			
subjects affected / exposed	15 / 160 (9.38%)	33 / 167 (19.76%)	
occurrences (all)	25	47	
Dyspepsia			
subjects affected / exposed	6 / 160 (3.75%)	11 / 167 (6.59%)	
occurrences (all)	6	17	
Nausea			
subjects affected / exposed	12 / 160 (7.50%)	34 / 167 (20.36%)	
occurrences (all)	18	61	
Vomiting			

subjects affected / exposed	11 / 160 (6.88%)	24 / 167 (14.37%)	
occurrences (all)	14	35	
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	7 / 160 (4.38%)	10 / 167 (5.99%)	
occurrences (all)	9	10	
Night sweats			
subjects affected / exposed	18 / 160 (11.25%)	12 / 167 (7.19%)	
occurrences (all)	19	13	
Pruritus			
subjects affected / exposed	14 / 160 (8.75%)	22 / 167 (13.17%)	
occurrences (all)	18	40	
Rash			
subjects affected / exposed	5 / 160 (3.13%)	14 / 167 (8.38%)	
occurrences (all)	6	22	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	15 / 160 (9.38%)	30 / 167 (17.96%)	
occurrences (all)	16	42	
Back pain			
subjects affected / exposed	16 / 160 (10.00%)	15 / 167 (8.98%)	
occurrences (all)	17	22	
Muscle spasms			
subjects affected / exposed	9 / 160 (5.63%)	18 / 167 (10.78%)	
occurrences (all)	10	20	
Muscular weakness			
subjects affected / exposed	1 / 160 (0.63%)	8 / 167 (4.79%)	
occurrences (all)	2	10	
Myalgia			
subjects affected / exposed	7 / 160 (4.38%)	15 / 167 (8.98%)	
occurrences (all)	7	17	
Pain in extremity			
subjects affected / exposed	8 / 160 (5.00%)	11 / 167 (6.59%)	
occurrences (all)	9	12	
Infections and infestations			

Bronchitis			
subjects affected / exposed	10 / 160 (6.25%)	10 / 167 (5.99%)	
occurrences (all)	13	10	
Herpes zoster			
subjects affected / exposed	3 / 160 (1.88%)	10 / 167 (5.99%)	
occurrences (all)	3	12	
Pharyngitis			
subjects affected / exposed	4 / 160 (2.50%)	8 / 167 (4.79%)	
occurrences (all)	4	10	
Sinusitis			
subjects affected / exposed	10 / 160 (6.25%)	4 / 167 (2.40%)	
occurrences (all)	10	6	
Upper respiratory tract infection			
subjects affected / exposed	37 / 160 (23.13%)	43 / 167 (25.75%)	
occurrences (all)	57	68	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	9 / 160 (5.63%)	20 / 167 (11.98%)	
occurrences (all)	9	25	
Hypokalaemia			
subjects affected / exposed	6 / 160 (3.75%)	10 / 167 (5.99%)	
occurrences (all)	6	19	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 October 2009	The sample size was increased to 322 patients to enable detection of a hazard ratio of 0.667 in favor of brentuximab vedotin. Based on regulatory guidance, more frequent CT scanning and lymphoma assessments were incorporated to better characterize the primary endpoint of PFS. To better inform patient care after disease progression, the protocol was revised to allow unblinding of a patient's treatment assignment once disease progression had occurred. Investigator assessment of response to prior salvage therapy was added as a stratification factor to ensure that patients with different outcomes to salvage therapy were equally distributed between the treatment arms. Based on regulatory and investigator guidance and because of the blinded nature of the study, the prospective pathology review for confirmation of HL was removed.
16 August 2010	Administration of the EQ-5D health questionnaire and collection of MRU data was added to conduct exploratory health economics and outcomes research. A recommendation was added such that patients who experienced Grade 2 neuropathy were to resume treatment at 1.2 mg/kg to minimize additional or worsening events of neuropathy. The follow-up period for events of peripheral neuropathy and other AEs of interest was extended beyond the 30-day post-treatment reporting period to better characterize their resolution.
03 October 2011	The eligibility criteria were clarified to ensure exclusion of patients with PML. In addition, information and guidance were provided on the signs and symptoms of PML and diagnostic work-up/recommendations for suspending or discontinuing treatment with brentuximab vedotin in the event of PML.
29 November 2011	The safety assessments section was revised to better define the different subcategories of adverse events and provide guidance on their relative safety reporting periods; and to clarify sponsor safety reporting requirements in the US. The study assessments section was revised to require that any CT scans performed as standard of care after the 24-month scan were submitted for central review and study visits for patients who discontinued treatment before 16 cycles included all required assessments including CT scans and lymphoma assessments.
07 June 2012	The procedure for emergency unblinding was revised to allow investigators who needed treatment assignment information (for safety reasons or for clinical decision-making) to directly obtain treatment assignment information through the IWRS without having to first contact the sponsor. This change was made to better align with the recommendations of the EMA GCP Inspector's Working Group and Clinical Trial Facilitation Group.
13 December 2013	The timing of the primary efficacy analysis was changed after an evaluation of blinded, pooled PFS data from the current study showed a flattening of the PFS curve after 24 months; thus, it was unlikely that additional follow up after 24 months would provide significant additional events. The primary efficacy analysis was therefore changed to occur after all study scheduled CT scans had been performed. At this time, all patients had been off therapy for at least one year. The IDMC was consulted regarding this change to the primary analysis and they agreed that the scientific integrity of the study should remain intact.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported