



Clinical trial results:

A pivotal study of SGN-35 in treatment of patients with relapsed or refractory systemic anaplastic large cell lymphoma (ALCL)

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2008-006035-12 |
| Trial protocol | BE DE IT FR GB |
| Global end of trial date | 06 June 2016 |

Results information

| | |
|--------------------------------|-----------------|
| Result version number | v1 (current) |
| This version publication date | 05 January 2017 |
| First version publication date | 05 January 2017 |

Trial information

Trial identification

| | |
|-----------------------|------------|
| Sponsor protocol code | SG035-0004 |
|-----------------------|------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT00866047 |
| WHO universal trial number (UTN) | - |

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. , 1 855 473-2436, medinfo@seagen.com |
| Scientific contact | Chief Medical Officer, Seattle Genetics, 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? | Yes |

Notes:

Results analysis stage

| | |
|--|-----------------|
| Analysis stage | Final |
| Date of interim/final analysis | 26 October 2016 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 16 August 2010 |
| Global end of trial reached? | Yes |
| Global end of trial date | 06 June 2016 |
| 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 SGN-35 (1.8 mg/kg administered intravenously every 3 weeks) as measured by the overall objective response rate in patients with relapsed or refractory systemic anaplastic large cell lymphoma following front-line chemotherapy (CHOP or equivalent)

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 | 16 March 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 | United Kingdom: 3 |
| Country: Number of subjects enrolled | Belgium: 1 |
| Country: Number of subjects enrolled | France: 8 |
| Country: Number of subjects enrolled | Canada: 3 |
| Country: Number of subjects enrolled | United States: 43 |
| Worldwide total number of subjects | 58 |
| EEA total number of subjects | 12 |

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) | 4 |
| Adults (18-64 years) | 45 |
| From 65 to 84 years | 9 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Enrollment period: March 2009 - May 2010

Pre-assignment

Screening details:

Patients with relapsed or refractory systemic ALCL who have previously received front line chemotherapy.

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 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 | 58 |
| Completed | 10 |
| Not completed | 48 |
| Adverse event, serious fatal | 6 |
| Physician decision | 14 |
| Patient decision | 5 |
| Adverse event, non-fatal | 10 |
| Progressive disease | 13 |

Baseline characteristics

Reporting groups

| Reporting group title | Treatment |
|--------------------------------|-----------|
| Reporting group description: - | |

| Reporting group values | Treatment | Total | |
|--|-----------|-------|--|
| Number of subjects | 58 | 58 | |
| 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) | 4 | 4 | |
| Adults (18-64 years) | 45 | 45 | |
| From 65-84 years | 9 | 9 | |
| 85 years and over | 0 | 0 | |
| Age continuous | | | |
| Units: years | | | |
| median | 52 | | |
| full range (min-max) | 14 to 76 | - | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 25 | 25 | |
| Male | 33 | 33 | |
| Race | | | |
| Units: Subjects | | | |
| Asian | 1 | 1 | |
| Black or African American | 7 | 7 | |
| White | 48 | 48 | |
| Other | 2 | 2 | |
| 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 | 19 | 19 | |
| One | 38 | 38 | |
| Two to Five | 1 | 1 | |
| ALK Status | | | |
| Units: Subjects | | | |
| Positive | 16 | 16 | |
| Negative | 42 | 42 | |

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 specified. H0: ORR <20% versus Ha: ORR ≥20%

| End point values | Brentuximab vedotin | | | |
|----------------------------------|---------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 58 ^[2] | | | |
| Units: Percent of Participants | | | | |
| number (confidence interval 95%) | | | | |
| ORR by Independent Review Group | 86 (74.6 to 93.9) | | | |

Notes:

[2] - The primary efficacy hypothesis was specified. H0: ORR <20% versus Ha: ORR ≥20%

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 | 58 ^[3] | | | |
| Units: Percent of Participants | | | | |
| number (confidence interval 95%) | | | | |
| CR Rate by Independent Review Group | 59 (44.9 to 71.4) | | | |

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 | |

| | | | | |
|---|---------------------|--|--|--|
| End point values | Brentuximab vedotin | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 50 ^[4] | | | |
| Units: Months | | | | |
| number (confidence interval 95%) | | | | |
| Duration of OR by Kaplan-Meier Analysis | 13.2 (5.7 to 26.3) | | | |

Notes:

[4] - Participants with objective response among the intention to treat population

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 | |

| End point values | Brentuximab vedotin | | | |
|--|---------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 34 ^[5] | | | |
| Units: Months | | | | |
| number (confidence interval 95%) | | | | |
| Duration of OR in Participants with CR | 26.3 (13.2 to 999) | | | |

Notes:

[5] - Participants w/CR (ITT population)

999 = NA; insufficient number of events to estimate upper bound

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 |

| End point values | Brentuximab vedotin | | | |
|--|---------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 58 | | | |
| Units: Months | | | | |
| number (confidence interval 95%) | | | | |
| Progression-free Survival by Kaplan-Meier Analysis | 14.6 (6.9 to 20.6) | | | |

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 7 years |

| End point values | Brentuximab vedotin | | | |
|----------------------------------|---------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 58 ^[6] | | | |
| Units: Months | | | | |
| number (confidence interval 95%) | | | | |
| Overall Survival | 999 (21.3 to 999) | | | |

Notes:

[6] - Intention to treat

999 = NA; insufficient number of events to estimate

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 | 58 ^[7] | | | |
| Units: Participants | | | | |
| number (not applicable) | | | | |
| Any TEAE | 58 | | | |
| TEAE related to study drug | 53 | | | |
| TEAE with severity grade ≥ 3 | 36 | | | |
| Serious adverse event | 25 | | | |
| Serious adverse event related to study drug | 11 | | | |
| Discontinued treatment due to adverse event | 16 | | | |

Notes:

[7] - All participants who received treatment

Statistical analyses

No statistical analyses for this end point

Secondary: Hematology Laboratory Abnormalities \geq Grade 3

| | |
|-----------------|--|
| End point title | Hematology Laboratory Abnormalities \geq 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 | 58 ^[8] | | | |
| Units: Participants | | | | |
| number (not applicable) | | | | |
| Any \geq Grade 3 hematology laboratory abnormality | 17 | | | |
| Leukocytes (low) | 3 | | | |
| Lymphocytes (low) | 10 | | | |
| Neutrophils (low) | 7 | | | |
| Platelets (low) | 3 | | | |

Notes:

[8] - All participants who received treatment

Statistical analyses

No statistical analyses for this end point

Secondary: Chemistry Laboratory Abnormalities \geq Grade 3

| | |
|-----------------|---|
| End point title | Chemistry Laboratory Abnormalities \geq 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 | 58 ^[9] | | | |
| Units: Participants | | | | |
| number (not applicable) | | | | |
| Any >= Grade 3 chemistry laboratory abnormality | 13 | | | |
| Aspartate Aminotransferase (High) | 1 | | | |
| Calcium (Low) | 3 | | | |
| Glucose (High) | 4 | | | |
| Potassium (Low) | 1 | | | |
| Sodium (Low) | 1 | | | |
| Urate (High) | 3 | | | |

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 | 17 ^[10] | | | |
| Units: Percent of Participants | | | | |
| number (confidence interval 95%) | | | | |
| B Symptom Resolution | 82 (56.6 to 96.2) | | | |

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 (TEAE) defined as newly occurring (not present at baseline) or worsening after first dose of investigational product

| | |
|-----------------|------------|
| 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 / 58 (43.10%) | | |
| number of deaths (all causes) | 25 | | |
| number of deaths resulting from adverse events | 0 | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Anaplastic large cell lymphoma T- and null-cell types recurrent | | | |
| subjects affected / exposed | 3 / 58 (5.17%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 3 | | |
| Mycosis fungoides | | | |
| subjects affected / exposed | 1 / 58 (1.72%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Tumour flare | | | |
| subjects affected / exposed | 1 / 58 (1.72%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vascular disorders | | | |
| Deep vein thrombosis | | | |

| | | | |
|--|----------------|--|--|
| subjects affected / exposed | 1 / 58 (1.72%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 1 / 58 (1.72%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Generalised oedema | | | |
| subjects affected / exposed | 1 / 58 (1.72%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Sudden death | | | |
| subjects affected / exposed | 1 / 58 (1.72%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 1 / 58 (1.72%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pulmonary oedema | | | |
| subjects affected / exposed | 1 / 58 (1.72%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory failure | | | |
| subjects affected / exposed | 1 / 58 (1.72%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Tracheal disorder | | | |
| subjects affected / exposed | 1 / 58 (1.72%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|---|----------------|--|--|
| Psychiatric disorders | | | |
| Mental status changes | | | |
| subjects affected / exposed | 1 / 58 (1.72%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Injury, poisoning and procedural complications | | | |
| Lower limb fracture | | | |
| subjects affected / exposed | 1 / 58 (1.72%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac disorders | | | |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 1 / 58 (1.72%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Arrhythmia supraventricular | | | |
| subjects affected / exposed | 2 / 58 (3.45%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 1 / 58 (1.72%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Atrioventricular block complete | | | |
| subjects affected / exposed | 1 / 58 (1.72%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Bradycardia | | | |
| subjects affected / exposed | 1 / 58 (1.72%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nervous system disorders | | | |
| Demyelinating polyneuropathy | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 1 / 58 (1.72%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Encephalopathy | | | |
| subjects affected / exposed | 1 / 58 (1.72%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Haemorrhage intracranial | | | |
| subjects affected / exposed | 1 / 58 (1.72%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Neuralgia | | | |
| subjects affected / exposed | 1 / 58 (1.72%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Peripheral motor neuropathy | | | |
| subjects affected / exposed | 1 / 58 (1.72%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Peripheral sensory neuropathy | | | |
| subjects affected / exposed | 1 / 58 (1.72%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Spinal cord compression | | | |
| subjects affected / exposed | 1 / 58 (1.72%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Syncope | | | |
| subjects affected / exposed | 1 / 58 (1.72%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 1 / 58 (1.72%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Neutropenia | | | |
| subjects affected / exposed | 1 / 58 (1.72%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Eye disorders | | | |
| Retinal vein occlusion | | | |
| subjects affected / exposed | 1 / 58 (1.72%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 1 / 58 (1.72%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Constipation | | | |
| subjects affected / exposed | 1 / 58 (1.72%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Diarrhoea | | | |
| subjects affected / exposed | 1 / 58 (1.72%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vomiting | | | |
| subjects affected / exposed | 1 / 58 (1.72%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Skin and subcutaneous tissue disorders | | | |
| Rash papular | | | |
| subjects affected / exposed | 1 / 58 (1.72%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|---|----------------|--|--|
| Renal and urinary disorders | | | |
| Hydronephrosis | | | |
| subjects affected / exposed | 1 / 58 (1.72%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal failure | | | |
| subjects affected / exposed | 1 / 58 (1.72%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal Failure Acute | | | |
| subjects affected / exposed | 1 / 58 (1.72%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Myositis | | | |
| subjects affected / exposed | 1 / 58 (1.72%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pain in extremity | | | |
| subjects affected / exposed | 2 / 58 (3.45%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| Cellulitis | | | |
| subjects affected / exposed | 1 / 58 (1.72%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Endocarditis staphylococcal | | | |
| subjects affected / exposed | 1 / 58 (1.72%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastroenteritis viral | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 1 / 58 (1.72%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Klebsiella bacteraemia | | | |
| subjects affected / exposed | 1 / 58 (1.72%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pneumonia | | | |
| subjects affected / exposed | 1 / 58 (1.72%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Septic shock | | | |
| subjects affected / exposed | 2 / 58 (3.45%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Superinfection bacterial | | | |
| subjects affected / exposed | 1 / 58 (1.72%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Urinary tract infection | | | |
| subjects affected / exposed | 2 / 58 (3.45%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 1 / 58 (1.72%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Fluid overload | | | |
| subjects affected / exposed | 1 / 58 (1.72%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypercalcaemia | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 1 / 58 (1.72%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Tumour lysis syndrome | | | |
| subjects affected / exposed | 1 / 58 (1.72%) | | |
| 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 | 58 / 58 (100.00%) | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Anaplastic large cell lymphoma T- and null-cell types recurrent | | | |
| subjects affected / exposed | 3 / 58 (5.17%) | | |
| occurrences (all) | 3 | | |
| Tumour flare | | | |
| subjects affected / exposed | 4 / 58 (6.90%) | | |
| occurrences (all) | 4 | | |
| Vascular disorders | | | |
| Hot flush | | | |
| subjects affected / exposed | 3 / 58 (5.17%) | | |
| occurrences (all) | 4 | | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 5 / 58 (8.62%) | | |
| occurrences (all) | 5 | | |
| Chills | | | |
| subjects affected / exposed | 8 / 58 (13.79%) | | |
| occurrences (all) | 11 | | |
| Fatigue | | | |
| subjects affected / exposed | 22 / 58 (37.93%) | | |
| occurrences (all) | 27 | | |
| Oedema peripheral | | | |

| | | | |
|---|------------------|--|--|
| subjects affected / exposed | 8 / 58 (13.79%) | | |
| occurrences (all) | 9 | | |
| Pain | | | |
| subjects affected / exposed | 6 / 58 (10.34%) | | |
| occurrences (all) | 7 | | |
| Pyrexia | | | |
| subjects affected / exposed | 20 / 58 (34.48%) | | |
| occurrences (all) | 25 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 10 / 58 (17.24%) | | |
| occurrences (all) | 10 | | |
| Dyspnoea | | | |
| subjects affected / exposed | 11 / 58 (18.97%) | | |
| occurrences (all) | 12 | | |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 4 / 58 (6.90%) | | |
| occurrences (all) | 4 | | |
| Productive cough | | | |
| subjects affected / exposed | 3 / 58 (5.17%) | | |
| occurrences (all) | 3 | | |
| Psychiatric disorders | | | |
| Anxiety | | | |
| subjects affected / exposed | 4 / 58 (6.90%) | | |
| occurrences (all) | 4 | | |
| Confusional state | | | |
| subjects affected / exposed | 3 / 58 (5.17%) | | |
| occurrences (all) | 3 | | |
| Depression | | | |
| subjects affected / exposed | 4 / 58 (6.90%) | | |
| occurrences (all) | 4 | | |
| Insomnia | | | |
| subjects affected / exposed | 9 / 58 (15.52%) | | |
| occurrences (all) | 10 | | |
| Investigations | | | |

| | | | |
|---|--|--|--|
| Weight decreased subjects affected / exposed occurrences (all) | 8 / 58 (13.79%) 10 | | |
| Injury, poisoning and procedural complications Excoriation subjects affected / exposed occurrences (all) | 3 / 58 (5.17%) 3 | | |
| Cardiac disorders Tachycardia subjects affected / exposed occurrences (all) | 3 / 58 (5.17%) 3 | | |
| Nervous system disorders Dizziness subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all) Memory impairment subjects affected / exposed occurrences (all) Neuralgia subjects affected / exposed occurrences (all) Paraesthesia subjects affected / exposed occurrences (all) Peripheral motor neuropathy subjects affected / exposed occurrences (all) Peripheral sensory neuropathy subjects affected / exposed occurrences (all) | 9 / 58 (15.52%) 9 11 / 58 (18.97%) 15 3 / 58 (5.17%) 3 3 / 58 (5.17%) 5 5 / 58 (8.62%) 6 3 / 58 (5.17%) 4 24 / 58 (41.38%) 43 | | |
| Blood and lymphatic system disorders Anaemia | | | |

| | | | |
|----------------------------------|------------------|--|--|
| subjects affected / exposed | 5 / 58 (8.62%) | | |
| occurrences (all) | 6 | | |
| Lymphadenopathy | | | |
| subjects affected / exposed | 6 / 58 (10.34%) | | |
| occurrences (all) | 9 | | |
| Neutropenia | | | |
| subjects affected / exposed | 11 / 58 (18.97%) | | |
| occurrences (all) | 14 | | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 8 / 58 (13.79%) | | |
| occurrences (all) | 10 | | |
| Gastrointestinal disorders | | | |
| Abdominal distension | | | |
| subjects affected / exposed | 3 / 58 (5.17%) | | |
| occurrences (all) | 3 | | |
| Abdominal pain | | | |
| subjects affected / exposed | 5 / 58 (8.62%) | | |
| occurrences (all) | 5 | | |
| Constipation | | | |
| subjects affected / exposed | 12 / 58 (20.69%) | | |
| occurrences (all) | 12 | | |
| Diarrhoea | | | |
| subjects affected / exposed | 16 / 58 (27.59%) | | |
| occurrences (all) | 19 | | |
| Dyspepsia | | | |
| subjects affected / exposed | 5 / 58 (8.62%) | | |
| occurrences (all) | 5 | | |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 3 / 58 (5.17%) | | |
| occurrences (all) | 3 | | |
| Haemorrhoids | | | |
| subjects affected / exposed | 3 / 58 (5.17%) | | |
| occurrences (all) | 3 | | |
| Nausea | | | |
| subjects affected / exposed | 23 / 58 (39.66%) | | |
| occurrences (all) | 28 | | |

| | | | |
|---|------------------------|--|--|
| Oral pain subjects affected / exposed occurrences (all) | 5 / 58 (8.62%) 5 | | |
| Vomiting subjects affected / exposed occurrences (all) | 9 / 58 (15.52%) 11 | | |
| Skin and subcutaneous tissue disorders | | | |
| Alopecia subjects affected / exposed occurrences (all) | 8 / 58 (13.79%) 8 | | |
| Dermatitis subjects affected / exposed occurrences (all) | 4 / 58 (6.90%) 5 | | |
| Dry skin subjects affected / exposed occurrences (all) | 6 / 58 (10.34%) 10 | | |
| Night sweats subjects affected / exposed occurrences (all) | 4 / 58 (6.90%) 4 | | |
| Pruritus subjects affected / exposed occurrences (all) | 11 / 58 (18.97%) 12 | | |
| Rash subjects affected / exposed occurrences (all) | 14 / 58 (24.14%) 23 | | |
| Rash pruritic subjects affected / exposed occurrences (all) | 4 / 58 (6.90%) 6 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia subjects affected / exposed occurrences (all) | 5 / 58 (8.62%) 7 | | |
| Back pain subjects affected / exposed occurrences (all) | 5 / 58 (8.62%) 5 | | |
| Groin pain | | | |

| | | | |
|------------------------------------|------------------|--|--|
| subjects affected / exposed | 5 / 58 (8.62%) | | |
| occurrences (all) | 5 | | |
| Muscle spasms | | | |
| subjects affected / exposed | 8 / 58 (13.79%) | | |
| occurrences (all) | 9 | | |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 4 / 58 (6.90%) | | |
| occurrences (all) | 4 | | |
| Myalgia | | | |
| subjects affected / exposed | 9 / 58 (15.52%) | | |
| occurrences (all) | 10 | | |
| Neck pain | | | |
| subjects affected / exposed | 5 / 58 (8.62%) | | |
| occurrences (all) | 5 | | |
| Pain in extremity | | | |
| subjects affected / exposed | 6 / 58 (10.34%) | | |
| occurrences (all) | 6 | | |
| Infections and infestations | | | |
| Bronchitis | | | |
| subjects affected / exposed | 3 / 58 (5.17%) | | |
| occurrences (all) | 5 | | |
| Folliculitis | | | |
| subjects affected / exposed | 5 / 58 (8.62%) | | |
| occurrences (all) | 6 | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 3 / 58 (5.17%) | | |
| occurrences (all) | 4 | | |
| Sinusitis | | | |
| subjects affected / exposed | 4 / 58 (6.90%) | | |
| occurrences (all) | 4 | | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 11 / 58 (18.97%) | | |
| occurrences (all) | 14 | | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |

| | | | |
|-----------------------------|-----------------|--|--|
| subjects affected / exposed | 8 / 58 (13.79%) | | |
| occurrences (all) | 8 | | |
| Dehydration | | | |
| subjects affected / exposed | 3 / 58 (5.17%) | | |
| occurrences (all) | 3 | | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 3 / 58 (5.17%) | | |
| occurrences (all) | 3 | | |
| Hypokalaemia | | | |
| subjects affected / exposed | 5 / 58 (8.62%) | | |
| occurrences (all) | 5 | | |
| Hypomagnesaemia | | | |
| subjects affected / exposed | 3 / 58 (5.17%) | | |
| occurrences (all) | 3 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|--|
| 01 December 2008 | Increased sample size from 30 to 55 patients. CD30 assessment was to be centrally confirmed. Explained why no formal interim efficacy and/or futility analyses were planned. Specified how patients who do not have the correct histological cancer type will be handled in the analysis. |
| 13 February 2009 | Allowed patients 12 years or older to enroll at sites in Canada. Refined entry criteria to ensure that all patients have active relapsed or refractory systemic ALCL at study entry. Increased the time since immunotherapy before study entry to ensure any therapeutic benefit is realized. Added descriptions of interim analyses that may be conducted for scientific meetings and/or regulatory submissions. |
| 16 November 2009 | Allowed patients who have previously received treatment with non-anthracycline or anthracendione-based multi-agent chemotherapy regimens to enroll in the study provided they had received a frontline multi-agent chemotherapy regimen with curative intent. Removed the requirement for central pathology review to confirm CD30-positivity at the time of enrollment. Slides were to be submitted for central review prior to initiation of treatment with brentuximab vedotin. Clarified that prior treatments must have been completed in the protocol-specified timeframe unless patient was progressing on therapy. Updated baseline platelet and bilirubin requirements for patients with bone marrow and hepatic lymphoma involvement. Clarified that patients with active infections Grade 3 or higher are not eligible for the study. |
| 03 October 2011 | Added a section to the protocol regarding the management of suspected progressive multifocal leukoencephalopathy (PML). |
| 30 January 2012 | Revised the timing of assessments during the study follow-up period. |
| 10 October 2013 | Removed the requirement for CT scanning during the long-term follow-up period. CT scans will only be done if progression is suspected based on clinical signs and symptoms. Added a long-term follow-up questionnaire to be taken by patients who remain 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/22614995>