26 May 2016
EMA/CHMP/655943/2016 - adopted
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Invented name: Adcetris

International non-proprietary name: brentuximab vedotin

Procedure No. EMEA/H/C/002455/II/0025

Marketing authorisation holder (MAH): Takeda Pharma A/S

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List of abbreviations

ADC	Antibody drug conjugate
AE	Adverse event
ALCL	Anaplastic large cell lymphoma
ALT	Alanine aminotransferase
ARDS	Acute respiratory distress syndrome
ASCT	Autologous stem cell transplantation
AST	Aspartate aminotransferase
ATA	Anti-therapeutic antibody
BSC	Best supportive care
BV	Brentuximab vedotin
CI	Confidence interval
cHL	Classical Hodgkin lymphoma
CR	Complete remission
CT	Computed tomography
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
EQ-5D	European Quality of Life 5-Dimensional
EU	European Union
GCP	Good Clinical Practice
HR	Hazard ratio
HRS	Hodgkin and Reed-Sternberg
HL	Hodgkin lymphoma
INV	Investigator
IRF	Independent review facility
IRR	Infusion-related reaction
ITT	Intent-to-treat
IV	Intravenous
KM	Kaplan meier
LP	Lymphocyte predominant
MDS	Myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Affairs
MID	Minimally important difference
MMAE	Monomethyl auristatin E
MRU	Medical resource utilization
NLPHL	Nodular lymphocyte predominant Hodgkin lymphoma
OS	Overall survival
PCP	*Pneumocystis jiroveci* pneumonia
PD	Pharmacodynamic
PD	Progressive disease
PET	Positron emission tomography
PFS	Progression-free survival
PK	Pharmacokinetic
PML	Progressive multifocal leukoencephalopathy
PN	Peripheral neuropathy
PP	Per protocol
PR	Partial remission
QoL	Quality of life

SAE	Serious adverse event
sALCL	Systemic anaplastic large cell lymphoma
SAP	Statistical analysis plan
SD	Stable disease
SOC	System organ class
TEAE	Treatment-emergent adverse event
TSH	Thyroid stimulating hormone
TTO	Time trade off
ULN	Upper limit of normal
VAS	Visual analogue scale

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Takeda Pharma A/S submitted to the European Medicines Agency on 11 March 2015 an application for a variation.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of Indication to include the treatment of adult patients with Hodgkin Lymphona (HL) at increased risk of relapse or progression following autologous stem cell transplantation (ASCT). As a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet and the RMP (v.6.3) are updated in accordance.

In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet.

The requested variation proposed amendments to the Summary of Product Characteristics, Package Leaflet and to the Risk Management Plan (RMP).

Adcetris was designated as an orphan medicinal product EU/3/08/595 and EU/3/08/596 on 15 January 2009 in the indications systemic anaplastic large cell lymphoma (sALCL) and HL, respectively.

The new indication, which is the subject of this application, falls within the second of the above mentioned orphan designations.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0263/2014 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0263/2014 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products, because there is no authorised orphan medicinal product for a condition related to the proposed indication.

MAH request for additional market protection

The applicant requested consideration of its application in accordance with Article 14(11) of Regulation (EC) 726/2004 - one year of market protection for a new indication (see separate assessment report on this request).

Protocol assistance

The applicant sought Protocol assistance at the CHMP on April 2009. The scientific advice working party (SAWP) gave advice on the proposed target indication, the primary endpoint PFS, the assessment criteria, and the placebo + best supportive care control arm, that were all acceptable. However, the SAWP indicated that PFS data should be supplemented by OS data even if the trial is not specifically powered for the OS endpoint. Alternatively, PFS at a fixed time point (about 3 years, at plateau phase) may be of interest.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP and the evaluation teams were:

Rapporteur: Pieter de Graeff Co-Rapporteur: Jan Mueller-Berghaus

Timetable	Actual dates
Rapporteur's preliminary assessment report circulated on:	26 May 2015
CoRapporteur's preliminary assessment report circulated on:	26 May 2015
Joint Rapporteur's updated assessment report circulated on:	18 June 2015
Request for supplementary information and extension of timetable adopted by the CHMP on:	25 June 2015
MAH's responses submitted to the CHMP on:	19 August 2015
Joint Rapporteur's updated assessment report on the MAH's responses circulated on:	28 September 2015
Updated Rapporteur's assessment report circulated on:	16 October 2015
2nd Request for supplementary information and extension of timetable adopted by the CHMP on:	22 October 2015
MAH's responses submitted to the CHMP on:	29 January 2016
Joint Rapporteur's updated assessment report on the MAH's responses circulated on:	24 February 2016
Updated Rapporteur's assessment report circulated on:	24 March 2016
3rd Request for supplementary information and extension of timetable adopted by the CHMP on:	01 April 2016
MAH's responses submitted to the CHMP on:	05 April 2016
Joint Rapporteur's updated assessment report on the MAH's responses circulated on:	13 April 2016
SAG experts meeting to address questions raised by the CHMP (Annex 6)	14 April 2016
Updated Rapporteur's assessment report circulated on:	22 April 2016
An Oral explanation took place on:	26 April 2016
4th Request for supplementary information and extension of timetable	28 April 2016

Timetable	Actual dates
adopted by the CHMP on:	
MAH's responses submitted to the CHMP on:	04 May 2016
Joint Rapporteur's updated assessment report on the MAH's responses circulated on:	12 May 2016
CHMP opinion:	26 May 2016

2. Scientific discussion

2.1. Introduction

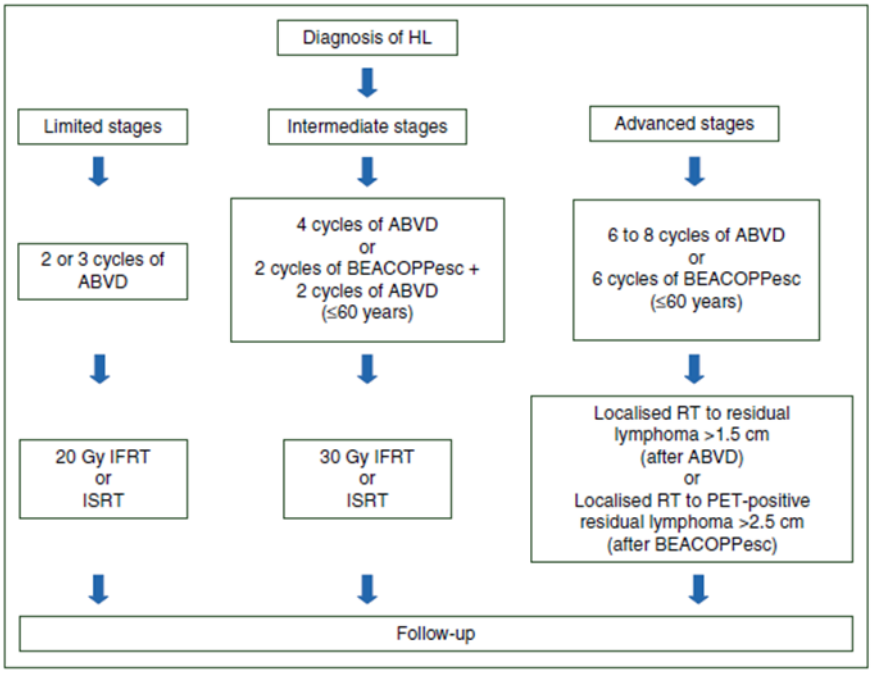
HL accounts for approximately 10 percent of all lymphomas. The incidence in Europe is approximately 2.4 cases per 100.000 persons. Young adults aged 20–40 years are most often affected; a second incidence peak is seen in individuals aged 55 and older. HL is characterized histologically by malignant Hodgkin and Reed Sternberg (HRS) cells that are surrounded by non-malignant inflammatory cells. HL is divided in two major subtypes: classical (cHL) and nodular lymphocyte predominant (NLPHL), based on immunohistological features and microscopic appearance of the malignant cells. The NLPHL subtype makes up 5% of all HL and has a generally more indolent course than cHL. Most, but not all NLPHL, are CD30 negative, whereas CD30 expression is a standard feature of HRS cells in cHL. Clinical symptoms are present in 2/3 of patients, and could include the presence of B symptoms (fever, night sweats, unexplained weight loss >10% in 6 months), fatigue, pruritus and alcohol-induced pain.

HL is highly curable, with 80% of patients reaching complete remission. Prognosis is worse in patients who present with advanced disease, with 30-40% relapse after initial treatment or immediate treatment failure. Staging is according to the Ann Arbor criteria, which are based on localisation, the extent of nodal and extranodal involvement and the presence of the classical B symptoms.

After diagnosis of HL, different chemotherapy and radiotherapy regimens are recommended, depending on the stage of the disease. According to the ESMO Clinical Practice guidelines[1], the following therapeutic algorithm can be used (Figure 1).

[1] Eichenauer DA, Engert A, André M, Federico M, Illidge T, Hutchings M, Ladetto M; ESMO Guidelines Working Group. Hodgkin's lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2014 Sep;25 Suppl 3:iii70-5.

Figure 1: Therapeutic algorithm for newly diagnosed Hodgkin's lymphoma



HL, Hodgkin's lymphoma; RT, radiotherapy; ABVD, adriamycin, bleomycin, vinblastine, dacarbazine; BEACOPPesc, bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine, procarbazine, prednisone escalated dose regimen; ISRT, involved-site radiotherapy; PET, positron emission tomography; NLPHL, nodular lymphocyte-predominant Hodgkin's lymphoma; IFRT, involved-field RT.

For most patients with refractory or relapsed HL after frontline therapy, the treatment of choice consists of high-dose chemotherapy followed by ASCT. Salvage regimens, such as dexamethasone/ high-dose Ara-C/ cisplatin (DHAP), ifosfamide/gemcitabine/vinorelbine (IGEV) or ifosfamide/ carboplatin/etoposide (ICE), are given to reduce the tumour burden and mobilize stem cells (often in combination with G-CSF) before high-dose chemotherapy and ASCT.

ASCT can provide a cure for approximately 50% of patients who are eligible for transplantation based on disease status and ability to tolerate the treatment. The 5-year event free survival (EFS) rates for patients with low-risk disease range from 65% to 80%, whereas the 5-year PFS rate for patients identified by different prognostic indexes as approximately 25% to 40% for moderate risk and 10% to 20% for high risk patients. Relapse or progression after ASCT generally occurs early; approximately 71% of progression events occurs within 1 year post-ASCT and 90% within 2 years post ASCT.

No established system of risk factors systematically guides clinicians to identify patients at risk of relapse or progression post-ASCT. It is accepted that multiple risk factors should be considered, including risk factors prior to ASCT. Risk factors repeatedly associated with a strong prognostic value include:

- History of HL refractory to frontline therapy or a short time to first relapse,
- Presence of extranodal disease pre-ASCT,
- Lack of chemo-responsiveness to pre-ASCT salvage therapy,
- Presence of residual disease at the time of ASCT,
- Presence of B symptoms at pre-ASCT relapse,
- Multiple relapses before ASCT,

and, more recently,

- FDG-PET positive disease pre-ASCT.

Most patients with relapsed or refractory HL who are not cured by ASCT will eventually die of their lymphoma. Historical outcomes for the approximately 50% of patients experiencing progressive disease post-ASCT are extremely poor, with a median post-progression survival of 1.3 years, and a 5-year survival rate of 20% or less. This indicates a need for new therapies for patients with relapsed or refractory HL, which might include patients at risk of disease progression post-ASCT. The relatively short EFS or PFS with intermediate or high risk disease indicates that these patients have residual viable lymphoma cells that have been insufficiently eradicated by ASCT. Consolidation, maintenance, or adjuvant therapy following ASCT may be an attractive approach for patients at increased risk of relapse or progression.

Brentuximab vedotin is a CD30-directed antibody-drug conjugate (ADC), that consists of the chimeric anti-human CD30 monoclonal antibody (cAC10) conjugated to the small molecule cytotoxic anti-tubulin agent MMAE by a protease-cleavable linker. Mechanistically, brentuximab vedotin acts by binding to the cell surface marker CD30, expressed on cells of several types of malignancy, including Hodgkin Lymhoma (HL). After binding to CD30 positive cells, brentuximab vedotin is internalized, and MMAE is released from the conjugate through proteolytic degradation of the drug linker. Released MMAE binds to the tubulin and leads to G2/M cell cycle arrest and cell death. CD30 expression on normal cells is rare (less than 1% of lymphoid cells), it's expressed on activated but not resting lymphocytes (T, B and NK cells) and weakly on activated monocytes.

The first marketing authorization for brentuximab vedotin in the EU was granted in October 2012. Brentuximab vedotin is currently approved for relapsed or refractory CD30+ HL following 1) autologous stem cell transplant (ASCT) or 2) following at least two prior therapies when ASCT or multi-agent chemotherapy is not a treatment option. In addition, brentuximab vedotin is indicated for the treatment of adult patients with relapsed or refractory systemic anaplastic large cell lymphoma (sALCL).

Brentuximab vedotin is formulated for intravenous administration as a 50 mg powder for concentrate for solution for infusion. The recommended dose is 1.8 mg/kg administered as an intravenous infusion over 30 minutes every 3 weeks.

The efficacy and safety of brentuximab vedotin regarding the currently approved indication in HL has been established based on an open-label, single arm, phase II study including 102 patients with relapsed or refractory HL. The overall response rate (ORR: CR+PR) per Independent Review Facility (IRF) assessment was 75% with single agent brentuximab vedotin, and tumour reduction was achieved in 94% of patients. Complete remission (CR) was 33%, and median overall survival was 40.5 months.

The use of brentuximab vedotin represents an option in patients relapsing after ASCT. Furthermore, reduced- intensity conditioning allogeneic stem cell transplantation (RIC-ASCT) can be considered in young, chemosensitive patients in good general condition who relapse after high-dose chemotherapy and ASCT. There are no approved therapies in the EU for the treatment of adult patients with HL at increased risk of relapse or progression following ASCT. The current standard of care is observation until disease progression or relapse.

Pursuant to Article 8(3), Directive 2001/83/EC, Takeda Pharma A/S submitted a Type II (C.I.6.a) variation to the European Medicines Agency for the following extension of the indication: "*ADCETRIS is indicated for the treatment of adult patients with HL at increased risk of relapse or progression following ASCT (see section 5.1)*". The proposed posology is similar to already approved indications.

The CHMP agreed to the following indication:

ADCETRIS is indicated for the treatment of adult patients with CD30+ HL at increased risk of relapse or progression following ASCT (see section 5.1).

Posology

For patients with HL at increased risk of relapse or progression following ASCT, ADCETRIS treatment should start following recovery from ASCT based on clinical judgment. These patients should receive up to 16 cycles (see section 5.1).

2.2. Non-clinical aspects

No new clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The clinical trials included in this dossier were performed in accordance with GCP as claimed by the applicant.

- Tabular overview of clinical studies

To support this variation application, the applicant has submitted data from one pivotal randomised, double blind, placebo controlled phase III study: AETHERA (Table 1). This study was designed to evaluate the efficacy and safety of brentuximab vedotin and best supportive care compared to placebo and best supportive care in the treatment of patients with HL at risk of disease progression following ASCT.

Table 1: Overview of Pivotal Study Details

Study Design Feature	Pivotal Study SGN35-005 (N = 329)
Design	Phase III, multi centre, randomised, double-blind, placebo controlled
Number of Sites and Countries	28 sites in the United States (US) and 50 sites in the European Union (EU), Russia, and Serbia
Study dates	Date first patient enrolled: 06-Apr-2010 (date first patient randomised) Date of last patient visit: 18-Aug-2014 (date last patient assessed for the primary analysis)
Planned and actual Enrollment	Planned: Approximately 322 patients (approximately 161 patients per treatment arm) Actual: 329 patients were randomised; 327 patients received study treatment
Gender (% M/F) **Median age (years) (Range)** **Race (%)**	53/47 32 (18, 76) White: 94%
Diagnosis incl. criteria	Eligible patients were to be ≥ 18 years, had histologically-confirmed classical HL, had received ASCT in the previous 30–45 days, and were at risk of disease progression post-ASCT as indicated by at least one of the following criteria: • History of refractory HL • Relapsed or progressive HL that occurred <12 months from the end of frontline standard chemotherapy or a combined modality treatment program • Extranodal involvement at the time of pre-ASCT relapse

Study Design Feature	Pivotal Study SGN35-005 (N = 329)
Treatment Regimen	Brentuximab vedotin (SGN-35; ADCETRIS®), 1.8 mg/kg, administered via outpatient IV infusion on Day 1 of each 21-day cycle. **or,** Placebo administered via outpatient IV infusion on Day 1 of each 21-day cycle.
Duration of Treatment	Planned: 16 cycles in both arms Median number of cycles was 15 in each arm.
Primary Study Objective	To compare the progression-free survival PFS) of brentuximab vedotin and best supportive care (BSC) versus placebo and BSC
Primary Efficacy Endpoint(s)	• PFS per independent review facility (IRF)
Secondary Efficacy Endpoints	• Overall survival (OS)
Other Efficacy Endpoints of Interest	• Medical resource utilization (MRU) based on the number of medical care encounters • Quality of Life (QoL) as measured by Utility instrument (EQ-5D) score

2.3.2. Pharmacokinetics

Brentuximab vedotin is indicated for the treatment of adult patients with relapsed or refractory CD30+ HL or with relapsed or refractory sALCL. In this procedure the applicant is applying for the treatment of adult patients with HL at increased risk of relapse or progression following ASCT. The recommended dose is 1.8 mg/kg administered as an intravenous infusion over 30 minutes every 3 weeks, which is the same dose regimen as for relapsed or refractory HL or sALCL.

Pharmacokinetics of brentuximab vedotin was not studied in the pivotal phase III study AETHERA. As the dosing regimen is identical and the intended target of CD30+ Hodgkin lymphoma also comparable, no differences in pharmacokinetics of brentuximab vedotin is expected. The incidence of anti-drug antibodies (ADA) was investigated and is presented in the safety section of this report.

2.4. Clinical efficacy

2.4.1. Main study

AETHERA trial (SGN35-005): 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)

Methods

Study participants

Table 2: Key Inclusion and Exclusion Criteria AETHERA Study

Inclusion criteria	Exclusion criteria
Histologically-confirmed classical HL, with ASCT in the previous 30-45 days	Previous treatment with brentuximab vedotin

Inclusion criteria	Exclusion criteria
At high risk of residual HL post-ASCT as indicated by at least one of the following criteria: - History of refractory HL - Relapsed or progressive HL that occurred <12 months from the end of frontline standard chemotherapy or a combined modality treatment program - Extranodal involvement at the time of pre-ASCT relapse	Patients who were determined to have a best clinical response of progressive disease with salvage treatment immediately prior to ASCT
≥ 18 years of age	Previous allogeneic transplant
ECOG performance status 0-1	History of another primary malignancy, that has not been in remission for at least 3 years.
	Known cerebral/meningeal disease, including history of progressive multifocal leukoencephalopathy (PML)
	Any grade 3 or higher active infection within 1 week prior to first study dose
- Absolute neutrophil count ≥1000/µL - Platelets ≥50.000/µL - Bilirubin ≤1.5xULN or ≤3xULN with Gilbert's disease - Serum creatinine ≤1.5xULN - ALT and AST ≤2.5xULN	Post-ASCT or current therapy with other systemic anti-neoplastic or investigational agents

Treatments

Patients were treated with brentuximab vedotin (SGN-35) with best supportive care or placebo and best supportive care.

Study treatment (brentuximab vedotin or placebo) was administered via outpatient IV infusion 1.8 mg/kg given over approximately 30 minutes on Day 1 of each 21-day cycle. Dose reductions to 1.2 mg/kg were allowed depending on the type and severity of toxicity. Doses reduced for treatment-related toxicity **c**ould not be re-escalated. The start of the next cycle could be delayed for up to 3 weeks if additional time was required for the patient to recover from study treatment-associated toxicity experienced during the current cycle.

Treatment duration and response assessment

Patients could continue study treatment for a maximum of 16 cycles or until disease progression (PD) or unacceptable toxicity, whichever occurred earlier.

Lymphoma progression was assessed using the Revised Response Criteria for Malignant Lymphoma. Computed tomography (CT) scans (chest, abdomen, and pelvis) were performed at screening/baseline and at 3, 6, 9, 12, 18, and 24 months from the first dose of study treatment.

Co-medication

Required concomitant therapy: Prophylaxis for herpes simplex virus, varicella-zoster virus, and Pneumocystis jiroveci pneumonia (PCP) after ASCT; and PCP prophylaxis for all patients on this study.

Prohibited concomitant therapy: Other anticancer treatment.

Cross-over

Patients who experienced progressive disease on study could receive subsequent therapy with brentuximab vedotin (in a clinical trial or by commercial supply in regions where the drug was approved) or other therapies.

Objectives

Primary objective
To compare the progression-free survival (PFS) of brentuximab vedotin and best supportive care (BSC) versus placebo and BSC.

Secondary objectives

- To compare overall survival (OS) between the two treatment arms
- To evaluate the safety and tolerability of brentuximab vedotin compared to placebo
- To characterize the incidence of anti-drug antibodies (ADA)

Exploratory objectives
To calculate utility values using a preference-based patient reported outcomes (PRO) instrument (European Quality of Life 5-Dimensional [EQ-5D]) and to evaluate medical resource utilization (MRU).

Outcomes / endpoints

Primary efficacy endpoint
The primary efficacy endpoint is PFS per an independent review facility (IRF). PFS analysis was performed in the intend-to-treat (ITT) population, using the Revised Response Criteria for Malignant Lymphoma. An adequate lymphoma progression assessment included diagnostic biopsy or radiographic assessment (CT of chest, abdomen and pelvis).

Secondary endpoints
The secondary efficacy endpoint is OS, based on the ITT population.

Exploratory endpoints

- Quality of Life (QoL), as measured by Utility Instrument (EQ-5D) score
- MRU based on the number of medical care encounters

Sample size

Approximately 202 PFS events (progression or death due to any cause) were originally planned for the primary efficacy analysis to detect a hazard ratio of 0.667 (18 months median PFS for brentuximab vedotin and BSC versus 12 months for placebo and BSC) using the log-rank test with 80% power and an overall one-sided alpha level of 0.025. The assumed median PFS of the placebo and BSC group were based on long-term results of ASCT for primary refractory or relapsed HL[2] .

With protocol amendment 6, the timing of the primary efficacy analysis was changed to be performed when all scheduled study radiographic progression assessments were completed. Approximately 161 events were projected at the time of the amendment, which would provide 73% power to detect an HR of 0.667 using the log-rank test with an overall one-sided alpha level of 0.025.

[2] Majhail NS, Weisdorf DJ, Defor TE, Miller JS, McGlave PB, Slungaard A, Arora M, Ramsay NK, Orchard PJ, MacMillan ML and Burns LJ (2006). Long-term results of autologous stem cell transplantation for primary refractory or relapsed Hodgkin's lymphoma. Biol Blood Marrow Transplant 12: 1065-72.

Randomisation

Patients were randomised in a 1:1 ratio. The randomization was to be stratified by:

- Best clinical response per the Revised Response Criteria for Malignant Lymphoma obtained after the completion of salvage therapy prior to ASCT, as assessed by the investigator:
    - Complete remission (CR)
    - Partial remission (PR)
    - Stable disease (SD)
- Refractory/relapsed status after the end of frontline standard chemotherapy or a combined modality treatment program:
    - Any refractory HL
    - Relapsed HL that occurs <12 months after the end of front-line standard chemotherapy therapy
    - Relapsed HL that occurs ≥12 months after the end of front-line standard chemotherapy therapy

Blinding (masking)

The pivotal study was double-blinded.

Statistical methods

Analysis sets

The primary population for efficacy analysis was the intent to treat (ITT) population, which included all randomised patients. The per-protocol analysis set included all randomised patients who were randomised, received at least one dose of assigned treatment and did not have major protocol deviations. This analysis set was used for secondary analysis of efficacy endpoints.

Analysis methods

The primary statistical hypothesis can be expressed in terms of the hazard ratio λ_{SGN-35} / $\lambda_{Placebo}$ where λ_{SGN-35} represents the hazard of progression on the brentuximab vedotin arm (SGN-35) and $\lambda_{Placebo}$ represents the hazard of progression on the placebo arm. A hazard ratio < 1 indicates that the duration of PFS is prolonged for patients on the brentuximab vedotin arm compared with patients on the placebo arm.

The null and alternative hypotheses can be written respectively as:

H0 = λ_{SGN-35} / $\lambda_{Placebo} \geq 1$

HA = λ_{SGN-35} / $\lambda_{Placebo} < 1$

The statistical hypotheses of OS are similar to that of PFS.

Multiplicity

A fixed sequential testing procedure was used to test between PFS and OS such that OS was tested only if the test of PFS was statistically significant. If the test for the primary analysis of PFS was statistically significant in favour of the brentuximab vedotin and BSC group at a one-sided alpha level of 0.025, a formal statistical test was performed for OS at an overall one-sided alpha level of 0.025.

Interim analysis

One interim analysis of futility based on PFS was planned (101 events in the ITT analysis). Early stopping of the trial due to overwhelming efficacy was not planned.

An interim analysis of OS was performed at the time of the primary analysis of PFS with a fixed one-sided p-value of 0.008. This alpha level is based on an O'Brien-Fleming boundary with the estimated information expected to be available at the time of the interim analysis. The final analysis of OS will be tested at a one-sided 0.017 level, ensuring an overall one sided 0.025 alpha level. If the test for primary analysis of PFS would not have been statistically significant, the p-value of the test for OS would not have been calculated, but the point estimate for the hazard ratio and the corresponding 95% confidence interval will be provided and considered descriptive.

Primary efficacy endpoint analysis

PFS was defined as the time from randomization to first documentation of disease progression (PD) by the independent review facility (IRF) or to death due to any cause, whichever comes first. The primary analysis was based on the ITT analysis set using a stratified log-rank test at one-sided alpha level of 0.025. In addition, a stratified Cox regression model was used to estimate the hazard ratio and the corresponding 95% CI for the treatment effect. If the proportional hazard assumption with the Cox regression model was violated, a parametric survival analysis may have been performed. Kaplan-Meier plots were provided by treatment group. The median PFS and its two-sided 95% CI for the median and 3-month intervals were calculated using the complementary log-log transformation method. Percentage of PFS at various time intervals (e.g., every 6 months) were also calculated using the Kaplan-Meier estimate.

Secondary Analyses of PFS used the same censoring method for the primary PFS analysis: PFS per Investigator on ITT; PFS per IRF – Unstratified Analysis; PFS per Investigator – Unstratified Analysis; PFS per IRF – Per Protocol Analysis Set.

Sensitivity analyses of PFS used alternative censoring methods, statistical tests and analysis sets: PFS per IRF – only censoring and events at scheduled visit dates based on ITT; PFS per Investigator – only censoring and events at scheduled visit dates based on ITT; PFS per Investigator – Including Investigator Claim of Progression as an event on ITT; PFS per IRF Based on EMA Guideline on the Evaluation of Anticancer Medicinal Products in Man, 2012, Appendix 1 (Methodological Considerations for Using Progression-free Survival or Disease-free Survival in Confirmatory Trials); PFS per IRF – Subsequent New Antitumor Therapy Considered an Event on ITT; PFS per Investigator – Subsequent New Antitumor Therapy Considered an Event on ITT.

Censoring rules for PFS

If PD is not documented and the patient is alive at the time of the data cut off or study withdrawal, whichever occurred first, PFS was censored as described in Table 3.

Table 3: Primary PFS Analysis (includes documented progression only)

Situation	Date of Progression or Censoring	Outcome
No adequate baseline tumor assessments	Date of randomization	Censored
Progression documented at scheduled visit	Date of documented progression	Event
Progression documented between scheduled visits	Date of documented progression	Event
No progression through end of study or patient withdrawal	Date of last visit with adequate assessment	Censored
No post-baseline tumor assessments	Date of randomization	Censored
Treatment discontinuation for undocumented progression	Date of last visit with adequate assessment	Censored
Treatment discontinuation for toxicity or other reason	Date of last visit with adequate assessment	Censored
New anti-cancer treatment started without prior progression	Date of last visit with adequate assessment prior to start of anti-cancer treatment	Censored
Documented progression after initiation of new anti-cancer treatment	Date of last visit with adequate assessment prior to start of anti-cancer treatment	Censored
Death before first tumor assessment	Date of death	Event
Death between adequate assessment visits	Date of death	Event
Death without prior progression	Date of death	Event
Death or progression documented after more than one consecutively missed visit	Date of last visit with adequate assessment prior to missed visits	Censored
Investigator claim of clinical progression including physical examination post month 24 visits	Date of last visit with adequate assessment	Censored

PFS per IRF based on the ITT analysis set was also defined based on the European Medicines Agency guideline (EMA Guideline on the Evaluation of Anticancer Medicinal Products in Man, 2012, Appendix 1: Methodological Considerations for Using Progression-free Survival or Disease-free Survival in Confirmatory Trials). The censoring/event method is presented in Table 4.

Table 4: PFS Based on EMA Guideline

Situation	Date of Progression or Censoring	Outcome
No adequate baseline tumor assessments	Date of randomization	Censored
Progression documented at scheduled visit	Date of documented progression	Event
Progression documented between scheduled visits	Date of documented progression	Event
No progression through end of study or patient withdrawal	Date of last visit with adequate assessment	Censored
No post-baseline tumor assessments	Date of randomization	Censored
Treatment discontinuation for undocumented progression	Date of last visit with adequate assessment	Censored
Treatment discontinuation for toxicity or other reason	Date of last visit with adequate assessment	Censored
New anti-cancer treatment started without prior progression	Date of last visit with adequate assessment	Censored
Death or documented progression after initiation of new anti-cancer treatment	Date of death or documented progression	Event
Death before first tumor assessment	Date of death	Event
Death between adequate assessment visits	Date of death	Event
Death without prior progression	Date of death	Event
Death or progression documented after more than one consecutively missed visit	Date of death or documented progression	Event
Investigator claim of clinical progression including physical examination post month 24 visits	Date of last visit with adequate assessment	Censored

Secondary endpoint analysis

The primary analysis of overall survival (OS) was based on the ITT analysis set. Overall survival was defined as the time from randomization to date of death due to any cause. The primary analysis of OS was the stratified log-rank test using the randomised stratification factors. In addition, a stratified Cox regression model was used to estimate the hazard ratio and the corresponding 95% CI for the treatment effect. In the absence of confirmation of death, OS was censored at the last date the patient is known to be alive.

Secondary analyses of OS: Unstratified analysis (unstratified log-rank test and an un-stratified Cox regression model for the hazard ratio) and a PP analysis.

Analysis adjusting for crossing-over: Patients who experience progressive disease on study were allowed to request unblinding and could have received subsequent therapy with brentuximab vedotin (on a clinical trial or commercial supply in regions where the drug is approved) or other therapies. This issue may potentially confound the overall survival analysis. To deal with this, a sensitivity analyses of OS using rank preserving structural failure time models (RPSFT) was conducted using unvalidated R software. Procedural controls will be in place for verification of the results. An exploratory analysis of OS using the Inverse probability of censoring weighted (IPCW) method was conducted.

Missing data handling

Patients with missing values of a variable other than the time-to-event endpoints (PFS and OS via censoring rules) and QoL endpoints were excluded from the analysis or summary of that endpoint. Missing data is imputed for:

- Missing or partial dates of AE onset and end dates
- Incomplete date of initiation of first new cancer-related therapy in long-term follow-up: the date was imputed to the last day of the month if only the day is missing, otherwise not.
- QoL analysis: EQ-5D TTO index scores was imputed at EOT and 3-month intervals through month 24 for all patients who were either still on study at the expected time-point or off-study for reason of death. Visits for patients who were last known to be alive were imputed using last observation carried forward (LOCF), while visits for patients who had died within or prior to a one-week window of the expected visit date were imputed as zero. Visits where the EQ-5D was partially completed had the index score imputed as if the entire visit was missing.

Post-hoc analyses: efficacy analyses by risk groups

Numerous factors have been associated with increased risk status; of these, 3 were selected as AETHERA inclusion criteria on the basis of multiple literature reports available at the time the study was designed and their feasibility for collection in the study:

- History of refractory HL (defined as patients progressing on or failing to achieve a complete remission following frontline standard chemotherapy or a combined modality treatment program)
- Relapsed or progressive HL that occurs <12 months from the end of frontline standard chemotherapy or a combined modality treatment program
- Extranodal involvement at the time of pre-ASCT relapse (including extranodal extension of nodal masses into adjacent vital organs)

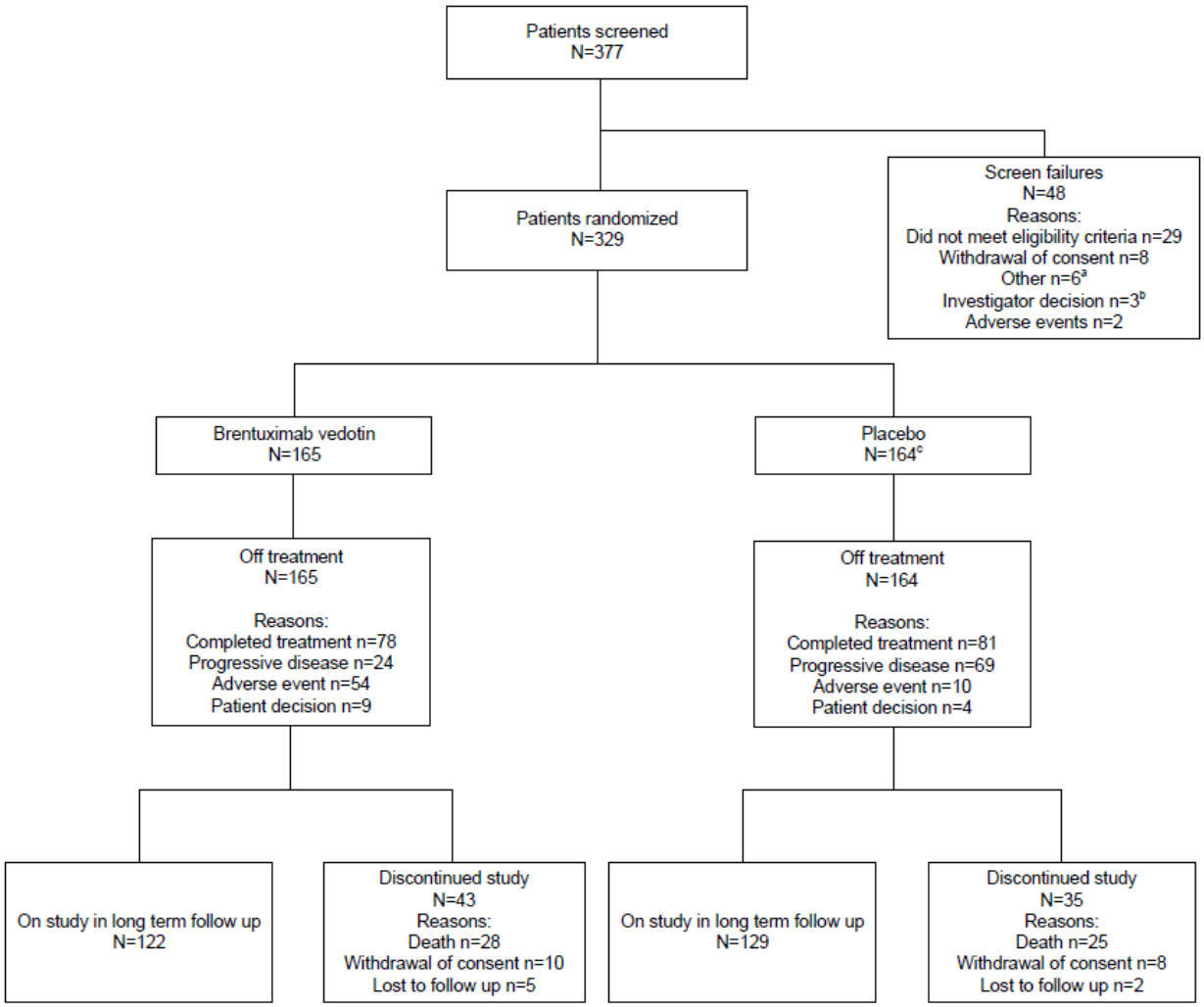
Patients eligible for AETHERA were to have had at least 1 of these conditions. A 5-factor analysis was explored and these inclusion criteria and other representative and important risk factors were assessed in the full study population:

5 Risk Factors Used in Subgroup Analyses

- Relapsed <12 months or refractory to frontline therapy
- Best response of PR or SD to most recent salvage therapy
- Extranodal disease at pre-ASCT relapse
- B symptoms at pre-ASCT relapse
- Two or more prior salvage therapies

Results

Participant flow



Source: Table 14.1.2, Table 14.1.1.3, and Listing 16.2.3.1

a Other reasons were lack of documented response to prior therapies (n=2), absence of post-salvage CT scans/exams (n=2), and radiographic evidence of progressive disease (n=2).

b Including 1 patient who had radiographic evidence of progressive disease.

c Two patients who were randomized to receive placebo withdrew consent prior to receiving any treatment. Two additional patients who were randomized to receive placebo each received one dose of brentuximab vedotin because of clinical site staff error.

Recruitment

First patient enrolled: 06-Apr-2010 (date first patient randomised).

Last patient assessed for primary analysis: 18-Aug-2014.

Conduct of the study

Study protocol amendments

The original study protocol was dated 21 April 2009 and was subsequently amended 6 times. The major changes were as follows:

Protocol amendment 1 (21 Oct 2009, 0 patients enrolled)

- Sample size increased to 322 patients to enable detection of a HR of 0.667.
- More frequent CT scanning and lymphoma assessments incorporated.
- Investigator assessment of response to prior salvage therapy added as stratification factor.

Protocol amendment 2 (16 Aug 2010, 17 patients enrolled)

- Administration of EQ-5D health questionnaire and MRU data added.
- Addition of recommendation that patients with Grade 2 neuropathy were to resume treatment at 1.2 mg/kg.
- Extension of follow up period for events of peripheral neuropathy and other AEs of interest beyond 30 day post-treatment.

Protocol amendment 3 (3 Oct 2011, 186 patients enrolled)

- Clarification of eligibility criteria to exclude patients with PML.

Protocol amendment 4 (29 Nov 2011, 206 patients enrolled)

- Revision safety section to a.o. better define subcategories of AEs.

Protocol amendment 5 (7 Jun 2012, 290 patients enrolled)

- The procedure for emergency unblinding was revised.

Protocol amendment 6 (13 Dec 2013, 329 patients enrolled)

- The timing of the primary efficacy analysis was changed to occur after all study scheduled CT scans had been performed. The sponsor considered it unlikely, after analysis of blinded pooled PFS data, that the originally planned 202 progression events would be observed in the study. At the time of amendment, all patients had been off therapy for at least one year.

Protocol compliance

Of the 329 patients randomised in the study, 69 (21%) had a protocol violation: 39 patients (24%) in the brentuximab vedotin arm and 30 (18%) in the placebo arm. The main reason for protocol violation in both arms was study conduct (9%) and drug administration (7%). Study conduct violations mainly were randomization stratification errors or missed radiographic assessments/visits, both at similar frequencies in the two arms. The majority of the study drug administration violations (17 of 23 patients) were because dose adjustments were not performed per protocol for weight changes greater than 10% from baseline or because of dose miscalculations by site staff. The remaining 6 patients who had study drug administration violations did not receive the correctly assigned study drug kits in one cycle (3 patients in each treatment arm).

Baseline data

Patient demographics and disease characteristics are presented in the following tables.

Table 5: Patient Demographics and Baseline Characteristics – Study SGN35-005

	Placebo (N=164)	Brentuximab Vedotin (N=165)	Total (N=329)
Age (years)			
n	164	165	329
Mean (STD)	33.5 (11.4)	35.6 (12.0)	34.6 (11.7)
Median	32.0	33.0	32.0
Min, Max	18, 76	18, 71	18, 76
Gender, n (%)			
Male	97 (59)	76 (46)	173 (53)
Female	67 (41)	89 (54)	156 (47)
Race, n (%)			
Asian	3 (2)	2 (1)	5 (2)
Black or African American	2 (1)	10 (6)	12 (4)
White	156 (95)	153 (93)	309 (94)
Other	3 (2)	0	3 (1)
ECOG Performance Status, n (%)			
0	97 (59)	87 (53)	184 (56)
1	67 (41)	77 (47)	144 (44)
2a	0	1 (1)	1 (0)

a Patient had an ECOG performance status of 1 at the time of randomization, which worsened to an ECOG performance status of 2 prior to the first dose of study treatment

Table 6: Baseline Disease Characteristics - Study SGN35-005

	Placebo (N=164)	Brentuximab Vedotin (N=165)	Total (N=329)
Time from HL diagnosis to first dose (months)			
n	162	165	327
Mean (STD)	24.57 (21.02)	24.95 (21.33)	24.76 (21.14)
Median	18.84	18.66	18.73
Min, Max	7.4, 180.8	6.1, 204.0	6.1, 204.0
Stage at initial diagnosis of HL, n (%)			
Stage I	5 (3)	1 (1)	6 (2)
Stage II	61 (37)	73 (44)	134 (41)
Stage III	45 (27)	48 (29)	93 (28)
Stage IV	51 (31)	43 (26)	94 (29)
Unknown	2 (1)	0	2 (1)
Bone marrow lymphoma involvement after failure of frontline therapy[a]	6 (4)	6 (4)	12 (4)
B symptoms after failure of frontline therapy[a]	40 (24)	47 (28)	87 (26)
Extranodal involvement at pre-ASCT relapse	53 (32)	54 (33)	107 (33)
PET status prior to ASCT, n (%)			
FDG-avid	51 (31)	64 (39)	115 (35)
FDG-negative	57 (35)	56 (34)	113 (34)
Not done[b]	56 (34)	45 (27)	101 (31)

a For refractory disease, or upon progression or relapse after frontline therapy
b Pre-ASCT FDG-PET scans were not required per protocol

Table 7: Prior Cancer-Related Therapies - Study SGN35-005

	Placebo (N=164) n (%)	Brentuximab Vedotin (N=165) n (%)	Total (N=329) n (%)
Any prior cancer-related systemic frontline therapy, n (%)	164 (100)	165 (100)	329 (100)
Prior cancer-related systemic frontline therapies, n (%)			
ABVD	129 (79)	119 (72)	248 (75)
BEACOPP[a]	20 (12)	26 (16)	46 (14)
Other[b]	15 (9)	20 (12)	35 (11)
Best response achieved with prior cancer-related systemic frontline therapy regimens, n (%)			
Complete response	58 (35)	59 (36)	117 (36)
Partial response	52 (32)	55 (33)	107 (33)
Stable disease	15 (9)	14 (8)	29 (9)
Progressive disease	38 (23)	36 (22)	74 (22)
Unknown	1 (1)	1 (1)	2 (1)
Number of prior cancer-related systemic salvage therapies per patient, n (%)			
n	164	165	329
Mean (STD)	1.7 (1.0)	1.8 (1.1)	1.7 (1.1)
Median	1.0	1.0	1.0
Min, max	1, 6	1, 7	1, 7
Best response achieved with the most recent prior cancer-related systemic salvage therapy, n (%)			
Complete response	70 (43)	67 (41)	137 (42)
Partial response	56 (34)	56 (34)	112 (34)
Stable disease	38 (23)	42 (25)	80 (24)
Number of patients with >1 prior ASCT, n (%)	10 (6)	5 (3)	15 (5)
Time from ASCT to first dose of study treatment (days)			
n	162	165	327
Mean (STD)	40.1 (4.1)	39.8 (3.9)	40.0 (4.0)
Median	41.0	41.0	41.0
Min, max	30, 51	28, 49	28, 51

BEACOPP: bleomycin, etoposide, adriamycin, cyclophosphamide, oncovin, procarbazine, and prednisone
ABVD: adriamycin, bleomycin, vinblastine, and dacarbazine
a Includes BEACOPP standard and escalated
b Includes combinations of ABVD and/or BEACOPP and other regimens

Numbers analysed

Primary and secondary efficacy analyses were based on the ITT analysis set, defined as all 329 randomised patients (165 patients in the Brentuximab vedotin arm and 164 in the Placebo arm).

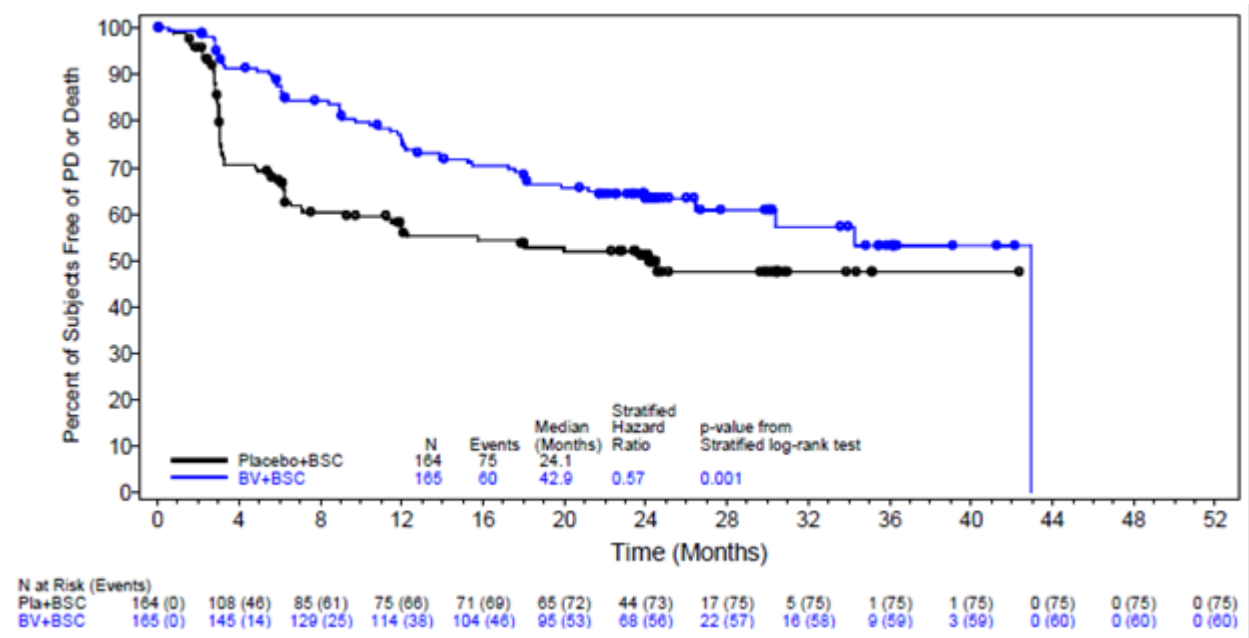
Efficacy endpoints were also analysed using the per-protocol (PP) analysis set, which included 258 patients; (126 patients brentuximab vedotin and 132 placebo). The PP population was comprised of all randomised patients receiving at least one dose of assigned treatment and without major protocol deviations.

Outcomes and estimation

Primary endpoint - Progression free survival

The PFS follow up from randomization approximately 22 months. The median PFS per IRF in the ITT population was 42.9 months (95% CI 30.4, 42.9) in the brentuximab vedotin arm compared with 24.1 months (95% CI 11.5, -) with placebo, indicating a 18.8 month difference in favour of brentuximab vedotin. The difference between the two arms was statistically significant (p=0.001; stratified log rank test). The estimated 24-month PFS rate was 63% (brentuximab vedotin) vs 50% (placebo). As assessed by Cox regression analysis, the stratified hazard ratio was 0.57 (95% CI 0.4, 0.8; Figure 2).

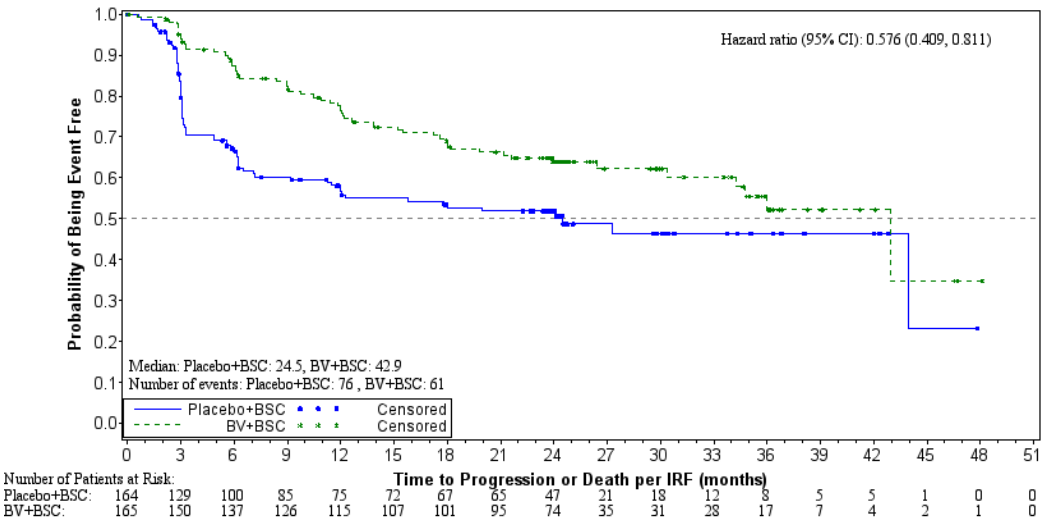
Figure 2: Kaplan-Meier Analysis of Progression-free Survival per IRF (ITT Population) September 2014 analysis - Study SGN35-005



The number of patients censored for the primary analysis was higher in the brentuximab vedotin arm (64%) compared with the placebo arm (46%), mainly caused by a higher percentage of patients without documented progression, still on study in the brentuximab vedotin arm (56% vs 42% placebo).

Since 2014, independent review reported 2 PFS events; investigators reported 5 PFS events. The PFS event velocity has slowed such that 95% of events detected as of October 2015 per investigator and 94% of events detected as of October 2015 per IRF occurred within the first 25 months (Figure 3).

Figure 3: Kaplan-Meier Analysis of Progression-free Survival per IRF (ITT Population) October 2015 analysis - Study SGN35-005



BSC=best supportive care, BV=brentuximab vedotin, IRF=independent review facility, ITT=intent-to-treat.

Secondary analyses of PFS

PFS per IRF – Per Protocol population

The median PFS per IRF in the PP population was not met in the brentuximab vedotin arm (95% CI 30.4,-) compared with 17.8 months (95% CI 6.5,-) with placebo. The stratified hazard ratio was 0.45 (0.30, 0.68), supporting the primary PFS analysis per IRF in the ITT population.

PFS per IRF using EMA censoring guidelines

A sensitivity analysis was conducted using censoring rules defined in the EMA scientific guideline, which disregards missed visits or initiation of new anticancer treatment for the purposes of censoring. By this analysis, the median PFS per IRF was 39.9 months in the brentuximab vedotin arm, versus 24.1 months in the placebo arm. The stratified HR was 0.55 (95% CI 0.39, 0.77).

PFS per investigator

The median PFS per investigator in the ITT population was not met in the brentuximab vedotin arm (95% CI 26.4,-) compared with 15.8 months (95% CI 8.5, -) with placebo. The estimated 24-month PFS rate was 65% (brentuximab vedotin) vs 45% (placebo). As assessed by Cox regression analysis, the stratified hazard ratio was 0.50 (95% CI 0.36, 0.70; Figure 5). Assessment of PD (yes/no) was discordant between IRF and investigator assessment for 11% in the brentuximab vedotin arm and 15% in the placebo arm.

Figure 4: Kaplan-Meier Analysis of Progression-free Survival per IRF (ITT Population) October 2015 analysis - Study SGN35-005

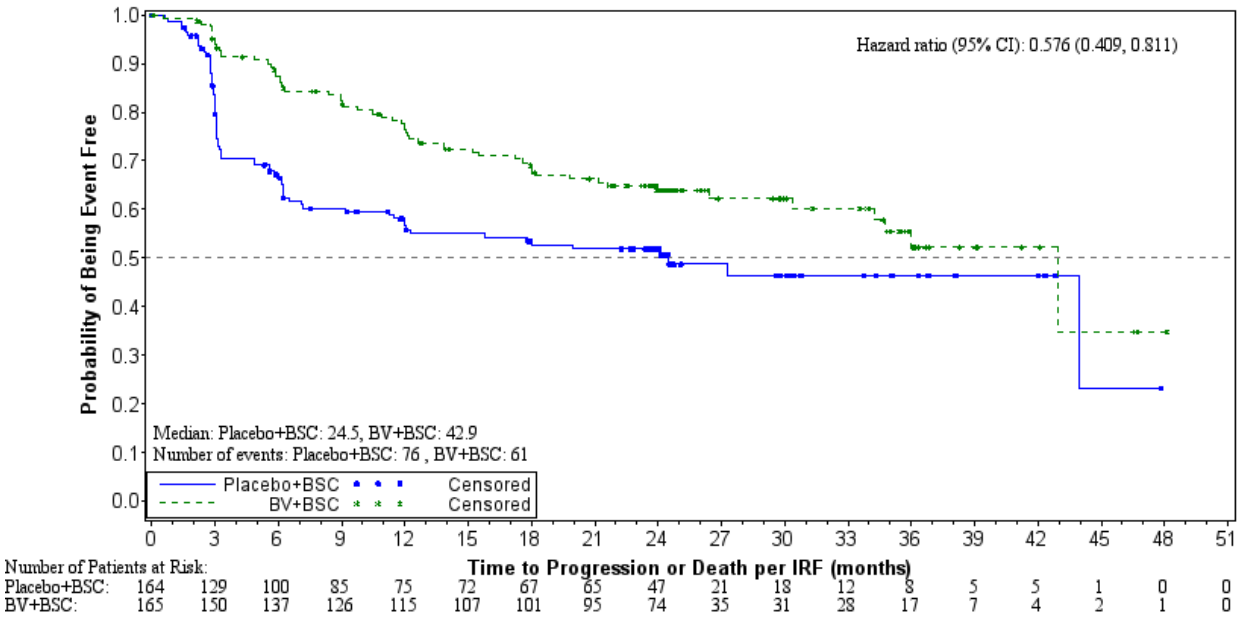
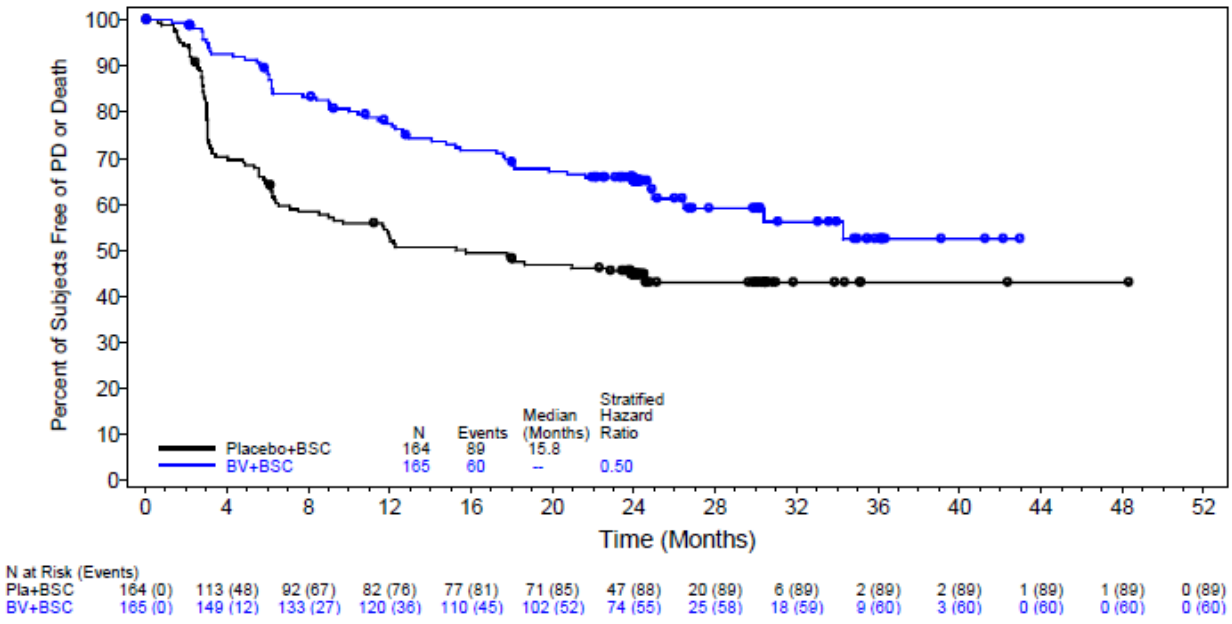


Figure 5: Kaplan-Meier Analysis of Progression-free Survival per IRF (ITT Population) September 2014 analysis - Study SGN35-005



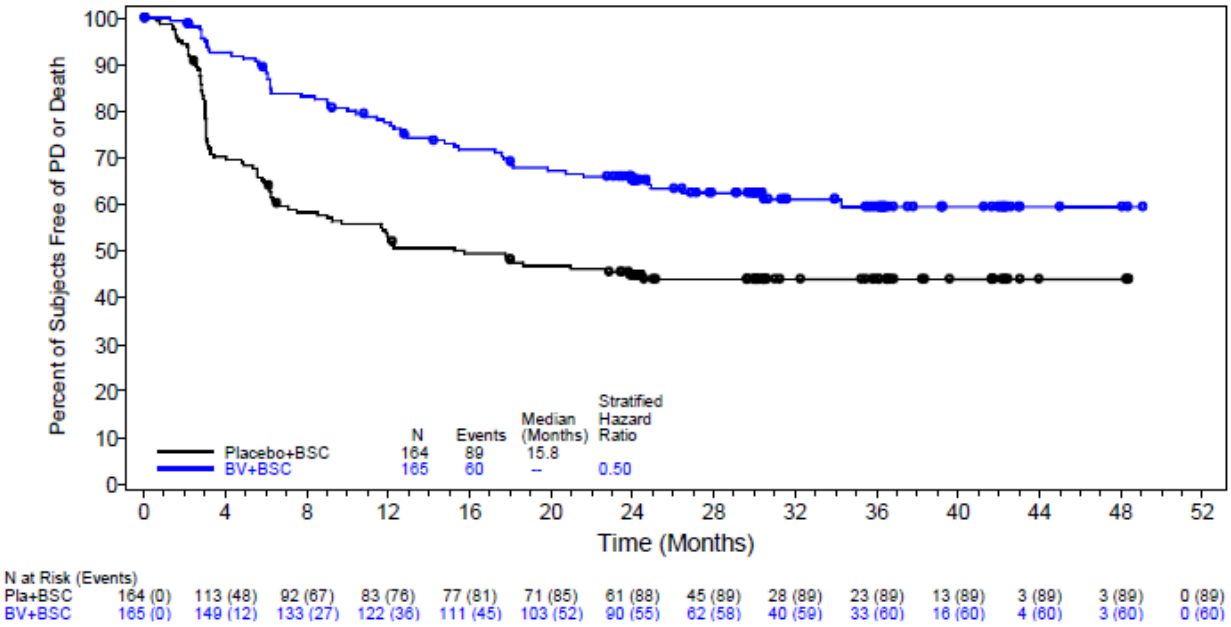
BSC=best supportive care, BV=brentuximab vedotin, IRF=independent review facility, ITT=intent-to-treat.

PFS per investigator including clinical lymphoma assessments

The majority of patients had no radiographic assessments after the last protocol mandated CT scan at 24 months and were therefore censored at this time for analysis of PFS per IRF. Although CT scans were not required after 24 months, clinical lymphoma assessments continued to be performed every 6 months by investigators for patients who had not yet progressed. A secondary PFS analysis was performed including these clinical lymphoma assessments for defining events of progression. By this analysis, the median PFS

for the brentuximab vedotin arm was not reached (95% CI -,-), compared with 15.8 months (95% CI 8.5, -) in the placebo arm. The stratified HR was 0.5 (95% CI 0.36-0.70; Figure 6).

Figure 6: PFS per Investigator Including Clinical Lymphoma Assessments - Study SGN35-005



Secondary endpoint - Overall survival

At the time of analysis, the survival follow up was immature: the median OS was not reached for patients in either treatment arm.

At the time of the PFS analysis an interim analysis of OS was performed, showing no difference between the treatment arms (HR 1.15 (95% CI 0.67, 1.97; p=0.620;Figure 7)). A total of 28 patients (17%) in the brentuximab vedotin arm and 25 patients (15%) in the placebo arm had died, and the estimated 24-month OS rate was 88% (brentuximab vedotin) vs. 89% (placebo).

Figure 7: Kaplan-Meier Analysis of Overall Survival (ITT Population) September 2014 analysis – updated - Study SGN35-005

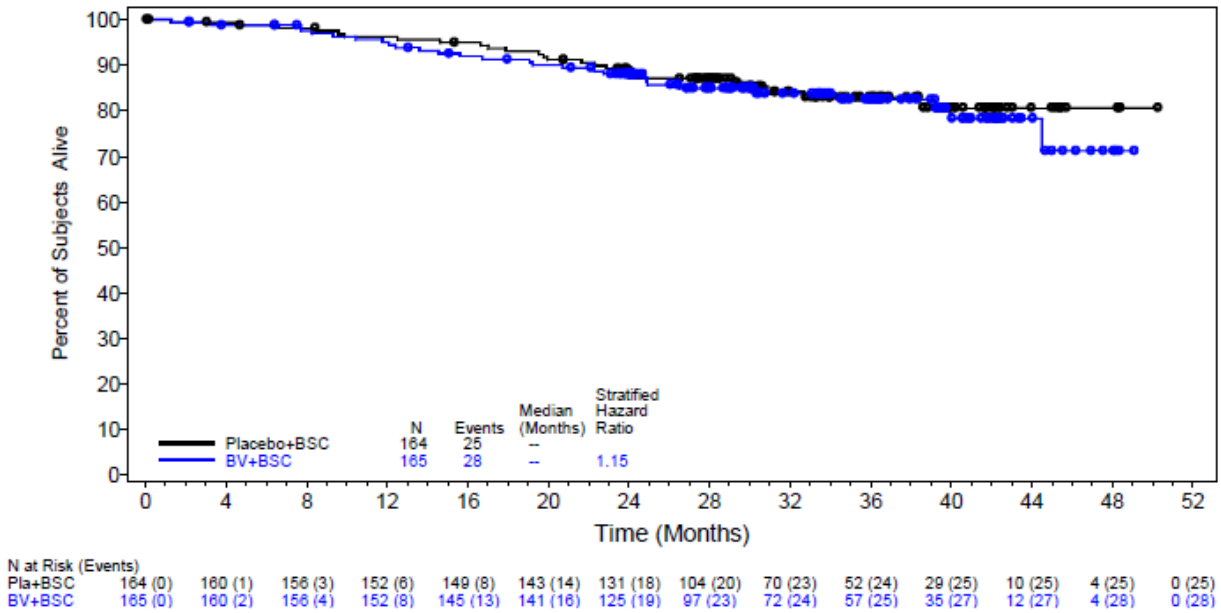
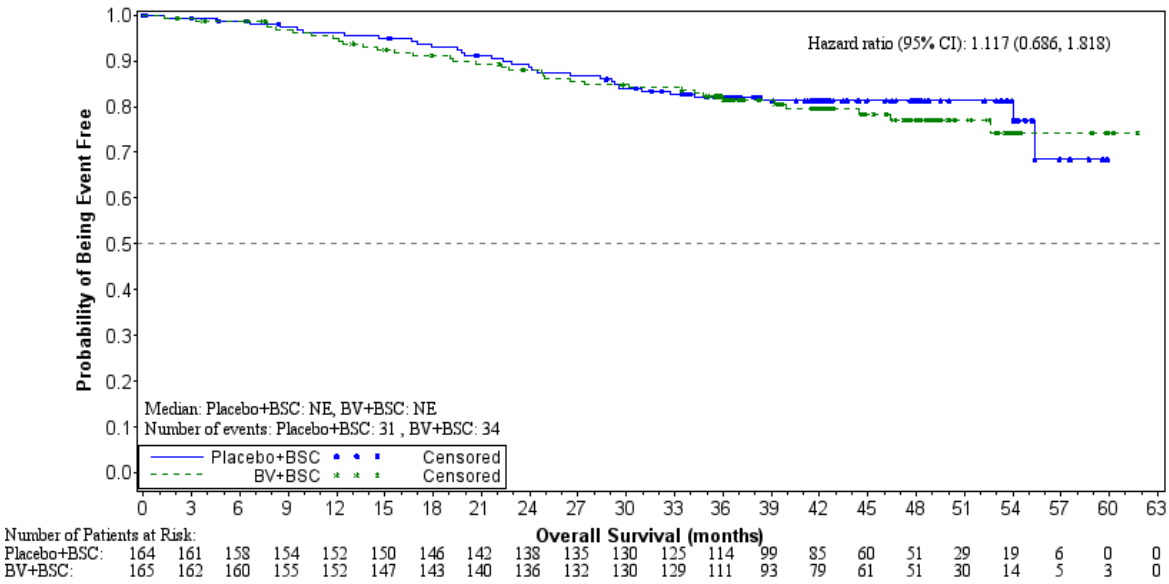


Figure 8: Kaplan-Meier Analysis of Overall Survival (ITT Population) October 2015 analysis – updated - Study SGN35-005



BSC=best supportive care, BV=brentuximab vedotin, ITT=intent-to-treat.

Exploratory endpoint - Quality of life

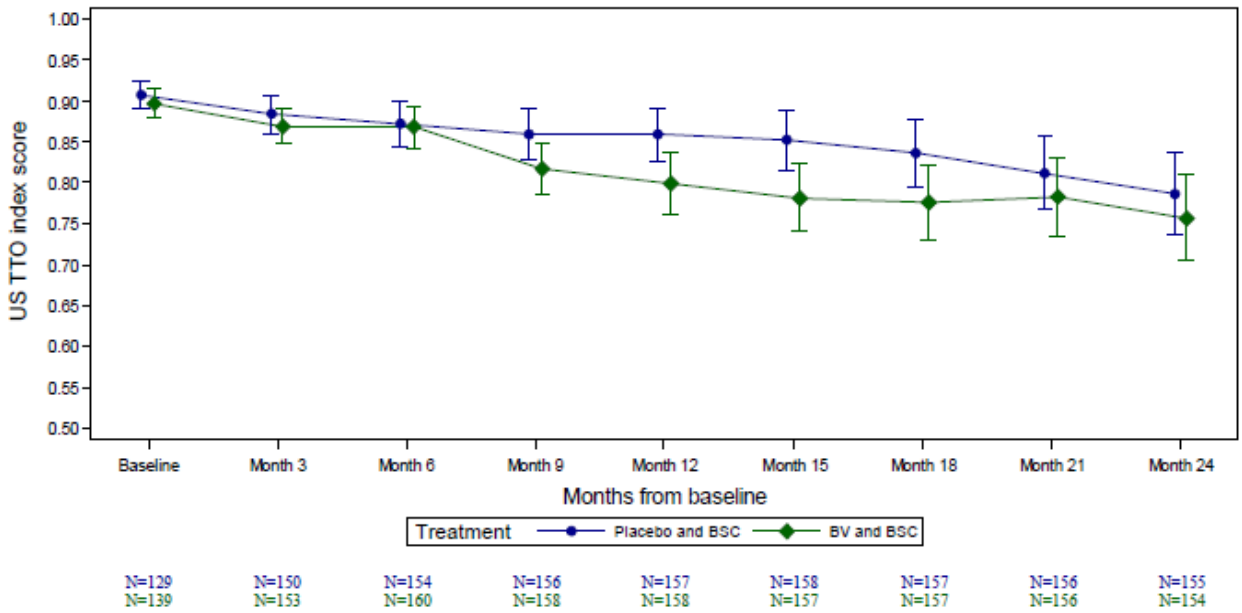
Quality of life was measured using a preference-based patient reported instrument: European Quality of Life 5-Dimensional [EQ-5D].

Adherence rates for completion of the self-report questionnaire were generally high throughout the study and completion rates were similar between the 2 treatment arms at all stages of the trial.

A small but progressive decline in TTO index scores in both treatment arms was observed from baseline to Month 24 (Figure 9) when death was inputed. When death is not imputed, TTO scores are stable over time (data not shown). Scores on the brentuximab vedotin treatment arm were slightly lower than those on the placebo arm from Months 9 to 18. Mean differences in EQ-5D TTO index scores (US- and UK-

value sets) generally did not exceed the minimally important difference (MID) between treatment arms, except for months 15 and 18.

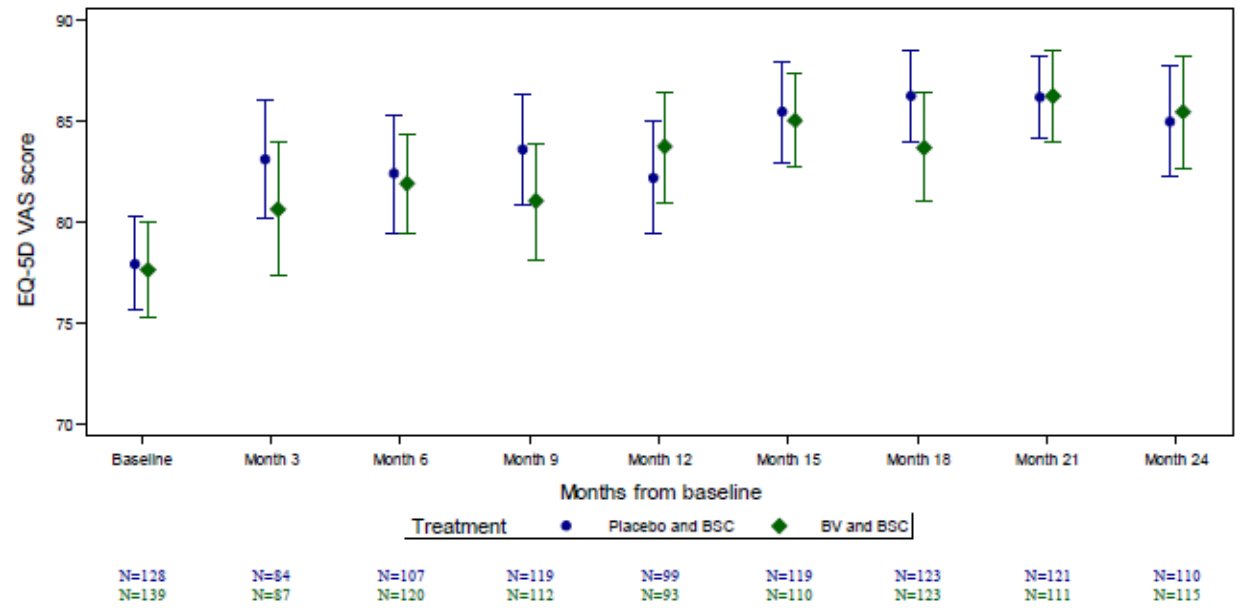
Figure 9: ITT US indexed mean (±95% CI) EQ-5D TTO scores - Study SGN35-005



Disease progression was associated with lower mean scores at subsequent time points, often exceeding the MID in both treatment arms, and patients who experienced PD experienced lower mean scores versus patients who never experienced PD on study. Differences between treatment arms could not be localized to a single component of the EQ-5D descriptive system. Lower scores could not be explained by treatment-emergent peripheral neuropathy on the brentuximab vedotin arm. When death is imputed, TTO scores decrease over time as well. The relationship between the TTO scores by treatment arm is similar, supporting the primary analysis results.

EQ VAS scores did not show a significant difference between treatment arms (Figure 10).

Figure 10: Intent to treat mean (±95% CI) EQ VAS scores - Study SGN35-005



Exploratory endpoint - Medical resource utilization

The medical resource utilization (MRU) analysis as exploratory endpoint, was planned to be based on the number of medical care encounters in the ITT analysis set. The MRU data on outpatient visits, hospitalizations, and working days/other activities missed by patients and caregivers suggest that there is a trend toward lower MRU upon brentuximab vedotin use in the HL disease prevention treatment setting. This information will be reflected in the SmPC.

Ancillary analyses

Additional sensitivity analyses of PFS

Some additional sensitivity analyses of PFS per IRF and investigator have been performed, all supporting the results of the primary PFS analysis (Table 8).

Table 8: Summary of PFS sensitivity analyses - Study SGN35-005

	Placebo (N=164)		Brentuximab Vedotin (N=165)		
Sensitivity Analysis	Events n (%)	Mediana (95% CI)	Events n (%)	Mediana (95% CI)	Hazard Ratiob,c (95% CI)
IRF: correcting for bias in tumor assessment schedules	75 (46)	24.1 (11.5, -)	60 (36)	42.9 (30.4, 42.9)	0.57 (0.40, 0.81)
IRF: subsequent new antitumor therapy considered an event	96 (59)	12.0 (6.5, 23.6)	66 (40)	42.9 (26.4, 42.9)	0.50 (0.36, 0.69)
INV: EMA censoring guidelines	91 (55)	15.8 (8.5, 32.7)	60 (36)	- (26.4, -)	0.49 (0.35, 0.68)
INV: correcting for bias in tumor assessment schedules	89 (54)	17.8 (8.5, -)	60 (36)	- (26.4, -)	0.50 (0.36, 0.70)
INV: subsequent new antitumor therapy considered an event	91 (55)	15.3 (7.5, 24.5)	60 (36)	- (26.4, -)	0.49 (0.35, 0.68)

a Calculated using the complementary log-log transformation method (Collett 1994)
b Hazard ratio comparing brentuximab vedotin to placebo. A hazard ratio <1.0 indicates a lower average event rate and a longer survival time for the brentuximab vedotin arm relative to the placebo arm.
c Computed using stratification factors (best response to salvage therapy pre-ASCT and HL status) at randomization

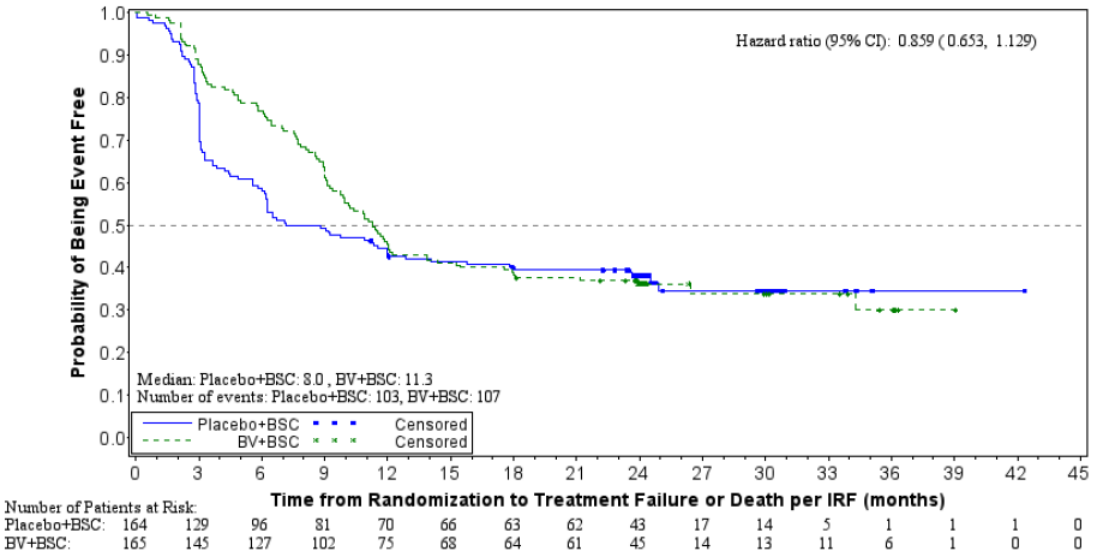
Time to Treatment Failure (TTF)

A post hoc analysis of TTF was conducted for the AETHERA intent-to-treat (ITT) population. For this analysis, a treatment failure event was defined as:

- Early discontinuation of treatment (received fewer than 16 cycles due to disease progression, toxicity, patient decision, or investigator decision).
- Starting subsequent therapy (Autologous or allogeneic stem cell transplantation, originally to have been exempted, are counted as events. In a potentially cured population, the need for subsequent transplantation signals treatment failure.).
- Disease progression, including progression events during the follow-up period.
- Death due to any cause.

Time to treatment failure was calculated as the time from randomization to the earliest of any of the above events. Figure 11 shows the TTF per IRF.

Figure 11: Kaplan-Meier Analysis of Time to Treatment Failure per IRF (ITT Population) - Study SGN35-005



Source: \biostatistics\SGN-035\35-05\Dev\EU_Responses\F14.1.1.1-Time_to_TreatFail_per_IRF_Plot, run time 23JUL2015 16:06

Time to treatment failure or death is defined as time from randomization to the earliest of 1) early discontinuation of treatment (received fewer than 16 cycles due to disease progression, toxicity, patient decision, or investigator decision), 2) starting subsequent therapy, 3) disease progression, including progression events during the follow-up period, or 4) death due to any cause.BSC=best supportive care, BV=brentuximab vedotin, CI=confidence interval, IRF=independent (radiologic) review facility.

Subsequent therapy

More patients in the placebo arm received subsequent anticancer therapy (52%) compared with the brentuximab vedotin arm (31%) (Table 9). Of these, 18% (n=9/51, 5% of all brentuximab vedotin patients) in the brentuximab vedotin arm and 85% (n=72/85) in the placebo arm received subsequent brentuximab vedotin. Twelve patients on brentuximab vedotin and 23 patients on placebo received a subsequent allogeneic stem cell transplantation.

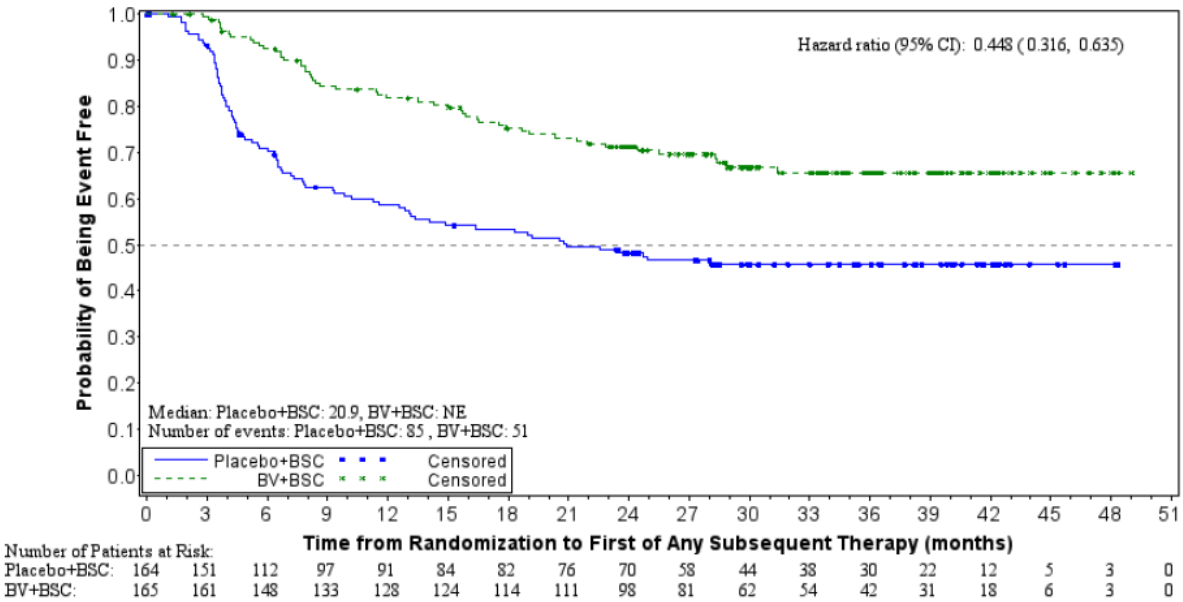
Table 9: Subsequent Antitumor Therapies (ITT Set) - Study SGN35-005

	Placebo (N=164) n (%)	Brentuximab Vedotin (N=165) n (%)
Received any subsequent new antitumor therapy during LTFU	85 (52)	51 (31)
Brentuximab vedotin	72 (44)	9 (5)
Multiagent regimen	34 (21)	35 (21)
Single-agent therapy	22 (13)	22 (13)
Radiation	23 (14)	22 (13)
Allogeneic stem cell transplant	23 (14)	12 (7)

In a post hoc analysis of time-to-next-treatment (TTNT), investigator-reported receipt of therapy for HL subsequent to placebo (placebo arm) or brentuximab vedotin (brentuximab vedotin arm) was considered a TTNT event. Patients without a TTNT event were censored at the date of their last follow-up.

Figure 12 presents the Kaplan-Meier analysis of time to any of next subsequent therapy. This analysis, although not prespecified, yielded a positive HR (0.45, 95% CI=0.32, 0.64).

Figure 12: Kaplan-Meier Analysis of Time from Randomization to First of Any Subsequent Therapy (ITT Population) - Study SGN35-005



Source: \biostatistics\SGN-035\35-05\Dev\EU_Responses\F14.1.1.3-Time_to_FirstSubTherapy_Plot, run time 23JUL2015 12:33.
BSC=best supportive care, BV=brentuximab vedotin, CI=confidence interval, NE=not estimable.

Assessing Crossover Effects: Time to Second Subsequent Treatment (TTSST) or Death

Patients whose disease does not respond to first subsequent therapy or relapses after first subsequent therapy are likely to receive a second subsequent therapy or die. An analysis of the subsequent therapy following progression on first therapy is shown in Table 10 and Figure 13. Placebo patients who received brentuximab vedotin as first subsequent therapy after randomization had a proportionally fewer second subsequent therapy or death events than patients who had received brentixumab vedotin. It is important to note that placebo cannot be regarded as an active treatment, meaning that brentuximab vedotin upon relapse/progression in the placebo group is truly the first next line treatment.

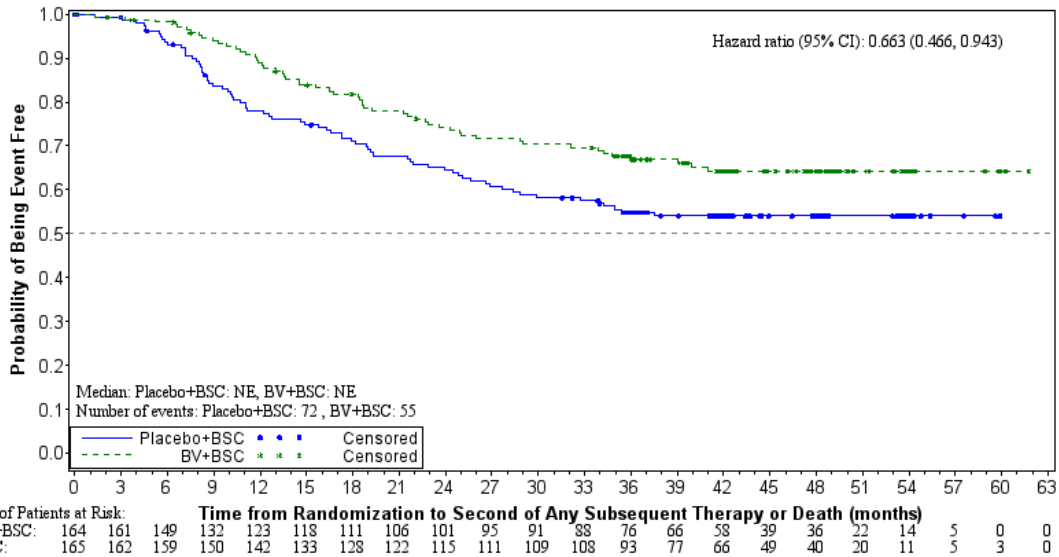
This aspect was included in our assessment report, but not reported in this version. There were 2 deaths in the larger brentuximab vedotin as first subsequent therapy group (N=63), compared to 4 deaths in the smaller Other Therapies as first-subsequent therapy group (N=22). The K-M plot showed a HR of 0.711 (95%CI 0.491, 1.029).

Table 10: Summary of Receipt of Second Subsequent Therapy or Death (ITT Population, Placebo Arm) - Study SGN35-005

	First Subsequent Therapy	
	BV N=63	Other Therapies N=22
Patients who received a second subsequent therapy or died, n (%)	42 (67)	19 (86)
Patients who received a second subsequent therapy, n (%)	40 (63)	15 (68)

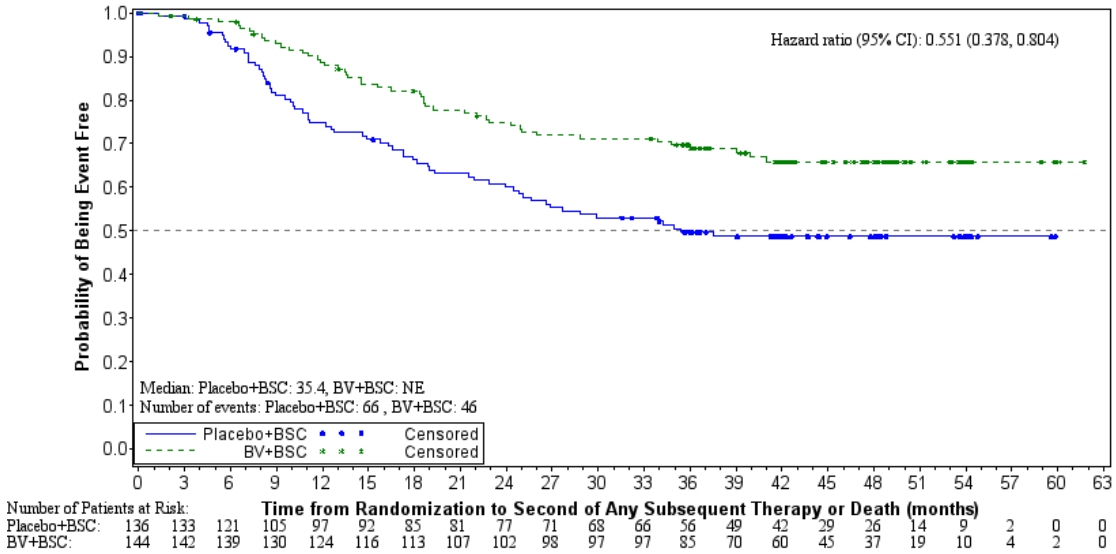
Source: \biostatistics\SGN-035\35-05\Dev\EU_Responses\T14.1.6.1-Therapy, run time 31JUL2015 11:19
BV=brentuximab vedotin, ITT=intent-to-treat.

Figure 13: Kaplan-Meier Plot of Time from Randomization to Second of Any Subsequent Therapy or Death (ITT Population) October 2015 analysis - Study SGN35-005



BSC=best supportive care, BV=brentuximab vedotin, CI=confidence interval, NE=not evaluable.

Figure 14: Kaplan-Meier Plot of Time from Randomization to Second of Any Subsequent Therapy or Death (Subset of ITT Population With ⩾2 Risk Factors) October 2015 - Study SGN35-005

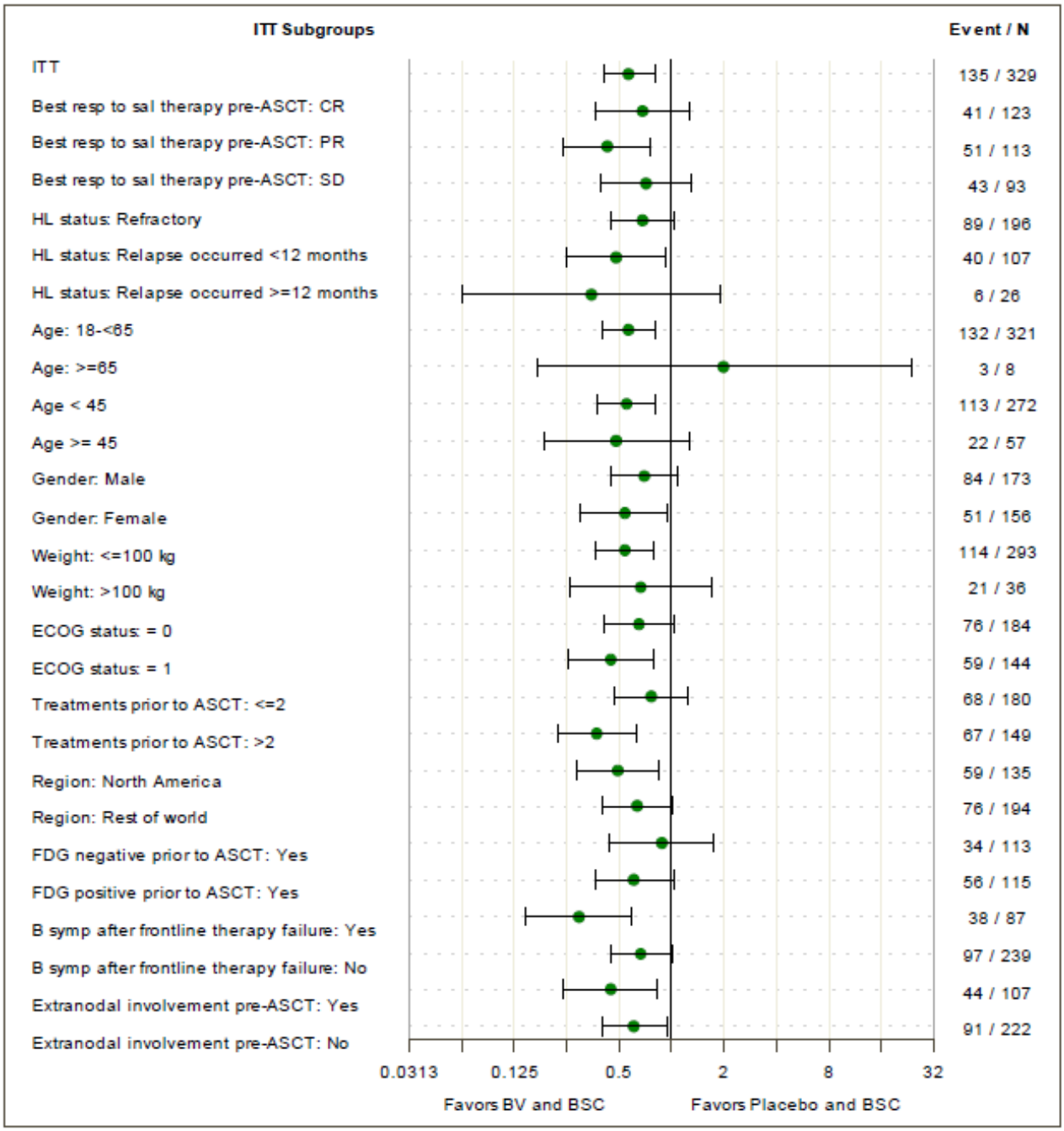


Representative risk factors for this analysis: HL that occurred <12 months or HL that was refractory to frontline therapy, best response of PR or SD to most recent salvage therapy, extranodal disease at pre-ASCT relapse, B symptoms at pre-ASCT relapse, or ≥2 prior salvage therapies.
BSC=best supportive care, BV=brentuximab vedotin, CI=confidence interval, NE=not evaluable.

Subgroup analysis of PFS

Subgroup analysis of PFS was performed by demographic and baseline characteristics, stratification factors, and other prespecified risk factors (Figure 15).

Figure 15: Forest Plot of PFS Subgroup Analyses per IRF (ITT Population) - Study SGN35-005



Stratified hazard ratios are presented, with the exception of stratification factors for which the unstratified hazard ratios are presented. Analyses are based on randomized stratum.

Table 11: PFS Subgroup Analysis per IRF (ITT set by Investigator Assessed Best Response to Pre-ASCT Salvage Therapy) - Study SGN35-005

	Complete Response		Partial Response		Stable Disease	
	Placebo (N=62) n (%)	BV (N=61) n (%)	Placebo (N=56) n (%)	BV (N=57) n (%)	Placebo (N=46) n (%)	BV (N=47) n (%)
Patients with PFS event	22 (35)	19 (31)	31 (55)	20 (35)	22 (48)	21 (45)
Estimated progression-free rate[a] at						
12 months (95% CI)[b]	66% (52%, 77%)	82% (70%, 90%)	46% (32%, 59%)	79% (66%, 88%)	57% (40%, 70%)	63% (47%, 75%)
24 months (95% CI)[b]	62% (48%,73%)	69% (54%,79%)	41% (28%,55%)	65% (51%,77%)	47% (30%,62%)	54% (39%,67%)
Median PFS (months) (95% CI)[b]	- (23.7, -)	42.9 (34.3, 42.9)	12.0 (3.3, -)	- (26.4, -)	17.8 (5.6, -)	- (9.1, -)
Unstratified Hazard Ratio[c] (95% CI)[c]		0.685 (0.365, 1.286)		0.423 (0.240, 0.746)		0.716 (0.392, 1.307)

a As estimated using Kaplan-Meier methods.
b Calculated using the complementary log-log transformation method (Collett, 1994).
c Hazard ratio (HR) comparing brentuximab vedotin (BV) with placebo. A HR < 1.0 indicates a lower average event rate and a longer survival time for the BV arm relative to the placebo arm.

Post hoc Risk Factor Analyses

Post hoc analyses were performed to evaluate the impact of increased risk (number of risk factors) on clinical benefit. Representative risk factors for these analyses were:

- HL that occurred <12 months or HL that was refractory to frontline therapy
- Best response of PR or SD to most recent salvage therapy as determined by CT and/or PET scanning
- Extranodal disease at pre ASCT relapse
- B symptoms at pre ASCT relapse
- Two or more prior salvage therapies.

Post-hoc analyses for PFS by numbers of risk factors present was performed (Table 12).

Table 12: PFS Subgroup Analysis per IRF (ITT Set by Number of Risk Factors) - Study SGN35-005

	≥1 Risk Factor		≥2 Risk Factors		≥3 Risk Factors	
	Placebo (N=164) n (%)	BV (N=165) n (%)	Placebo (N=136) n (%)	BV (N=144) n (%)	Placebo (N=84) n (%)	BV (N=82) n (%)
Patients with PFS event	75 (46)	60 (36)	68 (50)	51 (35)	49 (58)	32 (39)
Estimated progression-free rate[a] at						
12 months (95% CI)[b]	57% (48%, 64%)	76% (68%, 82%)	52% (43%,60%)	75% (67%,82%)	45% (33%,56%)	71% (59%,80%)
24 months (95% CI)[b]	51% (43%, 59%)	63% (55% 70%)	45% (36% 54%)	64% (56% 72%)	34% (23%,46%)	60% (48%,70%)
Median PFS (months) (95% CI)[b]	24.1 (11.5, -)	42.9 (30.4, 42.9)	12.3 (6.2, -)	42.9 (30.4, 42.9)	7.1 (3.3, 17.8)	- (18.0, -)
Stratified Hazard Ratio[c,d] (95% CI)[c]		0.571 (0.404, 0.808)		0.488 (0.337, 0.706)		0.433 (0.274, 0.683)

a As estimated using Kaplan-Meier methods.
b Calculated using the complementary log-log transformation method (Collett, 1994).
c Hazard ratio (HR) comparing brentuximab vedotin (BV) with placebo. A HR < 1.0 indicates a lower average event rate and a longer survival time for the BV arm relative to the placebo arm.
d Computed using stratification factors (Best response [Cheson 2007] to Salvage Therapy pre-ASCT and HL status) at randomization.

Efficacy analyses based on risk factors was performed. Approximately half of randomised patients (84/164 placebo, 51%; 82/165 brentuximab vedotin, 50%) had ⩾3 risk factors. Approximately one-third of randomised patients (52/164 placebo, 32%; 62/165 brentuximab vedotin, 38%) had 2 risk factors, and the remaining patients (28/164 placebo, 17%; 21/165 brentuximab vedotin, 13%) had only 1 risk factor.

Alternatively, Table 13 presents the results of a stratified Kaplan-Meier analysis of PFS by risk factor subgroup (1, 2, or ⩾3 risk factors; analyses of the 1 risk factor group were unstratified due to the small sample size). Of these subsets, only the placebo patients with ⩾3 risk factors had recorded >50% of possible PFS events. For patients with 2 and ⩾3 risk factors, HRs <1 were observed.

Table 13: Analysis of Progression-Free Survival per IRF (ITT Population by Risk Factor 1, 2, or ≥3 Subsets) - Study SGN35-005

	BV and BSC N=165 Patients (Events)	Placebo and BSC N=164 Patients (Events)	Hazard Ratio (95% CI)
Risk Factors (a)			
1 (N=49)	21 (9)	28 (7)	1.65 (0.60, 4.55)(b)
2 (N=114)	62 (19)	52 (19)	0.63 (0.33, 1.22)
≥3 (N=166)	82 (32)	84 (49)	0.43 (0.27, 0.68)

Source: O:\Biostatistics\SGN-35\sg035-0005\csr\outputs\tlfs\pgms\t-pfs-irf-nrisk.sas Output: t-pfs-irf-nrisk-itts.rtf (06OCT14:11:24) Data: adsl, adeff.
ASCT=autologous stem cell transplant, BSC=best supportive care, BV=brentuximab vedotin, CI=confidence interval, HL= Hodgkin lymphoma, IRF=independent (radiologic) review facility, ITT=intent-to-treat, PR=partial remission, SD=stable disease.
(a) Representative risk factors for this analysis: HL that occurred <12 months or HL that was refractory to frontline therapy, best response of PR or SD to most recent salvage therapy, extranodal disease at pre-ASCT relapse, B symptoms at pre-ASCT relapse, or ≥2 prior salvage therapies.
(b) Results based on unstratified analysis.

Table 14 shows the median duration of PFS per IRF by risk factor group and randomization therapy. Median estimates are not yet possible for several risk factors.

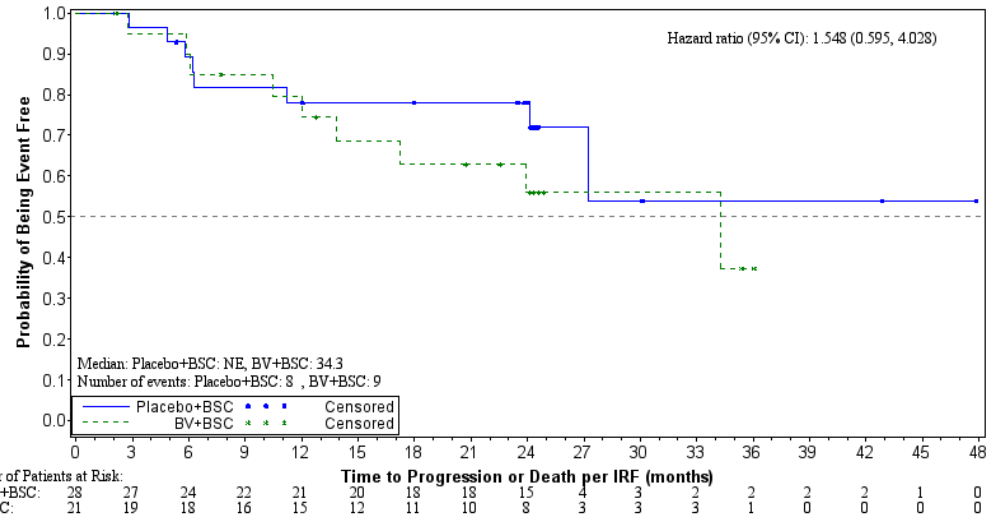
Table 14: Progression-Free Survival Duration per IRF (ITT Population by Risk Factor 1, 2, or ≥3 Subsets) - Study SGN35-005

	1 Risk Factor		2 Risk Factors		≥3 Risk Factors	
	Placebo and BSC (N=28) n (%)	BV and BSC (N=21) n (%)	Placebo and BSC (N=52) n (%)	BV and BSC (N=62) n (%)	Placebo and BSC (N=84) n (%)	BV and BSC (N=82) n (%)
Median PFS (months) (95% CI) (a)	- (24.1, -)	34.3 (12.0, -)	- (6.2, -)	42.9 (30.4, 42.9)	7.1 (3.3, 17.8)	- (18.0, -)
25th-75th Percentile	24.1,-	12.0,-	3.1,-	19.8,42.9	3.1,-	9.0,-
Observed min, max	2.83,33.84+	2.14+,36.07+	0.03+,35.12+	0.56,42.94	0.03+,42.35+	0.03+,41.23+
Follow-up time (b) since randomization (months)						
n	28	21	52	62	84	82
Mean (STD)	26.9 (14.8)	21.0 (13.3)	19.6 (15.5)	25.4 (13.2)	12.1 (12.9)	22.3 (14.1)
Median	27.9	20.7	23.8	25.3	6.0	24.0
Min, Max	3, 48	2, 49	0, 45	1, 48	0, 44	2, 48

Source: O:\Biostatistics\SGN-35\sg035-0005\csr\outputs\tlfs\pgms\t-pfs-irf-nrisk.sas Output: t-pfs-irf-nrisk-itts.rtf (06OCT14:11:24) Data: adsl, adeff, Data Snapshot: 19Sep2014.
Representative risk factors for this analysis: HL that occurred <12 months or HL that was refractory to frontline therapy, best response of PR or SD to most recent salvage therapy, extranodal disease at pre-ASCT relapse, B symptoms at pre-ASCT relapse, or ≥2 prior salvage therapies.
ASCT=autologous stem cell transplant, BSC=best supportive care, BV=brentuximab vedotin, CI=confidence interval, HL=Hodgkin lymphoma, IRF=independent (radiologic) review facility, ITT=intent to treat, PFS=progression-free survival, PR=partial remission, SD=stable disease, STD=standard deviation.
(a) Calculated using the complementary log-log transformation method (Collett, 1994).
(b) Follow-up time is defined as time to earliest of progressive disease per IRF, death, time to last adequate assessment for permanent censoring or last contact.

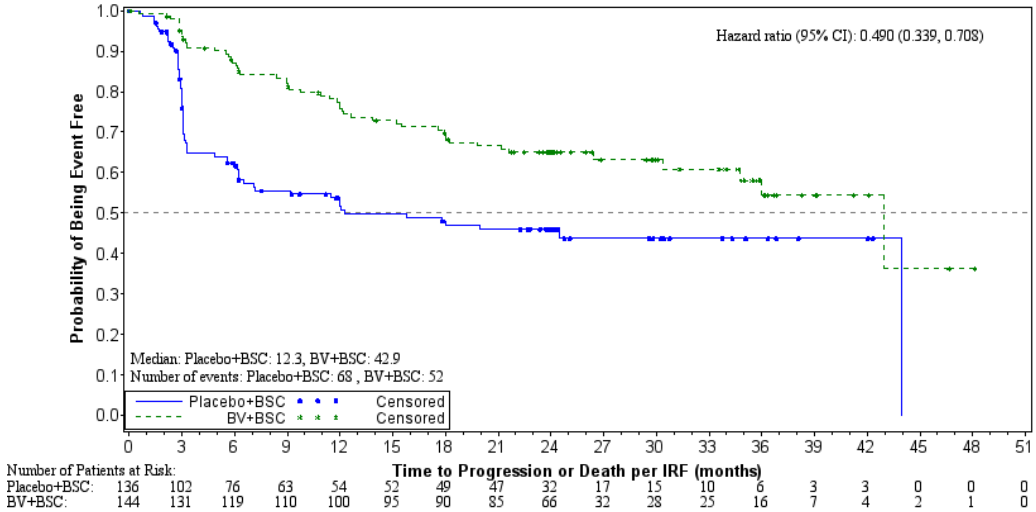
A Kaplan-Meier analysis of PFS per IRF by risk factor subgroup and randomization therapy is shown in Figure 16.

Figure 16: Kaplan-Meier Analysis of Progression-free Survival per IRF (Subset of ITT Population With 1 Risk Factor) October 2015 analysis - Study SGN35-005



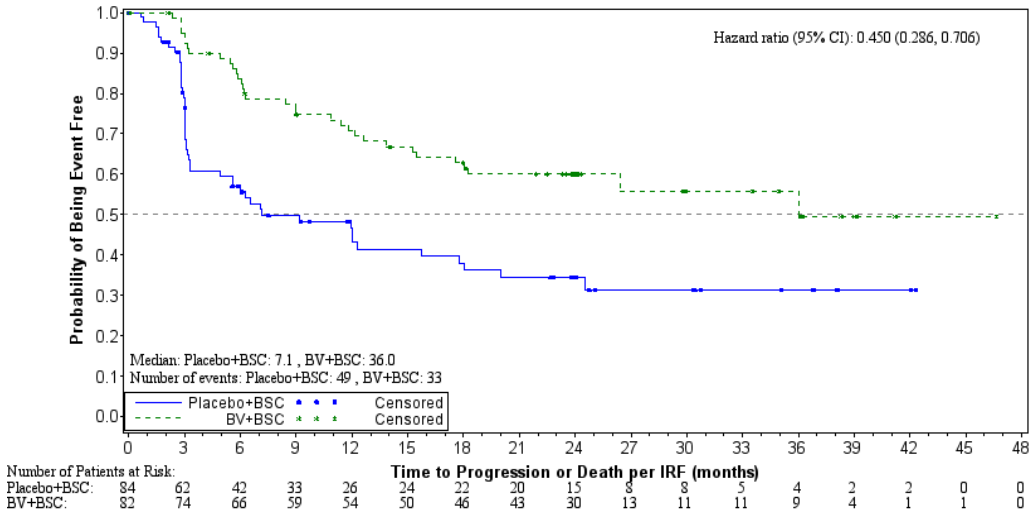
Representative risk factors for this analysis: HL that recurred <12 months after or HL that was refractory to frontline therapy, best response of PR or SD to most recent salvage therapy, extranodal disease at pre-ASCT relapse, B symptoms at pre-ASCT relapse, or ≥2 prior salvage therapies.
BSC=best supportive care, BV=brentuximab vedotin, IRF=independent review facility, ITT=intent-to-treat.

Figure 17: Study SGN35-005: 2015 Kaplan-Meier Analysis of Progression-free Survival per IRF (Subset of ITT Population With ≥2 Risk Factors) October 2015 analysis - Study SGN35-005



Representative risk factors for this analysis: HL that occurred <12 months or HL that was refractory to frontline therapy, best response of PR or SD to most recent salvage therapy, extranodal disease at pre-ASCT relapse, B symptoms at pre-ASCT relapse, or ≥2 prior salvage therapies.
BSC=best supportive care, BV=brentuximab vedotin, IRF=independent review facility, ITT=intent-to-treat.

Figure 18: Kaplan-Meier Analysis of Progression-free Survival per IRF (Subset of ITT Population With ≥3 Risk Factors) October 2015 analysis - Study SGN35-005



Representative risk factors for this analysis: HL that occurred <12 months or HL that was refractory to frontline therapy, best response of PR or SD to most recent salvage therapy, extranodal disease at pre-ASCT relapse, B symptoms at pre-ASCT relapse, or ≥2 prior salvage therapies.
BSC=best supportive care, BV=brentuximab vedotin, IRF=independent review facility, ITT=intent-to-treat.

An additional post-hoc analysis for OS, similar to the one performed for PFS, by numbers of risk factors present was also performed.

The following tables and figures present parallel subgroup analyses of OS.

Table 15: Analysis of Overall Survival per IRF (ITT Population by Risk Factor 1, 2, or ≥3 Subsets) - Study SGN35-005

	BV and BSC N=165 Patients (Events)	Placebo and BSC N=164 Patients (Events)	Hazard Ratio (c) (95% CI)
Risk Factors (b)			
1 (N=49)	21 (5)	28 (1)	7.94 (0.93, 68.06) (d)
2 (N=114)	62 (8)	52 (8)	0.82 (0.30, 2.28)
≥3 (N=166)	82 (15)	84 (16)	0.92 (0.45, 1.88)

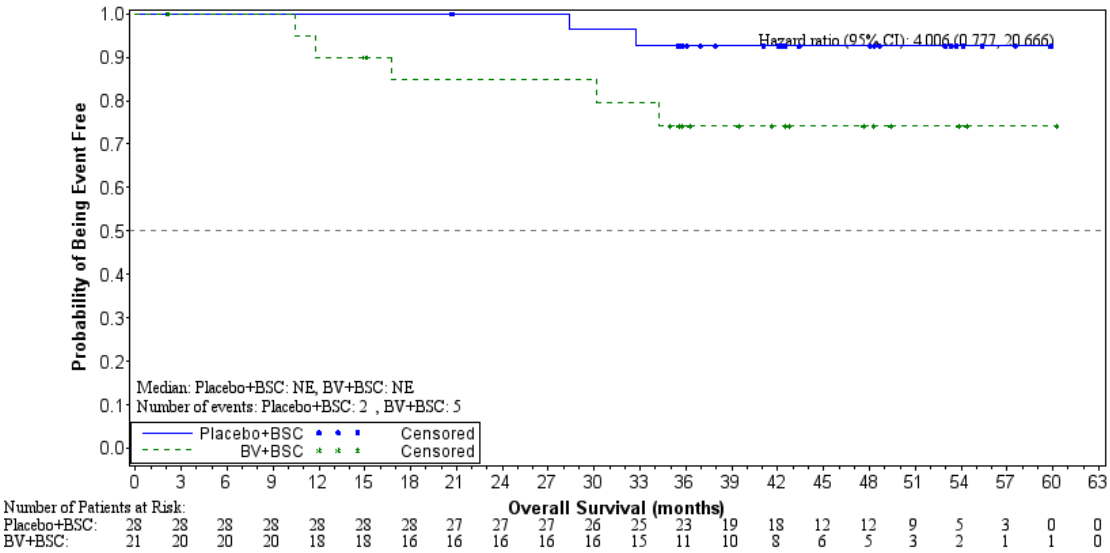
Source: O:\Biostatistics\SGN-35\sg035-0005\csr\outputs\tlfs\pgms\t-os-nrisk.sas Output: t-os-nrisk3-itts.rtf (06OCT14:11:14) Data: adsl, adeff.
ASCT=autologous stem cell transplant, BSC=best supportive care, BV=brentuximab vedotin, CI=confidence interval, HL=Hodgkin lymphoma, IRF=independent (radiologic) review facility, ITT=intent-to-treat, PR=partial remission, SD=stable disease.
(a) Events are due to death by any cause.
(b) Representative risk factors for this analysis: HL that occurred <12 months or HL that was refractory to frontline therapy, best response of PR or SD to most recent salvage therapy, extranodal disease at pre-ASCT relapse, B symptoms at pre-ASCT relapse, or ≥2 prior salvage therapies.
(c) Hazard ratio for treatment is estimated based on a Cox proportional hazard model stratified by 2 stratification factors at randomization. A hazard ratio <1.0 indicates a lower average event rate and a longer survival time for the BV+BSC arm relative to the placebo arm.
(d) Results based on unstratified analysis.

Table 16: Overall Survival Duration (ITT Population by Risk Factor 1, 2, or ≥3 Subsets) - Study SGN35-005

	1 Risk Factor		2 Risk Factors		≥3 Risk Factors	
	Placebo and BSC (N=28) n (%)	BV and BSC (N=21) n (%)	Placebo and BSC (N=52) n (%)	BV and BSC (N=62) n (%)	Placebo and BSC (N=84) n (%)	BV and BSC (N=82) n (%)
Median OS (months) (95% CI) (a)	- (-, -)	- (30.2, -)	- (-, -)	- (44.5, -)	- (-, -)	- (-, -)
25th-75th Percentile	-,-	34.3,-	-	44.5,-	-,-	-,-
Observed min, max	20.73+,48.36+	2.14+,49.05+	0.13+,45.37+	1.31,48.33+	0.03+,50.23+	2.14+,48.13+
Observation time (b) since randomization (months)						
n	28	21	52	62	84	82
Mean (STD)	34.0 (8.6)	28.5 (12.1)	29.5 (9.3)	29.7 (10.5)	29.1 (11.3)	30.5 (11.0)
Median	32.9	30.2	29.8	29.4	30.1	30.9
Min, Max	21, 48	2, 49	0, 45	1, 48	0, 50	2, 48

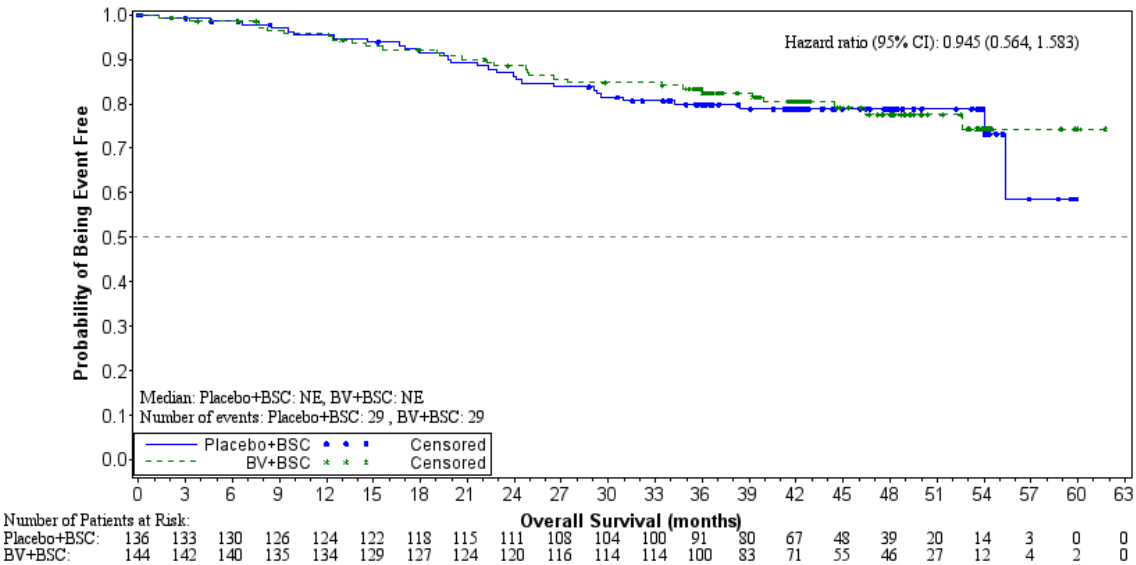
Source: Source: O:\Biostatistics\SGN-35\sg035-0005\csr\outputs\tlfs\pgms\t-os-nrisk.sas Output: t-os-nrisk3-itts.rtf (06OCT14:11:14) Data: adsl, adeff, Data Snapshot: 19Sep2014.
Representative risk factors for this analysis: HL that occurred <12 months or HL that was refractory to frontline therapy, best response of PR or SD to most recent salvage therapy, extranodal disease at pre-ASCT relapse, B symptoms at pre-ASCT relapse, or ≥2 prior salvage therapies.
ASCT=autologous stem cell transplant, BSC=best supportive care, BV=brentuximab vedotin, CI=confidence interval, HL=Hodgkin lymphoma, ITT=intent to treat, OS=overall survival, PR=partial remission, SD=stable disease, STD=standard deviation.
(a) Events are death due to any cause.
(b) Observation time is defined as time to earliest of death or last contact.

Figure 19: Study SGN35-005: 2015 Kaplan-Meier Analysis of Overall Survival (Subset of ITT Population With 1 Risk Factor)



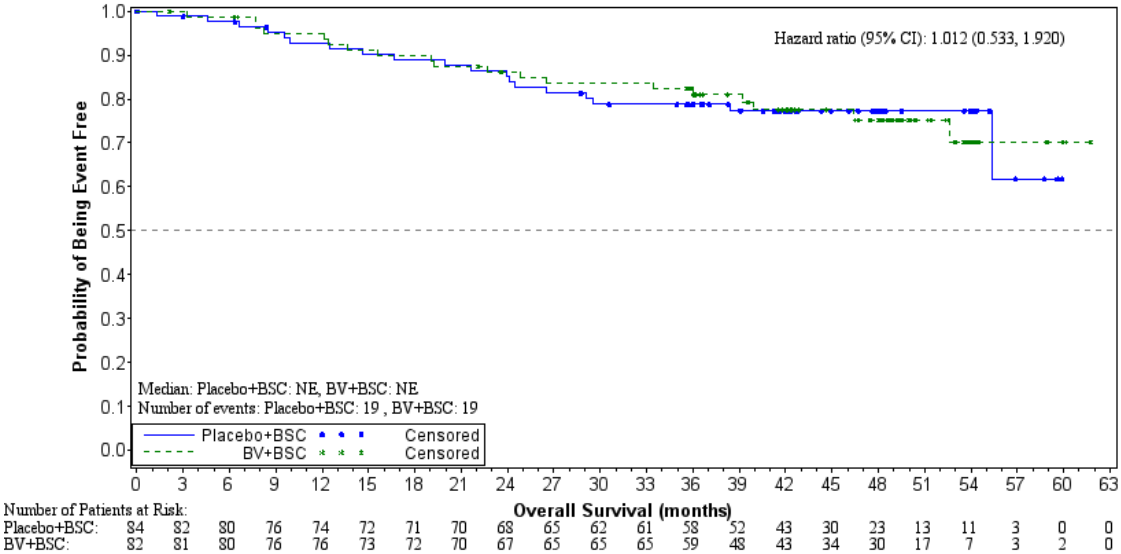
Representative risk factors for this analysis: HL that occurred <12 months or HL that was refractory to frontline therapy, best response of PR or SD to most recent salvage therapy, extranodal disease at pre-ASCT relapse, B symptoms at pre-ASCT relapse, or ≥2 prior salvage therapies.
BSC=best supportive care, BV=brentuximab vedotin, ITT=intent-to-treat.

Figure 20: Study SGN35-005: 2015 Kaplan-Meier Analysis of Overall Survival (Subset of ITT Population With ⩾2 Risk Factors)



Representative risk factors for this analysis: HL that occurred <12 months or HL that was refractory to frontline therapy, best response of PR or SD to most recent salvage therapy, extranodal disease at pre-ASCT relapse, B symptoms at pre-ASCT relapse, or ≥2 prior salvage therapies.
BSC=best supportive care, BV=brentuximab vedotin, ITT=intent-to-treat.

Figure 21: Study SGN35-005: 2015 Kaplan-Meier Analysis of Overall Survival (Subset of ITT Population With ⩾3 Risk Factors)



Representative risk factors for this analysis: HL that occurred <12 months or HL that was refractory to frontline therapy, best response of PR or SD to most recent salvage therapy, extranodal disease at pre-ASCT relapse, B symptoms at pre-ASCT relapse, or ≥2 prior salvage therapies.
BSC=best supportive care, BV=brentuximab vedotin, ITT=intent-to-treat.

The KM curves for OS showed that there is no difference between the corresponding subgroups of the two study arms, at least for the 2 and the ≥3 risk factor groups. For the 1 risk factor group, the KM curve points at a detrimental effect of brentuximab vedotin treatment in terms of OS (though a limited number of patients is involved).

The MAH has undertaken the requested post-hoc analysis of updated OS data using a data snapshot date of 14 October 2015. Since 2014, a total of 12 new OS events were recorded, with 6 events occurring in each treatment arm. Results of this analysis are provided for the ITT population and for the risk factor subgroups in Table 17.

Table 17: 2014 and 2015 Overall Survival Hazards Ratios - Study SGN35-005

Population or Subset (N)	2014 Number of death events (BV/PLA)	2014 OS HR (95% CI)	2015 Number of death events (BV/PLA)	2015 OS HR (95% CI)
ITT (329)	53 (28/25)	1.147 (0.667, 1.972)	65 (34/31)	1.117 (0.686, 1.818)
1 Risk Factor (49)	6 (5/1)	7.941* (0.927, 68.064)	7 (5/2)	4.006* (0.777, 20.666)
≥2 Risk Factors (280)	47 (23/24)	0.937 (0.527, 1.666)	58 (29/29)	0.945 (0.564, 1.583)
≥3 Risk Factors (166)	31 (15/16)	0.918 (0.450, 1.875)	38 (19/19)	1.012 (0.533, 1.920)

*Per unstratified log-rank test
BV=brentuximab vedotin, HR=hazard ratio, OS=overall survival, PLA=placebo, RPSFT=rank-preserving structural failure time.

PET scan prior to ASCT

In AETHERA, PET scan results were available for 228/329 patients (69%), with approximately one third of patients PET positive (115/329, 35%), one third PET negative (113/329, 34%), and one third not assessed by PET after salvage therapy but before ASCT (101/329, 31%) (Table 18). PET status was captured by patients' best response to pre-ASCT salvage therapy. No PET- patient in the AETHERA study

had a best overall response of partial remission (PR) or stable disease (SD) to salvage therapy, and no PET+ patient had a best overall response of CR.

Table 18: Study SGN35-005: PET status versus number of risk factors and best response to salvage therapy (ITT population with PET status

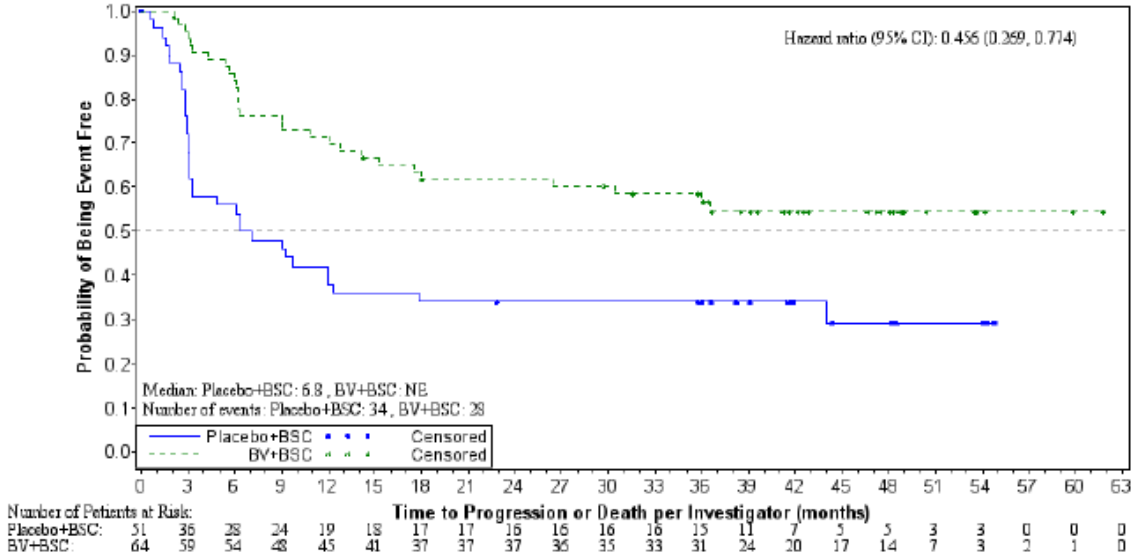
	PET Negative			PET Positive		
	Pla+BSC N=57 n %	BV+BSC N=56 n %	Total N=113 n %	Pla+BSC N=51 n %	BV+BSC N=64 n %	Total N=115 n %
Best Response						
CR	57 (100)	56 (100)	113 (100)	0	0	0
PR	0	0	0	27 (53)	32 (50)	59 (51)
SD	0	0	0	24 (47)	32 (50)	56 (49)
Risk Factors						
1	25 (44)	20 (36)	45 (40)	1 (2)	0	1 (1)
≥2	32 (56)	36 (64)	68 (60)	50 (98)	64 (100)	114 (99)

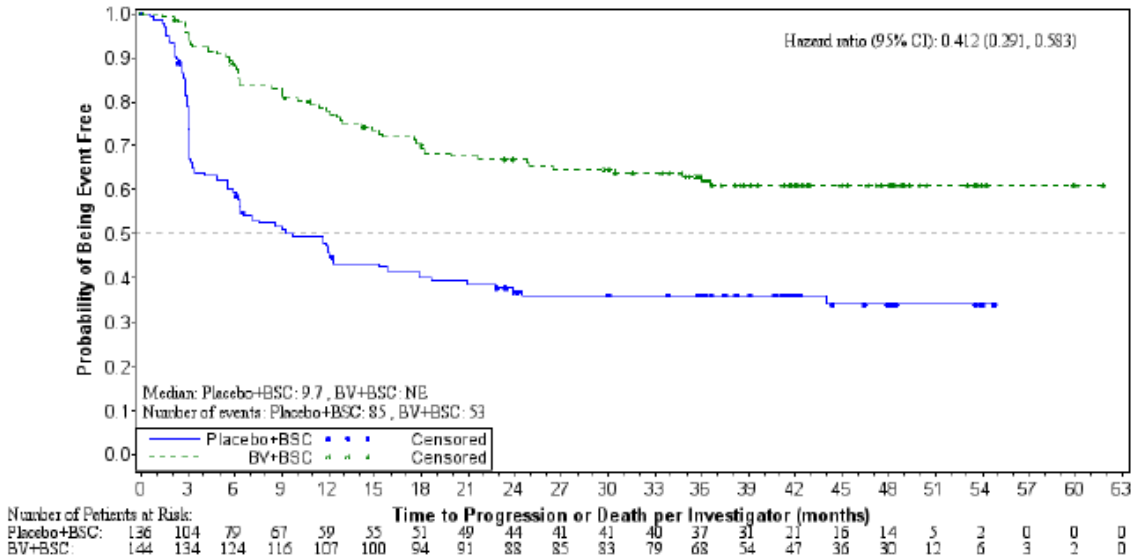
Source: biostatistics\SGN-035\35-05\CSR_Addendum2\EU_Responses\Additional Responses\T15.1.1.140-SummaryPETvsBestResp, run time 29 April 2016 12:09, data snapshot date 14 October 2015.
BSC=best supportive care, BV=brentuximab vedotin, CR=complete remission, ITT=intent-to-treat, PET=positron emission tomography, PLA=placebo, PR=partial remission, SD=stable disease.

The impact of PET status on progression-free survival (PFS) per independent review facility (IRF) was evaluated separately in a prespecified analysis at the time of the primary assessment of the primary endpoint; PET+ status (PFS per IRF hazard ratio 0.611 [95% confidence interval (CI) 0.360, 1.035]) and the presence of ≥2 of the 5 evaluated risk factors (HR=0.488 [95% CI 0.337, 0.706]) were each predictive of relapse (2014 data cut date).

As illustrated in Figure 22 and Figure 23, this effect was stable as of the 2015 updated PFS per investigator data and showed the presence of ≥2 risk factors to be a strong predictor of PFS per investigator response.

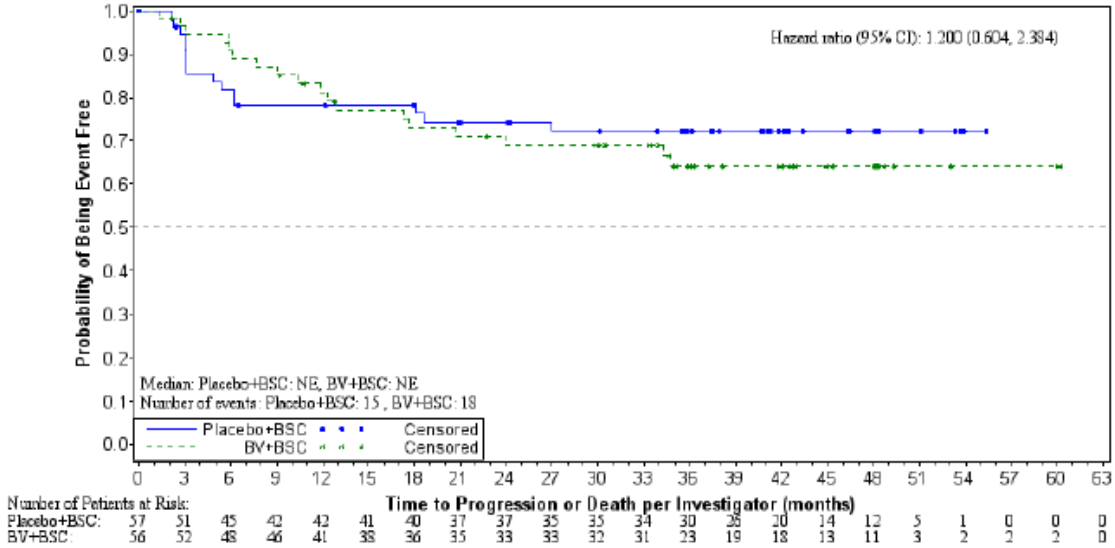
Figure 22: Kaplan-Meier analysis of PFS per investigator (ITT subset: PET+top; ≥ 2 risk factors, bottom) - Study SGN-35-005 (2015)

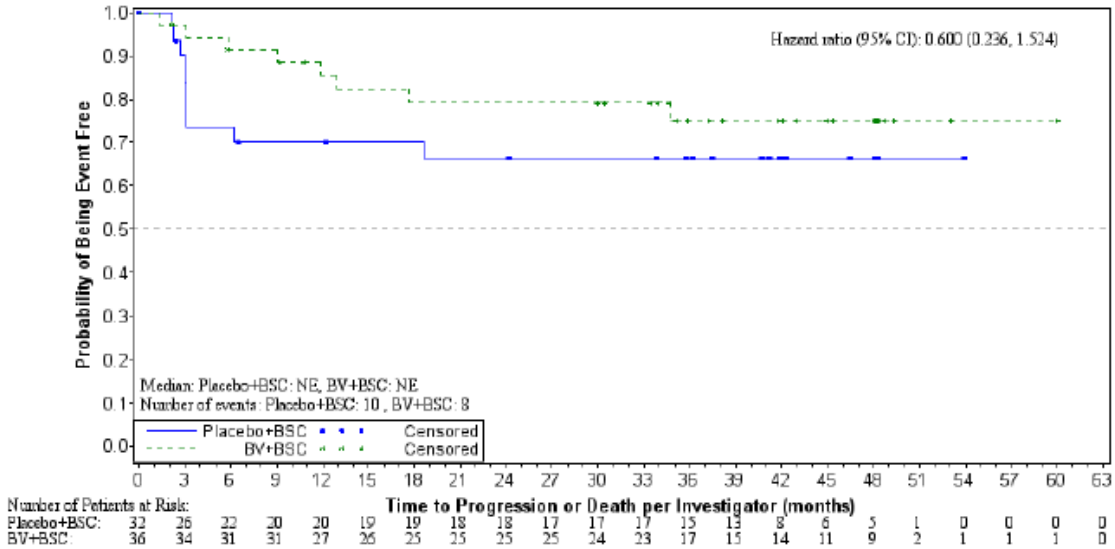




Source: \biostatistics\SGN-035\35-05\CSR_Addendum2\EU_Responses\Additional Responses\ F15.1.1.144-PFS_per_Inv_PETPos_Plot, run time 29APR2016 10:00 and \ F15.1.1.20-PFS_per_Inv_Plot, run time16NOV2015 13:01, data snapshot date 14 October 2015.
Representative risk factors for bottom analysis: HL that occurred <12 months or HL that was refractory to frontline therapy, best response of PR or SD to most recent salvage therapy, extranodal disease at pre-ASCT relapse, B symptoms at pre-ASCT relapse, or ≥2 prior salvage therapies.
BSC=best supportive care, BV=brentuximab vedotin, IRF=independent review facility, ITT=intent-to-treat, PFS=progression-free survival.

Figure 23: Kaplan-Meier analysis of PFS per investigator (ITT subset: PET- patients top; PET – patients with ≥ 2 risk factors, bottom) - Study SGN-35-005 (2015)





Source: \biostatistics\SGN-035\35-05\CSR_Addendum2\EU_Responses\Additional Responses\ F15.1.1.143-PFS_per_Inv_PETNeg_Plot, run time29 April 2016 12:18 data snapshot date 14 October 2015.
Representative risk factors for bottom analysis: HL that occurred <12 months or HL that was refractory to frontline therapy, best response of PR or SD to most recent salvage therapy, extranodal disease at pre-ASCT relapse, B symptoms at pre-ASCT relapse, or ≥2 prior salvage therapies.
BSC=best supportive care, BV=brentuximab vedotin, IRF=independent review facility, ITT=intent-to-treat, PFS=progression-free survival.

Multivariate analyses to investigate treatment effect for risk factor covariates

Multivariate analyses using a Cox proportional hazards model were also used to investigate treatment effect when adjusted for the 5 individual risk factor covariates (Table 19).

Treatment was a highly statistically significant variable, both in a model unadjusted for covariates (p=0.002) and with adjustment (p=0.001). When explored individually, all 5 risk factors had a negative impact on PFS per IRF (HR 1.3-2.6), and this negative impact was statistically significant for 2 of the 5 risk factors. The negative effect on PFS per IRF was most statistically significant for a best response to salvage therapy of partial response or stable disease (HR 1.58; 95% CI 1.087, 2.296; p=0.016) and was most marked for patients whose HL was refractory to frontline therapy or relapsed within 12 months (HR 2.56; 95% CI 1.129, 5.834; p=0.024).

Table 19: Cox Regression Analysis of Progression-free Survival per IRF (ITT Population) - Study SGN35-005

Factor / Covariate	Parameter Estimate (SE)	Hazard Ratio	95% CI	P-value
Treatment (BV vs. Placebo) without covariates (N= 329)	-0.552 (0.174)	0.576	(0.409, 0.811)	0.002
Patients With Available Risk Factor Information (N= 326)				
Treatment (BV vs. Placebo) Adjusted for other covariates	-0.575 (0.175)	0.562	(0.399, 0.793)	0.001
B symptoms at pre-ASCT relapse (Y vs N)	0.235 (0.195)	1.264	(0.863, 1.853)	0.229
Extranodal involvement pre-ASCT (Y [a] vs N)	0.240 (0.196)	1.272	(0.866, 1.867)	0.220
HL Status at Randomization (Refractory/Relapse < 12 months [a] vs Relapse ≥12 months)	0.943 (0.419)	2.567	(1.129, 5.834)	0.024
Best Response to Salvage Therapy Pre-ASCT (Partial Response/Stable Disease vs Complete Response)	0.457 (0.191)	1.580	(1.087, 2.296)	0.016
Number of Prior Salvage Treatments (≥2 vs 1)	0.237 (0.175)	1.267	(0.900, 1.784)	0.175

Source: \biostatistics\SGN-035\35-05\CSR_Addendum2\EU_Responses\Additional Responses\T15.1.1.42-Cox_PFS_per_IRF, run time 14JAN2016 11:51 (data snapshot date 14 October 2015)
Hazard ratio for treatment is estimated based on Cox proportional Hazard model stratified by two stratification factors: Best response to Salvage Therapy pre-ASCT and HL status at randomization.
The hazards ratio is the ratio of the hazards functions that correspond to a change of one unit of the given variable and conditional on fixed values of all other variables.
A hazard ratio less than 1 for treatment indicates better prevention of death in brentuximab vedotin arm as compared with placebo.
(a) Study entry criterion
ASCT=autologous stem cell transplant, BV=brentuximab vedotin, CI=confidence interval, HL=Hodgkin lymphoma, IRF=independent review facility, ITT=intent to treat, SE=standard error.

Other Measures of Clinical Benefit

Medical resource utilization (MRU) analyses showed that hospitalisation and outpatient visits, as well as working days/other activities missed by patients and caregivers were lower with brentuximab vedotin compared with placebo in patients with HL at increased risk of relapse, suggesting a trend towards lower MRU (Table 20).

Table 20: Trend towards Lower MRU with BV Treatment October 2015 analysis – Study SGN35-005

	All Patients (N=329)		Patients with >= 2 Risk Factors (N=280)	
	Placebo (N=164)	BV (N=165)	Placebo (N=136)	BV (N=144)
Hospitalization Events				
# of patients n(%)	61 (37)	68 (41)	55 (40)	60 (42)
Total Hospitalization Events	198	176	185	144
Outpatient Visit				
# of patients n(%)	133 (81)	119 (72)	110 (81)	102 (71)
Total Outpatients Visits	3803	2687	3136	2248
Missed Work/Activity Days				
# of **Patients** n(%)	94 (57)	85 (52)	79 (58)	74 (51)
Total Missed Work Days by **Patients**	3147	1648	2929	1502
# of **Care Giver** n(%)	24 (15)	7 (4)	18 (13)	7 (5)
Total Missed Work Days by **Care Giver**	436	48	353	48

Summary of main study(ies)

Table 21 summarise the efficacy results from the main study supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 21: Summary of Efficacy for Pivotal AETHERA Trial

Title: AETHERA study		
Study identifier	SGN35-005	
Design	Randomised, double-blind, placebo-controlled Phase III 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)	
	Study Initiation Date: Study Completion Date	6 Apr 2010 18 Aug 2014
Hypothesis	Superiority	
Treatments groups	Brentuximab Vedotin	IV infusion 1.8 mg/kg given over approximately 30 minutes on Day 1 of each 21-day cycle. Max 16 cycles n=165 randomised
	Placebo	IV infusion 1.8 mg/kg given over approximately 30 minutes on Day 1 of each 21-day cycle. Max 16 cycles n=164 randomised

Endpoints and definitions	Primary endpoint	PFS	The time from randomization until objective tumor progression per IRF or death.
	Secondary endpoint	OS	The time from randomization to date of death due to any cause.
	Exploratory endpoint	QoL	Measured by Utility Instrument (EQ-5D) score.
		MRU	Based on the number of medical care encounters.
Data cut off primary analysis	18 Aug 2014		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	ITT: 329 patients: 165 brentuximab vedotin, 164 placebo Per protocol: 258 patients, 126 brentuximab vedotin, 132 placebo		
Descriptive statistics and estimate variability	Treatment group	Brentuximab vedotin	Placebo
	Number of subject	165	164
	Median PFS	42.9 months	24.1 months
	95% CI	(30.4, 42.9)	(11.5, -)
	Median OS	Not (yet) reached	Not (yet) reached
	95% CI	-	-
Effect estimate per comparison	PFS	Comparison groups	Brentuximab vs placebo
		Hazard Ratio (HR)	0.57
		95% CI	(0.40, 0.81)
		P-value	0.001
	OS	Comparison groups	Brentuximab vs placebo
		Hazard Ratio (HR)	1.15
		95% CI	(0.67, 1.97)
		P-value	0.620
Notes	PFS and OS HR and 95% CI were estimated using a stratified Cox proportional hazards model. PFS and OS p-value was based on a stratified log-rank test.		

Clinical studies in special populations

Elderly

In the pivotal study, only 8 patients were 65 years or older. Subgroup analysis in patients ≥65 years of age indicated absence of brentuximab vedotin effect (HR>1). However, interpretation of PFS data for patients of age ≥65 years was limited due to the small number of patients in this category and their underlying age-related comorbidities. Of the 8 patients in this group there were 3 PFS events per IRF (2 of 5 patients in the brentuximab vedotin arm, including 1 death related to a secondary malignancy, and 1 of 3 patients in the placebo arm).

2.4.2. Discussion on clinical efficacy

Design and conduct of clinical studies

The pivotal study AETHERA was a phase III, randomised, double blind, and placebo controlled, comparing brentuximab vedotin and best supportive care (n=165) with placebo and best supportive care (n=164). Patients were required to have histologically confirmed classical HL, with autologous SCT in the previous 30-45 days and were to be at increased risk of relapse or progression post-ASCT. The double-blinded design of the AETHERA trial is considered acceptable. The proposed dose of 1.8 mg/kg as an intravenous infusion every 3 weeks for a maximum of 16 cycles used in the pivotal study is based on previous submitted dose finding studies, and is similar to the posology included in the SmPC for the approved HL indications.

There were a number of protocol amendments and violations, but these were considered minor and are not expected to have affected the outcomes from the pivotal study. The other changes in analysis/SAP are not considered to have impacted the analysis or interpretation, especially not of the most important efficacy outcomes (i.e., PFS and OS). The applicant obtained national scientific advice in January 2014 on the proposal to revise the triggering of the primary analysis. The newly proposed time-driven analysis was considered acceptable assuming a HR <0.73. In general, the statistical methods are considered standard and acceptable. The CHMP did not raise any specific issue with the overall conduct of the trial.

The selection of PFS as the primary endpoint of the pivotal study is considered acceptable in view of the relatively long life expectancy of patients with HL after ASCT. As disease progression was defined only in terms of a diagnostic biopsy or radiographic assessment, demonstration of a sustained clinical benefit for patients is considered important. As brentuximab vedotin was approved in relapsed/ refractory HL after ASCT halfway during the AETHERA study, cross over to brentuximab vedotin in the placebo arm after progression was inevitable and is likely to have affected the OS results.

Patient demographics and baseline disease characteristics were generally balanced between the two treatment arms, except for a slight imbalance in gender: 59% of patients were male in the placebo arm compared with 46% in the brentuximab vedotin arm. This imbalance is considered to not have an important effect on the analyses.

The included patient population was very heterogeneous regarding disease state at the time of study inclusion. In both treatment arms, 42% had achieved CR as best response with the most recent prior salvage therapy, 34% PR, and 24% stable disease. In addition, 35% of patients were PET FDG-avid prior to ASCT, and 34% was PET FDG-negative.

Similar numbers of patients were off study treatment at the time of the primary analysis in both arms, while the main reason for patients being off study was different in both arms. For brentuximab vedotin-treated patients, the main reason was an adverse event (n=54, vs n=10 in the placebo arm). In the placebo arm, the main reason was progressive disease (n=69, vs n=24 in the brentuximab vedotin arm). A low number of withdrawals of consent/off-treatment due to patient decision in the placebo arm was observed, which was similar in the brentuximab vedotin arm. This suggests that informative censoring (e.g. study discontinuation due to absence of brentuximab vedotin specific AEs, and thereby possible unblinding) did not play a role in patients discontinuing the treatment.

Efficacy data and additional analyses

Progression free survival

The primary endpoint of the pivotal trial was met: an 18.8 months PFS improvement has been observed with brentuximab vedotin treatment (42.9 months vs. 24.1 months placebo; HR 0.57, 95% CI 0.4, 0.8, IRF analysis). The magnitude of the increase in PFS is considered clinically relevant. However, it appears that most PFS benefit is obtained in the first months after start of treatment where a rapid increase in

events in the placebo arm was observed in the first 6 months of treatment and less steep PFS Kaplan Meier (KM) curves after that point in time in both arms. Furthermore, the KM curves of the investigator-based PFS sensitivity analysis, including clinical lymphoma assessments, showed a plateau phase at the end of the curve, with a larger difference between the curves compared with the primary IRF-based PFS analysis, suggesting that PFS could be a surrogate marker for some patients that may have been cured in the experimental arm that did not experience an event up to reaching the plateau phase in the PFS KM curve. For the patients in the placebo arm, brentuximab vedotin is still a treatment option upon progression/relapse resulting in an additional long-term PFS for about 15-20% of the patients..

Patients with the highest risk for relapse in almost every subgroup category (e.g. best response to salvation therapy of PR, ECOG status = 1, >2 treatments prior to ASCT, FDG positivity prior to ASCT, B symptoms after frontline therapy failure or extranodal involvement pre-ASCT) seemed to have more benefit from brentuximab vedotin as indicated by lower hazard ratio's, compared with the lower risk categories in the respective subgroups. When comparing the actual PFS rate in the brentuximab vedotin and placebo arm, this improved benefit can most likely be explained by a lower PFS rate in the placebo arm for a number of subgroup categories.

The PFS subgroup analysis showed a consistent trend towards benefit for patients who received brentuximab vedotin compared with patients who received placebo with the exception of patients $\geqslant$ 65 years of age. However, this subgroup consisted of few patients (n=8), limiting the possibility to draw a final conclusion.

Post hoc subset analyses of both PFS and OS were undertaken using 5 risk factors, i.e. relapsed <12 months or refractory to frontline therapy, best response of PR or SD to most recent salvage therapy, extranodal disease at pre-ASCT relapse, B symptoms at pre-ASCT relapse and two or more prior salvage therapies, in an attempt to understand the impact of the number of risk factors on efficacy outcomes. The most PFS benefit is observed in the group of brentuximab vedotin-treated patients with ≥2 risk factors. This is clearly absent in the 1 risk factor group, although the number of patients in this group was limited (21 patients vs. 28 patients on placebo). These observations are supported by the results from the PFS HR analyses.

A post hoc analysis of time to treatment failure (TTF) was conducted for the AETHERA intent-to-treat (ITT) population. The curves of the TTF analyses per investigator and per IRF are highly similar, meaning that the results are consistent. The results of the (variants of) the requested TTF analyses show that the brentuximab vedotin treatment is effective in the early treatment phase relative to placebo, fitting the results from the primary PFS analyses. Moreover, early discontinuation in general, starting subsequent therapy, disease progression and death due to any cause did all not influence this effect. The results from the TTF analyses excluding early discontinuation due to an adverse event imply that brentuximab vedotin treatment is associated with substantial toxicity leading to early discontinuation of therapy. Together, this strengthens the findings that brentuximab vedotin may bring clinical benefit to a selected population at higher risk of relapse as this population would be able to better tolerate the added toxicity of the maintenance regimen.

A post hoc analysis of time-to-next-treatment (TTNT) was performed based on investigator-reported receipt of therapy for HL subsequent to placebo or brentuximab vedotin was considered a TTNT event. The data showed that brentuximab vedotin can postpone the next or any subsequent therapy, indicating a meaningful clinical benefit of the treatment. It is important to note that placebo cannot be regarded as an active treatment, meaning that brentuximab vedotin upon relapse/progression in the placebo group is truly the first next line treatment. This has important consequences for the assessment of time to first subsequent therapy after progression is not the same between the two treatment arms where the time to 2nd subsequent therapy (the first therapy after brentuximab) in the placebo group should be compared with the time to 1st subsequent therapy in the brentuximab vedotin group (15 months vs 18.7 months,

respectively). Likewise, the time to 3rd therapy in the placebo group should be compared with the time to 2nd therapy in the brentuximab vedotin arm (23 months vs 22 months, respectively). In this respect it is important to remember that brentuximab vedotin is a highly effective treatment, even in the relapsed/refractory setting (relative to the other options). Direct comparison of brentuximab vedotin and placebo treated patients in the time to next treatment analyses is hampered by the fact that most placebo patients cross over to brentuximab vedotin after progression.

The PET-positive result in the placebo arm and in the brentuximab vedotin arm yielded similar PFS per investigator data as compared to the results of the patients selected based on ≥2 risk factors in the respective study arms. Patients with a PET-positive scan had ≥2 risk factors, i.e. approximately 99%, while 60% of the patients with PET-negative results had ≥2 risk factors. Hence, there is an overlap between patients with PET scans (either positive or negative) and patients with ≥2 risk factors. It is of note that patients with CR after salvage therapy had PET-scan negative results, while no patients with a PET-scan positive results had a CR. Considering that all but 1 patient with positive PET scan results had ≥2 risk factors, these data together mean that all patients with ≥2 risk factors had PR or SD as best response and hence are at risk for progression. The PFS results according to PET positive or negative are consistent with the results from the results of the patients selected based on ≥2 risk factors in the respective study arms. There was no difference in PFS in favour of brentuximab vedotin in PET-negative patients. However, in PET-negative patients having ≥2 risk factors resulted in a trend for a PFS per investigator difference between the 2 study arms, also at the late time points. The same trend was seen for patients with CR, although also here few patients were at risk at 24 or 36 months. Therefore, it appears that selection of patients having ≥2 risk factors seems to be a better prognostic tool to use in the clinic to select those patients that experience PFS benefit at 34 and 36 months after transplantation than using PET scan data (see SmPC section 5.1).

Following the assessment of the responses, the indication was revised to take into account the inclusion criteria of the pivotal study which recruited only patients with classical HL: this subtype of HL is characterized by CD30 expression, the target of the antibody drug conjugate Adcetris. Hence, the indication includes the wording “treatment of adult patients with CD30+ HL” to more accurately reflect the inclusion criterion of the pivotal study concerning the CD30+ status. In addition, as it was shown that the subgroup of patients with ≥2 risk factors benefited the most from the maintenance treatment, the wording “at increased risk of relapse or progression” was included to reflect the population of patients which had the greatest increase in PFS. A reference to section 5.1 of the SmPC provides further information on the risk factors used to define those patients at higher/increased risk of progression.

Overall survival

The secondary endpoint OS did not show a difference between the treatment arms for the total study population and not for the 2 or ≥3 risk factors. The estimated 24-month OS rate was 88% (brentuximab vedotin) vs. 89% (placebo), which is in line with OS rates after ASCT in literature. It is unclear the reason why no improvement in OS was observed considering the magnitude of the effect observed for PFS. A possible explanation is that patients in the placebo group were allowed to cross-over once they progressed, confounding the OS results. As a result, the OS data will only be mature in 2020. Although an effect on OS would have been an important clinical benefit to patients, the CHMP was reassured that the maintenance treatment had no detrimental effect in OS in the long term.

Quality of life

Mean differences in EQ-5D TTO index or VAS scores generally did not exceed the minimally important difference (MID) between treatment arms. In both arms TTO index scores became slightly lower during the trial, but with/without imputation for death did not reveal differences between the treatment arms.

The reduction in the scores as compared to baseline could not be explained by treatment-emergent peripheral neuropathy (a known treatment-related AE of brentuximab vedotin) on the brentuximab vedotin arm. In contrast, VAS scores increased a few points in both arms during the trial. Therefore, the QoL data did not support the primary efficacy analysis, but at the same time also did not show a detrimental effect of brentuximab vedotin on the QoL as compared to placebo.

No differences were observed in quality of life between the treatment and placebo arms. Medical resource utilization (MRU) analysis showed that hospitalizations and outpatient visits, as well as working days/other activities missed by patients and caregivers were lower with brentuximab vedotin compared with placebo in patients with HL at increased risk of relapse.

Additional expert consultation

On the 14th April 2016, a SAG-O was convened to address a list of questions adopted by the CHMP.

Please discuss the rationale and the (potential) added value of an early maintenance treatment regimen like the currently proposed regimen with Adcetris (Brentuximab (B) Vedotin (V) compared to "watchful waiting" in patients with Hodgkin lymphoma at increased risk of relapse or progression following ASCT. The following issues should be taking into consideration:

a. Is the selection of patients for early treatment based on two or more risk factors for relapse or progression following ASCT, feasible and desirable in clinical practice?

There is a biologic rationale and clinical need for early ("maintenance") treatment of patients at high risk of relapse or progression after ASCT in particular due to the poor prognosis after progression, the limited number of salvage therapies, and the aim to avoid or delay, if possible, more intensive treatments such as allogeneic transplant, which are associated with significant morbidity and mortality.

The identification of patients at high risk of relapse or progression based on the five risk factors proposed is feasible as these are routinely available, and the importance of these risk factors is well established.

Although the threshold of two or more risk factors out of the five factors selected is plausible and feasible, it is difficult to ascertain if it is optimal. The proposed classification was a post-hoc exercise limited by the choice of data collected in the pivotal trial and the weaknesses of exploratory analyses. Concerning the limitations, available data did not allow exhaustive exploration of all possible important prognostic factors. For instance, evidence of residual disease based on PET-scan prior or following ASCT may be even more important than any of the five selected factors yet it was not systematically recorded or included in the analyses. Also, the exclusion of patients with just one risk factor is based on an exploratory subgroup analysis (showing a higher rate of progression associated with BV), lacks independent confirmation and a strong biological rationale. Still, from a clinical point of view, the aim of selecting patients at higher risk for early treatment with BV seems justified and the proposed approach is useful albeit possibly not optimal. Furthermore, the identification of prognostic markers and marker by treatment interactions is continuously evolving and the search for optimal thresholds and markers is difficult, particularly in a rare disease setting. Still, it should be considered if available or future data could allow a more comprehensive analysis to elucidate the association between prognostic factors and treatment effect.

b. Does the improvement in PFS of approximately 18.8 months upon maintenance treatment of HL patients indicate clinical benefit in the context of the results of the OS and QoL analyses?

The magnitude of the difference in PFS associated with BV compared to placebo is probably better expressed by comparing the Kaplan-Meier estimates at fixed time points (e.g., two years after

randomization) and in any case suffers of possible biases due to possible differences in the censoring mechanisms between treatment groups as well as adjudication. Such biases are difficult to rule out completely although rigorous analysis may provide further reassurance.

Still, even acknowledging possible bias, a sustained treatment effect in a significant proportion of patients being alive and free of progression two years from randomization is apparent, with the effect continuing several years after randomization. In view of the reasons explained above about the clinical importance of delaying progression and the burden of aggressive salvage treatments, the observed effect on PFS is a clear clinical benefit. The available data showing reduced need for salvage therapy including allo-transplant support this conclusion.

The hypothesis that the sustained effect on PFS associated with early treatment with BV represents cure from HD for some patients and that the effect on PFS is associated with a beneficial effect on OS compared to early treatment with placebo, is attractive. An effect on OS would indeed be expected given the sustained effect several years after starting treatment. Thus, failure to observe a treatment effect in terms of OS in the pivotal trial is unexpected.

Failure to observe a difference in OS may be due to a number of reasons, such as the high rate of treatment switching from placebo to BV after progression (assuming that BV in the salvage setting is associated with a comparable or higher effect on OS compared to the early treatment setting) or lack of power of the OS analysis. Absence of an observed difference might also be related to the more aggressive salvage and allotransplant in the observational arm (23 vs 11) for patients with at least 2 risk factors. Alternatively, it may be that early BV treatment strategy is not associated with superior effect on OS compared to placebo and salvage (including BV) or that indeed BV is not associated with any effect on OS (early or in salvage treatment). The available data do not allow definitively establishing the reason for failure to observe an effect on OS in the pivotal trial. Given the strong effect on PFS, the high proportion of treatment switching in the placebo group seems the most plausible hypothesis for failure to observe an effect on OS.

Regardless of the reason for failure to observe a difference in OS, it is reassuring that there is no indication of a possible detriment in terms of OS, except for patients with only one risk factor. Lack of a detrimental effect is a pre-requisite for clinical decisions based on PFS. More importantly, even in the absence of a demonstrated effect on OS, avoiding or delaying salvage treatment in a significant proportion of patients is in itself considered a clinical benefit.

The small detriment in QoL is expected in view of the toxicity associated with BV. However, the impact is not considered to outweigh the benefit in terms of delaying or avoiding subsequent salvage therapy, which is known to be associated with significant morbidity and mortality. The pivotal study supports the tolerability of treatment with BV. Overall 32% v. 6% of patients discontinued BV v. control due to AEs. Dose delays and reductions were 54% v. 25% and 32% v. 3% for BV v. control, respectively. However, treatment discontinuations occurred in the late course of treatment, with the median number of 15 delivered cycles out of 16 planned cycles (albeit at lower dose intensity).

The possibility of continuing follow-up for safety/efficacy of the pivotal trial should be considered in the light of the high risk of second cancers for Hodgkin patients, including second cancers due to subsequent treatments.

c. Please discuss the clinical value of the additional and updated efficacy results (e.g. 3 year PFS data, time to next treatment and number of subsequent treatments and PFS per Investigator Including Clinical Lymphoma Assessments) in the early HL treatment setting.

The different PFS analyses are broadly consistent. Although time to next treatment and number of subsequent treatments are subject to investigator choice, which may be arbitrary and prone to bias,

there are clear differences in terms of subsequent salvage treatments that support the clinical relevance of the PFS findings.

d. Is the safety profile of early treatment acceptable for the intended patient population, also taking into account that not all patients will benefit from this regimen?

From a clinical perspective, the toxicity associated with BV does not outweigh the clinical benefit described above for the overall population and the benefit-risk balance is clearly positive. The fact that not all patients will benefit from this treatment is unfortunately not uncommon for cancer treatments. Ultimately, acceptability of risks of toxicity compared to the importance of delaying progression, worse prognosis and salvage treatments is a matter of judgment that needs to take into account individual preferences, as is usually the case in clinical decisions about adjuvant treatments with the likelihood of better long-term control albeit at the risk of some severe and possibly life-threatening toxicity, in potentially cured patients. In this high-risk population, however, the tradeoff between benefits of early treatment with BV and risks of toxicity appears largely in favour of treatment with BV. The fact that treatment discontinuations due to toxicity was infrequent and the fact that toxicity was largely reversible, support this conclusion (see answers to question b).

2.4.3. Conclusions on the clinical efficacy

The substantial improvement in PFS is considered clinically relevant, however, the translation to objective clinical benefit for patients in terms of OS, or QoL could not be demonstrated in the overall population and for the subgroup population characterized by ≥ 2 risk factors. A statement in the SmPC has been included in section 5.1 that the results of the post hoc analyses indicate increased clinical benefit for patients with two or more risk factors but no difference based on any of the individual risk factors. No benefit in terms of PFS or OS has been observed in patients with one risk factor for relapse or progression. The maintenance treatment showed that the time to first subsequent treatment could be postponed by a few months (~3.7 months) and cause a small decrease in number of subsequent treatments (~12%) in HL patients following ASCT, especially in patients with ≥ 2 risk factors. For patients who relapse after ASCT, there are limited treatment options and patients will eventually die from their disease. Hence, delaying the time to progression and relapse (i.e. prolonging remission), and subsequent administration of toxic treatments is considered a clinically meaningful benefit to this high risk patient population.

The CHMP recommends the following measures necessary to address issues related to efficacy:

- Submission of the final OS data from study SGN35-005 in 2020.

2.5. Clinical safety

Introduction

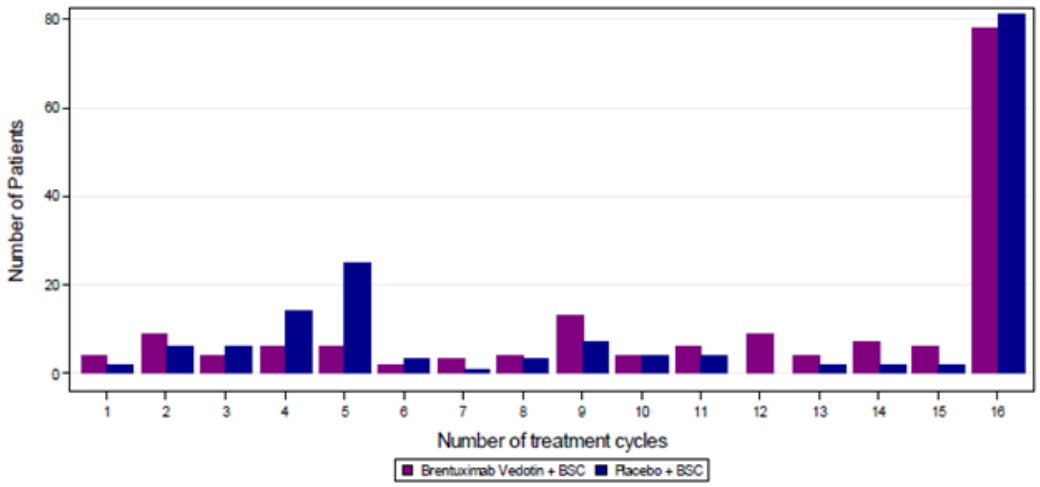
The existing safety profile of brentuximab vedotin monotherapy was mainly based on two single arm phase II studies in 160 HL and sALCL patients. The median number of cycles was 9 in patients with relapsed or refractory HL and 7 in patients with relapsed or refractory sALCL. Treatment-related adverse events were common, leading to treatment discontinuation in 19% of patients and dose modifications in 46% of patients. The most common brentuximab vedotin treatment-related AE in the pivotal studies were peripheral neuropathy (55%, leading to treatment discontinuation (12%), and dose reductions (10%)), myelosuppression, infections and infusion reactions. The majority of AEs were managed by dose delays or reduction. One of the patients suffering from PML upon the use of brentuximab vedotin died.

The safety and tolerability of brentuximab vedotin in patients with HL at increased risk of relapse or progression following ASCT was analysed in one pivotal study, the AETHERA trial. The safety analysis set comprised of 327 patients with at least 1 dose of study treatment.

Patient exposure

ADCETRIS was administered as monotherapy in 160 patients in two phase 2 studies in patients with relapsed or refractory HL or sALCL. The median number of cycles was 9 in patients with relapsed or refractory HL and 7 in patients with relapsed or refractory sALCL. ADCETRIS was also administered as monotherapy in 167 out of 329 patients in a randomized, placebo-controlled phase 3 study in patients with HL at increased risk of relapse or progression following ASCT. In the pivotal study 167 patients were exposed to brentuximab vedotin and 160 patients received placebo. The median number of cycles received in both arms was 15: 47.9 weeks (15 cycles) in the brentuximab vedotin arm, compared with 47.4 weeks (15 cycles) in the placebo arm. Approximately half of the patients in each treatment arm received 16 cycles of study treatment (Figure 24). At the data cut-off for the primary efficacy analysis (18 Aug 2014), 251 patients (76%) remained in long-term follow up; 74% in the brentuximab vedotin arm and 79% in the placebo arm.

Figure 24: Duration of Treatment (number of cycles) - Study SGN35-005



The median relative dose intensity was 95% in the brentuximab vedotin arm versus 99.8% in the placebo arm.

Adverse events

Adverse events (AEs) were classified by system organ class (SOC) and preferred term using MedDRA. In the safety analysis set, at least 1 AE of any grade was reported in 98% of patients in the brentuximab vedotin arm compared with 89% in the placebo arm (Table 22). At least 1 treatment related AE was reported in 88% (brentuximab vedotin) vs. 49% (placebo), and at least one SAE in 25% vs. 13%. An AE that led to treatment discontinuation was reported in 32% vs. 6% of patients.

Table 22: Overview of Adverse Events (Safety Analysis Set) - Study SGN35-005

	Placebo N=160 n (%)	Brentuximab vedotin N=167 n (%)	Total N=327 n (%)
Any AE (a)	142 (89)	163 (98)	305 (93)
Treatment-related AE (b)	79 (49)	147 (88)	226 (69)
Maximum severity of AE (a)			
Grade 1	28 (18)	18 (11)	46 (14)
Grade 2	63 (39)	52 (31)	115 (35)
Grade 3	39 (24)	67 (40)	106 (32)
Grade 4	10 (6)	21 (13)	31 (9)
Grade 5	2 (1)	5 (3)	7 (2)
<Grade 3	91 (57)	70 (42)	161 (49)
≥Grade 3	51 (32)	93 (56)	144 (44)
Any SAE[c]	20 (13)	41 (25)	61 (19)
Any treatment-related SAE (c)	7 (4)	19 (11)	26 (8)
Discontinued treatment due to AE (c)	10 (6)	54 (32)	64 (20)

Source: m5.3.5.1, SGN35-005 CSR, Table 14.3.1.4.1.
Abbreviations: AE=adverse event, SAE=serious adverse event.

(a) Treatment-emergent event, defined as newly occurring (not present at baseline) or worsening after first dose of investigational drug.
(b) Related to treatment as assessed by the investigator.
(c) All events, from time of informed consent to the end of the safety reporting period.

The impact of the following 5 risk factors on the safety profile of patients receiving brentuximab vedotin or placebo in the AETHERA study was analysed by risk factor group (1, 2, or ≥3):

- Relapsed <12 months or refractory to frontline therapy
- Best response of PR or SD to most recent salvage therapy
- Extranodal disease at pre-ASCT relapse
- B symptoms at pre-ASCT relapse
- Two or more prior salvage therapies

Table 23 shows this summary of adverse events by AETHERA treatment arm and risk factor group.

Table 23: Overall Summary of Adverse Events by Number of Risk Factors (Safety Set) - Study SGN35-005

	1 Risk Factor		2 Risk Factors		≥3 Risk Factors	
	Placebo and BSC N=28	BV and BSC N=21	Placebo and BSC N=50	BV and BSC N=63	Placebo and BSC N=82	BV and BSC N=83
Subjects with any event n (%) (a)	27 (96)	20 (95)	44 (88)	62 (98)	71 (87)	81 (98)
Treatment-related adverse event, n (%) (b)	19 (68)	20 (95)	24 (48)	60 (95)	36 (44)	67 (81)
<Grade 3	22 (79)	10 (48)	27 (54)	24 (38)	42 (51)	36 (43)
≥Grade 3	5 (18)	10 (48)	17 (34)	38 (60)	29 (35)	45 (54)
Subjects with any serious adverse event, n (%) (c)	2 (7)	6 (29)	6 (12)	17 (27)	12 (15)	18 (22)

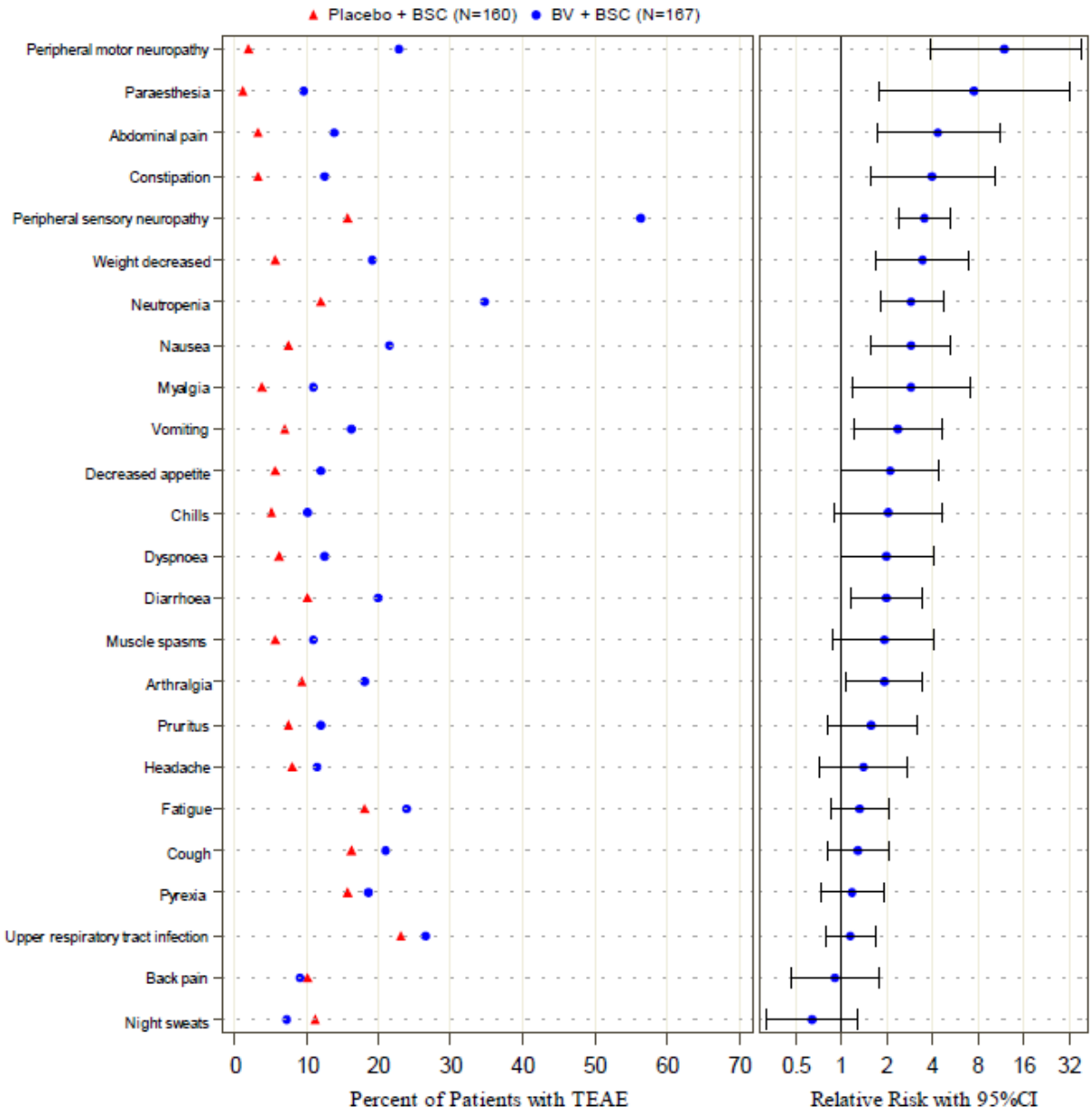
Source: \biostatistics\SGN-035\35-05\Dev\EU_Responses\T14.4.1.4-AESummary_NRiskAcross, run time 23JUL2015 15:07
Representative risk factors for this analysis: HL that occurred <12 months or HL that was refractory to frontline therapy, best response of PR or SD to most recent salvage therapy, extranodal disease at pre-ASCT relapse, B symptoms at pre-ASCT relapse, or ≥2 prior salvage therapies.
BSC=best supportive care, BV=brentuximab vedotin.
(a) Treatment-emergent event, defined as newly occurring (not present at baseline) or worsening after first dose of investigational drug.
(b) Related to treatment with Brentuximab Vedotin as assessed by the investigator.
(c) All events, from time of Study Day 1 (predose) to the end of the safety reporting period.

Treatment emergent adverse events

The treatment emergent adverse events (TEAEs) reported for ≥15% in the brentuximab vedotin arm were peripheral sensory neuropathy (56% vs 16% placebo), neutropenia (35% vs 12%), upper respiratory tract infection (26% vs 23%), fatigue (24% vs 18%), peripheral motor neuropathy (23% vs 2%), nausea (22% vs 8%), cough (21% vs 16%), diarrhoea (20% vs 10%), pyrexia (19% vs 16%), decreased weight (19% vs 6%), arthralgia (18% vs 9%), and vomiting (16% vs 7%).

TEAEs that had a higher risk of occurring in patients in the brentuximab vedotin arm than patients in the placebo arm, as indicated by a relative risk >1 and a confidence interval that does not include 1, were peripheral motor neuropathy, paraesthesia, abdominal pain, constipation, peripheral sensory neuropathy, decreased weight, neutropenia, nausea, myalgia, vomiting, diarrhoea, and arthralgia (Figure 25).

Figure 25: TEAEs Reported for ≥10% of Patients in Either Treatment Arm by Relative Risk (Safety Analysis Set, n=327) - Study SGN35-005



Treatment related adverse events

The treatment-related TEAEs reported for ≥10% of patients in the brentuximab vedotin arm (and more frequently compared with the placebo arm) were peripheral sensory neuropathy (54% of patients); neutropenia (32%); peripheral motor neuropathy (23%); nausea (16%); fatigue (13%); and diarrhoea, arthralgia, and vomiting (10% each; Table 24). Peripheral sensory neuropathy (14% of patients) was the only treatment-related TEAE reported for ≥10% of patients in the placebo arm.

Table 24: Treatment Related TEAEs Reported for At Least 10% of Patients in Either Treatment Arm (Safety Analysis Set) - Study SGN35-005

MedDRA Preferred Term	Placebo N=160 n (%)	Brentuximab vedotin N=167 n (%)	Total N=327 n (%)
Any event	77 (48)	146 (87)	223 (68)
Peripheral sensory neuropathy	23 (14)	90 (54)	113 (35)
Neutropenia	14 (9)	53 (32)	67 (20)
Peripheral motor neuropathy	3 (2)	38 (23)	41 (13)
Nausea	6 (4)	27 (16)	33 (10)
Fatigue	15 (9)	22 (13)	37 (11)
Diarrhoea	4 (3)	17 (10)	21 (6)
Arthralgia	2 (1)	17 (10)	19 (6)
Vomiting	2 (1)	17 (10)	19 (6)

Source: m5.3.5.1, SGN35-005 CSR, Table 14.3.1.6.1.
Treatment-emergent adverse events are presented and defined as newly occurring (not present at baseline) or worsening after first dose of investigational product; sorted by descending order of frequency in the brentuximab vedotin arm.

Grade 3 or higher adverse events

The Grade 3 or higher TEAEs reported for ≥5% of patients in the brentuximab vedotin arm were neutropenia (29% of patients vs 10% in placebo arm), peripheral sensory neuropathy (10% vs 1%), and peripheral motor neuropathy (6% vs 1%). Neutropenia (10% of patients) was the only Grade 3 or higher TEAE reported for ≥5% of patients in the placebo arm.

At least 1 Grade 4 TEAE was reported for 21 patients (13%) in the brentuximab vedotin treatment arm and 10 patients (6%) in the placebo arm. Neutropenia was the most commonly reported Grade 4 TEAE (7% brentuximab vedotin vs 4% placebo).

The number of patients with infection events is shown in Table 25. Patients could have experienced >1 infection event, and this is reflected in the number of events. The duration of infection events was calculated based upon individual infection events.

Table 25: Number and Duration of Treatment-Emergent Infection Events for Patients with Grade 3 or 4 Neutropenia (Safety Set) - Study SGN35-005

		Placebo N=160	BV N=167	Total N=327
Number of Patients with Grade 3 or 4 Neutropenia (AE)	n (%)	16 (10)	49 (29)	65 (20)
Duration of Grade 3 or 4 Neutropenia (AE) Events (a) (days)	n	24	102	126
	Mean	6.88	9.06	8.64
	(95% CI)	(5.05, 8.70)	(7.49, 10.63)	(7.33, 9.96)
	Median	8.00	8.00	8.00
	(Min, Max)	(1, 20)	(1, 71)	(1, 71)
Number of Patients with Grade 3 or 4 Neutropenia (AE) or Grade 3 or 4 Neutrophil count (Lab)	n (%)	25 (16)	67 (40)	92 (28)
Number of Patients with Infection Events (b)	n (%)	12 (48)	38 (57)	50 (54)
Duration of Infection events (b) (days)	n	27	78	105
	Mean	95.63	32.87	49.01
	(95% CI)	(-12.7, 203.9)	(6.94, 58.80)	(15.88, 82.14)
	Median	13.00	11.00	11.00
	(Min, Max)	(2, 1123)	(1, 883)	(1, 1123)
Number of Patients without Grade 3 or 4 Neutropenia (AE) or Grade 3 or 4 Neutrophil count (Lab)	n (%)	135 (84)	100 (60)	235 (72)
Number of Patients with Infection Events	n (%)	65 (48)	57 (57)	122 (52)
Duration of Infection events (b) (days)	n	133	116	249
	Mean	89.31	107.9	97.96
	(95% CI)	(45.24, 133.4)	(59.20, 156.5)	(65.48, 130.4)
	Median	13.00	14.00	14.00
	(Min, Max)	(1, 1404)	(1, 1196)	(1, 1404)

Source: \biostatistics\SGN-035\35-05\Dev\EU_Responses\T14.4.2.1c-Neutropenia, run time 02JUL2015 08:37
AE=adverse event, BV=brentuximab vedotin, CI=confidence interval.
(a) One patient may have multiple events.
(b) Infection events occurring on or after onset day of Grade 3 or 4 neutropenia or Grade 3 or 4 low neutrophil count.
The denominator for infection events is based on number of patients with or without Grade 3 or 4 neutropenia or Grade 3 or 4 low neutrophil count.
If the AE end date is missing, the cutoff date of 18 August 2014 is assigned; event durations are based on the imputed start and end dates.

The median duration of Grade 3 or 4 neutropenia events was the same for the brentuximab vedotin and placebo arms (8 days), and the median duration of infection events was comparable across the treatment and placebo arms (11 vs 13 days).

At least 1 Grade 5 TEAE was reported for 5 patients in the brentuximab vedotin arm and 2 patients in the placebo arm. The Grade 5 TEAEs reported for the brentuximab vedotin arm were acute respiratory distress syndrome (ARDS) (2 patients); and myelodysplastic syndrome (MDS), bladder cancer, and pancreatic cancer (1 patient each). The Grade 5 TEAEs reported for the placebo arm were ARDS and MDS (1 patient each).

Serious adverse event / deaths / other significant events

The SAEs reported for ≥2 patients in the brentuximab vedotin arm were pneumonia (4% vs 3% placebo); pyrexia (4% vs 1%); vomiting (3% vs 1%); nausea (2% vs 1%); hepatotoxicity (2% vs 1%), peripheral sensory neuropathy (2% vs 0%), ARDS and herpes zoster (both 1 % in each arm), and constipation, headache and pneumonitis (all 1% vs 0%).

Table 26: SAEs Reported for At Least 2 Patients in Either Treatment Arm (Safety Analysis Set) - Study SGN35-005

MedDRA Preferred Term	Placebo N=160 n (%)	Brentuximab vedotin N=167 n (%)	Total N=327 n (%)
Any event	20 (13)	41 (25)	61 (19)
Pneumonia	4 (3)	7 (4)	11 (3)
Pyrexia	2 (1)	6 (4)	8 (2)
Vomiting	1 (1)	5 (3)	6 (2)
Nausea	1 (1)	4 (2)	5 (2)
Hepatotoxicity	1 (1)	3 (2)	4 (1)
Peripheral sensory neuropathy	0	3 (2)	3 (1)
Acute respiratory distress syndrome	1 (1)	2 (1)	3 (1)
Herpes zoster	1 (1)	2 (1)	3 (1)
Constipation	0	2 (1)	2 (1)
Headache	0	2 (1)	2 (1)
Pneumonitis	0	2 (1)	2 (1)
Thrombocytopenia	2 (1)	0	2 (1)

Source: m5.3.5.1, SGN35-005 CSR, Table 14.3.1.10.1.
Sorted by decreasing frequency in the brentuximab vedotin arm.

SAEs considered related to study treatment were experienced by 11% of patients in the brentuximab vedotin arm and 4% in the placebo arm. Treatment-related SAEs reported in ≥2 patients in the brentuximab vedotin arm were vomiting in 4 patients (2%), nausea, peripheral sensory neuropathy, pneumonia, and pyrexia in 3 patients each (2%), and ARDS and headache in 2 patients each (1%). The only treatment-related SAE reported in ≥2 patients in the placebo arm was thrombocytopenia in 2 patients (1%).

Deaths

At the cut-off date for data analysis, death was reported for 28 patients (17%) in the brentuximab vedotin arm and 25 patients (16%) in the placebo arm. In the brentuximab vedotin arm, death was considered to be disease related for 18 patients, and not disease related for 9 patients. For the placebo arm, death was considered to be disease related for 17 patients, and not disease related for 7 patients. The disease relationship was unknown for 1 patient in each treatment arm.

The causes of death are described in Table 27.

Table 27: Patient Deaths (Safety Analysis Set) - Study SGN35-005

	Placebo N=160 n (%)	Brentuximab vedotin N=167 n (%)	Total N=327 n (%)
All deaths	25 (16)	28 (17)	53 (16)
Disease related	17 (11)	18 (11)	35 (11)
Not disease related	7 (4)	9 (5)	16 (5)
Unknown	1 (1)	1 (1)	2 (1)
Primary cause of death			
Deaths within 30 days of last dose	0	1 (1)	1 (0)
Acute respiratory distress syndrome	0	1 (1)	1 (0)
Deaths ≥30 days of last dose	25 (16)	27 (16)	52 (16)
Disease related	17 (11)	18 (11)	35 (11)
Acute respiratory distress syndrome	1 (1)	0	1 (0)
Disease progression	9 (6)	5 (3)	14 (4)
Hodgkin's disease	7 (4)	13 (8)	20 (6)
Not disease related	7 (4)	8 (5)	15 (5)
Acute respiratory distress syndrome	0	1 (1)	1 (0)
Aplastic anaemia	1 (1)	0	1 (0)
Bladder cancer	0	1 (1)	1 (0)
Cardiac arrest	0	1 (1)	1 (0)
Graft versus host disease	3 (2)	0	3 (1)
Influenza	1 (1)	0	1 (0)
Lung infection	0	1 (1)	1 (0)
Myelodysplastic syndrome	1 (1)	1 (1)	2 (1)
Myocardial infarction	0	1 (1)	1 (0)
Pancreatic carcinoma	0	1 (1)	1 (0)
Pneumonia	1 (1)	0	1 (0)
Sepsis	0	1 (1)	1 (0)
Disease relationship unknown	1 (1)	1 (1)	2 (1)
Death	0	1 (1)	1 (0)
Pneumonia fungal	1 (1)	0	1 (0)
Death prior to progression by IRF, n (%)	3 (2)	4 (2)	7 (2)
Death prior to progression by INV, n (%)	3 (2)	5 (3)	8 (2)

Source: m5.3.5.1, SGN35-005 CSR, Table 14.3.2.1.
Abbreviations: INV=investigator, IRF=independent review facility.

According to investigator assessment, 5 patients in the brentuximab vedotin arm and 3 patients in the placebo arm died before they experienced disease progression (4 and 3 patients resp. by IRF). For the 5 patients in the brentuximab vedotin arm who died before disease progression, the cause of death was reported as:

- Acute respiratory distress syndrome (ARDS) for 2 patients
    - In 1 patient associated with pneumonitis, considered treatment related (died within 30 days of last dose of study treatment)
    - In 1 patient associated with pneumonia, considered not treatment related. This followed an episode of acute pancreatitis and earlier episode of ARDS both considered treatment related and resolved at time of death (patient died on study day 40).

- Myelodysplastic syndrome (MDS), cardiac arrest and bladder cancer 1 patient each.

For the three patients in the placebo arm who died before disease progression, the cause of death was reported as MDS, aplastic anemia, and fungal pneumonia.

Adverse events of special interest

Adverse events of interest were selected based on the known safety profile of brentuximab vedotin.

Peripheral neuropathy

Pre-existing peripheral neuropathy (PN) was reported for 41% of patients in the brentuximab vedotin arm and 34% in the placebo arm, and attributed to prior neurotoxic chemotherapeutic regimens or other pre-existing conditions. At least one treatment-emergent PN event during the study was reported for 67% of patients in the brentuximab vedotin group and 19% in the placebo group. It was considered treatment related in 63% and 18%, respectively.

PN events of Grade 3 in severity were reported for 13% of patients in the brentuximab vedotin arm and 1% in the placebo arm. No Grade 4 events were reported.

Dose modifications for PN were instituted for 31% of patients in the brentuximab vedotin arm. Overall, 57% of patients with dose modifications for PN received the complete 16 cycles of treatment; for patients who completed fewer than 16 cycles, the median number of cycles was 10.5. Twenty-five percent of patients who had dose modifications for PN subsequently discontinued treatment because of PN (23% on brentuximab vedotin vs 2% placebo).

The median time to onset of a PN event in the brentuximab vedotin group was 13.7 weeks. For the 44 patients with at least one event of peripheral motor neuropathy, the median time of onset was 32.7 weeks. Among patients who experienced peripheral neuropathy in the phase 3 population, the median follow up time from end of treatment until last evaluation was approximately 98 weeks. At the time of last evaluation, 85% of patients who experienced peripheral neuropathy in the brentuximab vedotin arm experienced resolution or improvement of their peripheral neuropathy symptoms. Overall, the median time to resolution or improvement of peripheral neuropathy events in the brentuximab vedotin arm was 23.4 weeks (range from 0.1 weeks to 138.3 weeks).Complete resolution or improvement of all PN events occurred in 73% of patients and complete resolution of all PN events occurred in 59% of patients.

In the brentuximab vedotin safety set, 112 patients (67%) experienced a treatment-emergent event of PN. The majority of PN events had resolved or shown improvement as of the 2014 data cut date and were continuing to resolve or improve as of the 2015 data cut date (Table 28).

Table 28: Study SGN35-005: Reversibility of Treatment-Emergent Peripheral Neuropathy

	2014	2015
N=112	N (%)	N (%)
Resolution or improvement	95 (85)	99 (88)
Complete resolution	66 (59)	74 (66)

Pulmonary toxicity

Overall, 13 patients (4%) experienced at least 1 event of pulmonary toxicity, which included 8 patients (5%) in the brentuximab vedotin group and 5 patients (3%) in the placebo group (Table 29). Preferred terms reported in more than 1 patient in the brentuximab vedotin arm were pneumonitis in 4 patients (2% vs n=1, 1% placebo) and ARDS and pulmonary toxicity in 2 patients (1%) each. Lung infiltration was the only preferred term reported in more than 1 patient in the placebo arm.

Four patients in the brentuximab vedotin arm had pulmonary toxicity AEs considered related to study treatment; preferred terms were Grade 2 lung infiltration/pneumonitis, Grade 4 pneumonitis/Grade 5 ARDS, Grade 2 pneumonitis, and Grade 2 pulmonary toxicity.

Pulmonary toxicities of Grade 3 or higher in severity were reported for 4 patients in the brentuximab vedotin group (pneumonitis and ARDS in 2 patients each, and pulmonary toxicity in 1 patient) and 2 patients in the placebo group (ARDS, and idiopathic pneumonia syndrome).

Table 29: Treatment-Emergent Pulmonary Toxicity Events (Safety Analysis Set) - Study SGN35-005

	Placebo N=160 n (%)			Brentuximab vedotin N=167 n (%)		
MedDRA preferred term	All	≥Grade 3	SAE	All	≥Grade 3	SAE
Any event	5 (3)	2 (1)	2 (1)	8 (5)	4 (2)	4 (2)
Pneumonitis	1 (1)	0	0	4 (2)	2 (1)	2 (1)
Acute respiratory distress syndrome	1 (1)	1 (1)	1 (1)	2 (1)	2 (1)	2 (1)
Lung infiltration	2 (1)	0	0	1 (1)	0	0
Pulmonary toxicity	0	0	0	2 (1)	1 (1)	1 (1)
Idiopathic pneumonia syndrome	1 (1)	1 (1)	1 (1)	0	0	0
Radiation pneumonitis	0	0	0	1 (1)	0	0

Source: m5.3.5.1, SGN35-005 CSR, Table 14.3.1.16.1, Table 14.3.1.16.2, Listing 16.2.7.10.
Includes all terms corresponding to the interstitial lung disease SMQ.

Hepatotoxicity

Overall, 11 patients (7%) in the brentuximab vedotin arm and 4 patients (3%) in the placebo group experienced AEs consistent with hepatotoxicity. The preferred terms reported for ≥1 patient in the brentuximab vedotin arm were hepatoxicity (5 patients), increased alanine aminotransferase (ALT) (3 patients), and hepatic steatosis, increased aspartate aminotransferase (AST), and increased transaminases (2 patients each). Increased blood bilirubin was reported for 2 patients in the placebo arm.

Grade 3 or higher hepatotoxicity was reported for 7 patients in the brentuximab vedotin group and 4 patients in the placebo group. In the brentuximab vedotin arm these events were hepatoxicity (4 patients), increased ALT (3 patients), and increased AST (2 patients). In the placebo arm these were increased blood bilirubin, increased ALT and hepatotoxicity.

One patient in the brentuximab vedotin group was evaluated as a possible Hy's Law candidate. The investigator attributed the patient's hepatic dysfunction to a reactivation of viral hepatitis B and assessed the event as unrelated to brentuximab vedotin. This patient was therefore not considered to have met the criteria for Hy's Law.

Infections

At least one TEAE of infection and infestation SOC was reported for 60% in the brentuximab vedotin arm and 50% in the placebo arm. Grade 3 or higher was reported in 7% and 5% respectively, SAEs were reported in 9 and 4%.

Upper respiratory tract infection was the most commonly reported TEAE in this SOC, occurring in 26% of patients in the brentuximab vedotin arm vs 23% in the placebo arm. Pneumonia was the most commonly reported SAE in both arms (4% brentuximab vedotin and 3% placebo).

Opportunistic infections were reported for 12% in the brentuximab vedotin arm, and 4% in the placebo arm. With the exception of herpes zoster (7% vs 3%) and simplex (4% vs 1%), which were primarily

Grade 1 or Grade 2, the number of reported opportunistic infections was balanced between the treatment groups. No events of bacteraemia, sepsis or septic shock were reported in the brentuximab vedotin arm.

Grade 1 febrile neutropenia, associated with Grade 3 neutropenia and Grade 3 hepatotoxicity, was reported for 1 patient in the brentuximab vedotin arm and considered to be treatment related.

Haematologic toxicity

Neutropenia

Neutropenia was reported as a TEAE for 35% of patients in the brentuximab vedotin arm and 12% in the placebo arm. Grade 3 or higher neutropenia was reported for 29% in the brentuximab vedotin arm and 10% in the placebo arm. One case of febrile neutropenia was reported in the brentuximab vedotin arm. Despite being the most common reason for dose delays (22% vs 7% placebo), no patients had dose reductions or discontinued treatment for neutropenia.

Thrombocytopenia

In 7% of brentuximab vedotin treated patients, thrombocytopenia of any grade was reported, versus 3% in the placebo arm. Grade 3 was reported in 2% of brentuximab vedotin treated patients versus 1% with placebo, Grade 4 in 2% in both arms. Thrombocytopenia led to a dose delay for 2% (n=3) in the brentuximab vedotin arm, and to treatment discontinuation for 1 patient in each treatment arm.

Anaemia

In 8% of brentuximab vedotin treated patients versus 3% in the placebo arm anaemia was reported. Grade 3 was reported for 4% in the brentuximab vedotin arm versus 2% in the placebo arm. No Grade 4 anaemia, dose delay or discontinuation as a result of anaemia was reported.

Hyperglycaemia

Treatment-emergent hyperglycaemia was reported for 3% (n=5) in the brentuximab vedotin group and 1% (n=1; grade 2) in the placebo group. Four of the 5 patients in the brentuximab vedotin group had Grade 3 hyperglycaemia (including 1 patient with treatment emergent Grade 1 Type II diabetes), and one had Grade 1 hyperglycaemia. All 5 patients who had hyperglycaemia in brentuximab vedotin group had pre-existing Grade 3 or 4 obesity, 2 had pre-existing Grade 1 hyperglycaemia, and 1 had baseline Grade 1 fatty liver. Hyperglycaemia began in 3 patients while taking steroids and 3 of the 5 hyperglycaemia events were considered unrelated to study treatment.

Secondary malignancies

When recurrent HL and non-malignant neoplasms were excluded from this analysis, 4 patients (2%) in the brentuximab vedotin arm and 2 patients (1%) in the placebo arm had a secondary malignancy. Secondary malignancies in the brentuximab vedotin group were MDS, pancreatic cancer, lung cancer, and bladder cancer. Secondary malignancies in the placebo group were MDS and mantle cell lymphoma.

Two secondary malignancies (bladder cancer in a brentuximab vedotin patient and mantle cell lymphoma in a placebo patient) were reported during the treatment period and 4 secondary malignancies were reported during long-term follow up (2 reports of MDS [1 in each treatment group] and 1 report each of pancreatic cancer and lung cancer in the brentuximab vedotin group).

All of the patients who developed secondary malignancies died; in 4 of the 6 patients, the secondary malignancy was the primary cause of death.

Other rarely reported TEAEs of clinical importance

Grade 4 acute pancreatitis and Grade 3 myelitis (radiation myelitis in a previous radiation field) were reported for 1 patient each in the brentuximab vedotin treatment arm. Both TEAEs were reported as SAEs

and considered to be treatment related. The grade 4 acute pancreatitis resolved. The grade 3 myelitis did not resolve.

Stevens-Johnson syndrome, toxic epidermal necrolysis, tumour lysis syndrome or progressive multifocal leukoencephalopathy were not reported for any patient in this study.

Immunological events

Anti-drug antibodies (ADAs)

Patients with HL at increased risk of relapse or progression following ASCT in the phase 3 study were tested for antibodies to brentuximab vedotin every 3 weeks using a sensitive electrochemiluminescent immunoassay. At baseline, 12% of patients in the brentuximab vedotin arm, and 8% in the placebo arm were positive for anti-drug antibodies (ADAs). Of the 157 ADA-evaluable patients in the brentuximab vedotin arm, 59 (35%) tested ADA-positive at any post-baseline visit, compared with 32% in the placebo arm. Most patients in both treatment arms were transiently positive post-baseline. Approximately 7% of patients in the phase 2 studies and 6% of patients in the brentuximab vedotin arm of the phase 3 study developed persistently positive anti-drug antibodies (ADA). Post-baseline ADA titres were higher in the brentuximab vedotin arm compared with placebo at all treatment cycles, and post-baseline ADA titres in the placebo arm were similar to baseline titres. In the brentuximab vedotin arm, the majority of ADA-positive patients first showed a positive result at Cycle 2. In the placebo arm, the proportion of patients who first tested ADA positive was distributed among all time points tested. Two patients in the phase 3 study experienced adverse reactions consistent with IRRs that led to discontinuation of treatment.

The overall incidence of AEs and the incidence of more severe AEs did not appear to be greater in persistently ADA-positive patients relative to transiently ADA-positive or never positive patients (Table 30). The number of SAEs was slightly higher (10%, n=1/10) in persistently positive brentuximab vedotin treated patients compared with ADA negative brentuximab vedotin treated patients (5%, n=5/92). However, interpretation of these data is limited by the small number of patients who became persistently ADA positive.

Table 30: Overall summary of adverse events by ADA status (baseline ADA-negative) - Study SGN35-005

	Brentuximab Vedotin (N=138)		
Parameter	Negative (N=92) n (%)	Transiently Positive (N=36) n (%)	Persistently Positive (N=10) n (%)
Subjects with any AE, n (%)[a]	89 (97)	36 (100)	10 (100)
Treatment-related AE, n (%)[b]	76 (83)	34 (94)	10 (100)
Max severity of AE, n (%) [a]			
Grade 1	12 (13)	2 (6)	0
Grade 2	29 (32)	11 (31)	4 (40)
Grade 3	37 (40)	15 (42)	5 (50)
Grade 4	9 (10)	7 (19)	1 (10)
Grade 5	2 (2)	1 (3)	0
Max severity of AE, n (%)			
< Grade 3	41 (45)	13 (36)	4 (40)
≥ Grade 3	48 (52)	23 (64)	6 (60)
Subjects with any treatment-related SAE, n (%)[c]	5 (5)	7 (19)	1 (10)
Discontinued treatment due to AE, n (%)[c]	26 (28)	15 (42)	3 (30)

a Treatment-emergent event, defined as newly occurring (not present at baseline) or worsening after first dose of study drug.
b Related to treatment as assessed by the investigator.
c All events, from time of informed consent to the end of the safety reporting period.

Infusion related reactions (IRR)

For patients in the brentuximab vedotin arm who were ADA negative at baseline, a higher incidence of infusion-related reactions (IRRs) was observed in persistently ADA-positive patients (9/10, 90%) and transiently ADA-positive patients (9/36, 25%), relative to ADA-negative patients (4/92, 4%).

Overall, possible IRRs occurred in 15% of patients (n=25) in the brentuximab vedotin arm and 2% of patients (n=3) in the placebo group. The most frequently reported IRRs in the brentuximab vedotin arm were nausea and chills (4% each), and dyspnoea, headache, pruritus and rash in 2% each. Most patients (52%; 13/25) with an IRR had only 1 IRR, 28% (n=7) had 2 IRRs and 10% (n=5) had ≥3 events. The majority of patients (60%; 15/25) had their first IRR in Cycle 2.

In either the phase 2 population or the phase 3 population, the adverse events most commonly associated with IRRs were mild to moderate (Grade 1 or Grade 2), transient (occurring in 1 or 2 treatment cycles), and did not lead to significant dosing delays or reductions, or treatment discontinuation and included headache, rash, back pain, vomiting, chills, nausea, dyspnoea, pruritus, and cough. Grade 3 events were reported in 3 of the 25 patients who experienced IRRs. No Grade 4 IRRs were reported.

IRRs were reported as SAEs for two patients in the brentuximab vedotin arm (1 patient with Grade 2 bradycardia and Grade 3 syncope and another patient with Grade 2 bronchospasm, presyncope, and rash). Both patients discontinued because of the events. No other patients discontinued due to IRRs. No cases of anaphylaxis were reported.

Study procedures did not require premedication for patients before the brentuximab vedotin infusion, but it was allowed before subsequent infusions for patients who experienced a prior IRR, at the discretion of the investigator and according to institutional guidelines.

Laboratory findings

At least 1 Grade 3 or higher laboratory abnormality was reported for 41% of patients in the brentuximab vedotin arm and 18% of patients in the placebo arm. The Grade 3 or higher abnormal clinical laboratory values reported for ≥5% of patients in the brentuximab vedotin arm were low neutrophils (23% of patients), low leukocytes and lymphocytes (11% each), and low platelets (5%). Grade 3 or higher abnormal clinical laboratory values reported for ≥5% of patients in the placebo arm were low neutrophils (6% of patients) and low lymphocytes (5%).

Hematologic and clinical chemistry values were further discussed in the previous sections hepatotoxicity, hematologic toxicity and hyperglycaemia.

ECG changes

ECGs for 6 patients were noted as having clinically significant abnormalities; all were associated with cardiac AEs or baseline conditions. With the exception of Grade 3 pleural effusion at the end of treatment in a patient in the placebo arm, all cardiac AEs with clinically significant ECGs were Grade 1 or 2 in severity.

Of the patients with normal ECGs at baseline with available EOT ECG values, only 1 patient in the placebo arm demonstrated an abnormal ECG at EOT that was considered to be clinically significant. Of the patients with abnormal ECG values at baseline, 3 patients in the brentuximab vedotin arm demonstrated an abnormal ECG value at EOT; however, none of these was considered to be clinically significant.

ECOG

Worsening of ECOG status from baseline to any post-baseline time point occurred in 36% of patients in the brentuximab vedotin arm, compared with 25% in the placebo arm. In most patients, the change from baseline was 1 point. In 4% of patients in the brentuximab vedotin arm, and 1% in the placebo arm, the change was 2.

Improvement in ECOG status occurred for 22% in the brentuximab vedotin arm and 27% in the placebo arm, in all patients with 1 point.

In order to determine the clinical relevance of the observed difference in ECOG performance status deterioration between treatment arms, the Applicant provided information on ECOG deterioration in relation to the occurrence of (S)AEs, or treatment discontinuation/ dose modifications. The majority of SAEs, regardless of treatment arm, were not associated with a change in ECOG PS (64% brentuximab vedotin vs 53% placebo). However, ECOG score deterioration appears to be associated with occurrence of some SAEs (23/100, 23% brentuximab vedotin; 15/36, 42% placebo). The number of treatment discontinuation events was comparable between the treatment arms (152 events brentuximab vedotin vs 156 placebo). The majority of patients who discontinued treatment, regardless of treatment arm, experienced no change in ECOG PS. The number of patients experiencing any increase in ECOG PS was comparable between the treatment arms (28/156, 18% brentuximab vedotin; 23/152, 15% placebo). Dose modifications were more common for patients receiving brentuximab vedotin vs placebo (508 vs 105); nevertheless, the majority of dose modifications, regardless of treatment arm, were not associated with a change in ECOG PS. Although some dose modifications (<10% in each treatment arm) were associated with an increase from baseline in ECOG PS (+1, 6% brentuximab vedotin vs 9% placebo; +2 <1% brentuximab vedotin vs 0% placebo), no meaningful difference was observed between the treatment arms.

Safety in special populations

Elderly

In the pivotal study, only 8 patients were 65 years or older. No separate safety analysis has been performed for this subgroup.

Hepatic and renal impairment

Patients with hepatic or renal impairment were excluded from the pivotal study. No separate clinical studies in patients with hepatic or renal impairment have been submitted.

Paediatric patients

No data is available in children or adolescents under 18 years.

Pregnancy and lactation

It is known that brentuximab vedotin causes teratogenicity and embryo-foetal lethality in animals, and therefore woman should avoid pregnancy during treatment. Women of childbearing potential who enrolled in the pivotal study were required to have a negative serum or urine pregnancy test result within 7 days of receiving the first dose of the study treatment, and must have agreed to use an effective method of contraception during the study and for 30 days after the study treatment period. This period is extended to 6 months after treatment with a SmPC update in 2014.

Safety related to drug-drug interactions and other interactions

No new drug interactions were evaluated in the pivotal study.

The MAH provided data regarding drug-drug interactions with medications that are CYP3A substrates, already taken by patients in the pivotal study and the relation between the use of these drugs with the occurrence of neutropenia was explored. Patients who received brentuximab vedotin and concomitant strong inhibitors of CYP3A4/5 (n=20) or strong CYP3A4/5 inducers (n=1) were identified; 146 patients received brentuximab vedotin, but did not take any concomitant strong inhibitors or inducers of CYP3A4/5. The small sample of patients receiving a strong CYP3A4/5 inhibitor or inducer precludes definitive conclusions; however, strong CYP3A4/5 inhibitors did not appear associated with either adverse events of Grade 3 or 4 neutropenia, nor lab values of Grade 3 or Grade 4 low neutrophils. Only 1 patient received both brentuximab vedotin and a strong inducer of CYP3A4/5; this patient did not experience a Grade 3 or 4 AE or lab value consistent with neutropenia. Receipt of a strong inhibitor of CYP3A4/5 may have slightly increased the incidence of dose modifications. Of the 20 patients who received brentuximab vedotin and a concomitant strong inhibitor of CYP3A4/5, 14 patients (70%) had a dose modification compared with 58% (85/146) of patients who did not receive a concomitant strong inhibitor of CYP3A4/5. The 1 patient receiving a concomitant strong inducer of CYP3A4/5 had a dose modification.

Discontinuation due to adverse events

Adverse events that led to treatment discontinuation

In the AETHERA study, treatment discontinuation could occur due to disease progression, adverse event(s), completion of 16 cycles of study treatment, or investigator or patient decision, similar to the pivotal HL Study SG035-0003. Table 31 shows time to treatment discontinuation for AETHERA patients by treatment arm and for Study SG035-0003.

Table 31: Analysis of Time to Dose Discontinuation (Safety Sets [a]) - Studies SGN35-005 (AETHERA) and SG035-0003 (Pivotal HL)

	Placebo and BSC N=160	BV and BSC N=167	35-03 BV N=102
Time to Dose Discontinuation (months)			
Events n (%)	160 (100)	167 (100)	102 (100)
Censored n (%)	0	0	0
Median (95% CI)	10.9 (6.87, 11.04)	11.0 (9.66, 11.04)	6.2 (5.72, 7.98)
Min, Max	0.7, 14.3	0.7, 13.8	0.7, 12.9
Kaplan-Meier Estimates of Probability of being event free at (b):			
3 Months	83.1% [n=133]	88.0% [n=147]	85.3% [n=87]
6 Months	63.1% [n=101]	77.8% [n=130]	56.9% [n=58]
9 Months	52.5% [n=84]	61.1% [n=102]	35.3% [n=36]
12 Months	6.3% [n=10]	9.6% [n=16]	6.9% [n=7]

Source: \biostatistics\SGN-035\35-05\Dev\EU_Responses\T14.1.2.5-Time_to_TreatmentDisc_w03, run time 23JUL2015 15:01
Study 35-03 data is based upon the 2014-08-27 EU-RMP data cut.
BSC=best supportive care, BV=brentuximab vedotin, CI=confidence interval, NE=not estimable, 35-03=SG035-0003.
(a) In studies SGN35-005 and SG035-0003, patients receiving at least 1 dose of BV.
(b) Probability of being event-free [n=number of subjects at risk].

An AE led to treatment discontinuation for 32% in the brentuximab vedotin arm and 6% in the placebo arm. Peripheral sensory neuropathy (14% of patients vs 1% placebo) and peripheral motor neuropathy (7% vs 1%) were the 2 most commonly reported AEs that led to treatment discontinuation for the brentuximab vedotin arm. All other AEs that led to discontinuation occurred in ≤1% of patients in both arms. Serious adverse reactions that led to treatment discontinuation in two or more patients in either the phase 2 or the phase 3 population were peripheral sensory neuropathy, peripheral motor neuropathy, vomiting, and acute respiratory distress syndrome. Paresthesia also led to discontinuation in two or more patients in either the phase 2 or the phase 3 population.

Adverse events that led to dose modification

Table 32 shows time to dose modification for AETHERA patients by treatment arm and for Study SG035-0003.

Table 32: Analysis of Time to Dose Modification (Safety Sets [a]) - Studies SGN35-005 (AETHERA) and SG035-0003 (Pivotal HL)

	Placebo and BSC N=160	BV and BSC N=167	35-03 BV N=102
Time to Dose Modification (months)			
Events n (%)	50 (31)	100 (60)	63 (62)
Censored n (%)	110 (69)	67 (40)	39 (38)
Median (95% CI)	NE (9.92, NE)	4.8 (2.96, 6.90)	4.9 (2.37, 6.67)
Min, Max	0.0*, 11.3*	0.0*, 10.7*	0.0*, 10.8
Kaplan-Meier Estimates of Probability of being event free at (b):			
3 Months	83.9% [n=97]	57.0% [n=83]	56.8% [n=50]
6 Months	72.2% [n=73]	43.6% [n=56]	45.5% [n=24]
9 Months	63.8% [n=59]	32.8% [n=38]	19.4% [n=6]

Source: \biostatistics\SGN-035\35-05\Dev\EU_Responses\T14.1.2.8-Time_to_DoseModified_w03, run time 06JUL2015 14:10
Study 35-03 data is based upon the 2014-08-27 EU-RMP data cut.
BSC=best supportive care, BV=brentuximab vedotin, CI=confidence interval, NE=not estimable, 35-03=SG035-0003.
Censored observations are denoted by *
(a) In studies SGN35-005 and SG035-0003, patients receiving at least 1 dose of BV.
(b) Probability of being event-free [n=number of subjects at risk].

An AE led to a dose delay for 54% in the brentuximab vedotin treatment arm and 25% in the placebo arm. The most commonly reported AEs (≥2% of patients) that led to a dose delay for the brentuximab vedotin arm were neutropenia (22% of patients); peripheral sensory neuropathy (16%); upper respiratory tract infection and peripheral motor neuropathy (6% each); and herpes zoster and thrombocytopenia (2% each).

An AE led to a dose reduction for 32% in the brentuximab vedotin arm and 3% in the placebo arm. The most commonly reported AEs that led to dose reduction for the brentuximab vedotin arm were peripheral sensory neuropathy (22% of patients vs 1% on placebo) and peripheral motor neuropathy (6% vs 1%) with hepatotoxicity and paraesthesia reported for 2 patients each (both 1% vs 0%).

At least 1 dose delay was reported for per-protocol reasons (i.e. AEs) in 54% of the brentuximab vedotin treated patients and 26% on placebo. Overall, 9% of all doses (186/2004) in the brentuximab vedotin arm and 3% (56/1756) in the placebo arm were delayed for AEs.

Dose reductions occurred at least once in 32% of patients in the brentuximab vedotin arm, and in 3% in the placebo arm. The majority of patients who had brentuximab vedotin dose reductions had the first dose reduction after multiple cycles of treatment at the 1.8 mg/kg dose. Table 33 shows number of patients with dose modification by cycle.

Table 33: Dose modification by patient (safety dataset) - Studies SGN35-005

	Placebo and BSC (N=160) n (%)	Brentuximab Vedotin and BSC (N=167) n (%)	All Subjects (N=327) n (%)
Number of subjects with dose delay by cycle, n1/n2(%) (cont.)			
12	1/85 (1)	5/106 (5)	6/191 (3)
13	3/85 (4)	10/97 (10)	13/182 (7)
14	7/83 (8)	6/93 (6)	13/176 (7)
15	2/81 (2)	5/86 (6)	7/167 (4)
16	0	4/80 (5)	4/159 (3)
Number of subjects with dose reduced by cycle, n1/n2(%)			
1	0	1/167 (1)	1/327 (0)
2	0	5/163 (3)	5/321 (2)
3	0	7/154 (5)	7/306 (2)
4	0	13/150 (9)	13/296 (4)
5	1/132 (1)	18/144 (13)	19/276 (7)
6	3/107 (3)	20/138 (14)	23/245 (9)
7	3/104 (3)	23/136 (17)	26/240 (11)
8	3/103 (3)	28/133 (21)	31/236 (13)
9	3/100 (3)	31/129 (24)	34/229 (15)
10	3/93 (3)	30/116 (26)	33/209 (16)
11	3/88 (3)	31/112 (28)	34/200 (17)
12	4/85 (5)	33/106 (31)	37/191 (19)
13	4/85 (5)	32/97 (33)	36/182 (20)
14	3/83 (4)	33/93 (35)	36/176 (20)
15	3/81 (4)	32/86 (37)	35/167 (21)
16	3/79 (4)	31/80 (39)	34/159 (21)

Post marketing experience

Brentuximab vedotin was first approved on 19 August 2011 in the United States and has been granted

marketing authorization in 45 countries. It has been authorised under conditional approval in the EU through a Centralised Procedure since 25 October 2012.

Up to 19 August 2014, the cumulative estimated patient exposure to brentuximab vedotin is 14,614 patients, including 2382 subjects from company- and investigator-sponsored clinical trials, 2399 patients from the Named Patient Program, 53 patients from the Special Access Program, 36 patient from the compassionate-use program, and approximately 9744 patients from the post marketing setting.

The previously established favourable efficacy has not changed. Review of the serious adverse events reported for brentuximab vedotin post-marketing during interval period of the last PSUR (20 February 2014 – 19 August 2014) showed the main areas of concern SOCs General disorders and administration site conditions, followed by Nervous system disorders. The safety profile of the marketing experience on adverse event level in the monotherapy setting is considered to be in line with the safety profile as reflected in the SmPC.

Data from study SGN35-016 (a phase 1/2 study in which the safety and efficacy of the use of brentuximab vedotin in combination with bendamustine was investigated), a higher incidence and greater severity of infusion related reactions was observed compared to the results of the monotherapy pivotal trials. The risk of infusion related reactions will be closely monitored by the MAH and discussed in future PSURs.

2.5.1. Discussion on clinical safety

Patient population and exposure

The safety analysis set of the pivotal trial is considered sufficient, although information concerning uncommon adverse events may be limited. Since this is the first brentuximab vedotin pivotal trial with a comparator arm, the trial did, however, allow for more precise evaluation of treatment-related adverse events as compared with the previous single arm registration trials.

A high number of dose modifications was observed in the brentuximab vedotin arm compared with placebo, and with the registration phase II trials. In the AETHERA trial, 54% of patients in the brentuximab vedotin arm experienced a dose delay (vs 26% placebo) and 32% a dose reduction (vs 3% placebo). Exposure-adjusted analyses did not reveal a clear association between the number of brentuximab vedotin cycles and the number of adverse events within the pivotal study. The median relative dose intensity was >95% in both arms, indicating that patients were able to receive the planned doses of study treatment.

Patients in both AETHERA study arms experienced a similar median time to discontinuation that was longer than that experienced by patients treated on pivotal HL Study SG035-0003. This difference is due in large part to treatment discontinuation prior to receipt of 16 cycles due to disease progression (45/102, 44% of G035-0003 patients) and adverse events (20/102, 19.6%) in these heavily pretreated patients with active disease at the start of the study. Not all patients in the current study had active disease, 42% had achieved CR as best response with the most recent prior salvage therapy, 34% PR, and 24% stable disease. In addition, 35% of patients were PET FDG-avid prior to ASCT, and 34% was PET FDG-negative.

Adverse events, serious adverse events and deaths

As expected, higher percentages of AEs (98% vs 89%), treatment-related AEs (88% vs 49%), SAEs (25% vs 13%) and discontinuation due to AEs (32% vs 6%) were observed in the brentuximab vedotin arm compared with placebo. The type of AEs in the pivotal trial was comparable with the phase II HL and sALCL patient population, though frequencies were higher. The latter is likely due to the higher median number of treatment cycles received in the AETHERA trial (15, compared with 6-9 in the previous two phase II studies).

The most frequent observed treatment-related AEs occurring more frequently with brentuximab vedotin treatment compared to placebo were: peripheral sensory (54% vs 14% placebo) and motor (23% vs 2%) neuropathy, neutropenia (32% vs 9%), nausea (16% vs 4%), fatigue (13% vs 9%), diarrhoea (10% vs 3%), arthralgia and vomiting (both 10% vs 1%). The distribution over the different grades of AEs was comparable with the known safety profile in the phase II HL and sALCL patient population, most AEs being grade 2 or 3 in severity. A higher number of grade 5 TEAEs was reported in the brentuximab vedotin arm (n=5) compared with the placebo arm (n=2). TEAEs that had a higher risk of occurring in patients in the brentuximab vedotin arm than patients in the placebo arm and have changed frequency from common to very common are peripheral motor neuropathy, constipation, upper respiratory infection, arthralgia, chills. New ADRs that have been included following analysis of the safety database were decreased weight (very common) and abdominal pain (very common).

Among the separate risk groups the incidence of AEs was comparable indicating that compared to patients with 2 or more risk factors, the subgroup of patients with only 1 risk factor is equally exposed to the risk of experiencing adverse events, while benefitting less from the brentuximab vedotin treatment (the latter as concluded in the efficacy part of this report).

The frequency of SAEs with brentuximab vedotin treatment was higher compared with placebo (25% vs 13%), but lower compared with known safety data in the phase II HL and sALCL patient population (31%). Only pyrexia and vomiting were observed with >2% difference between the brentuximab vedotin and placebo arm, although the frequency in the brentuximab vedotin arm was still low (4 and 3%, respectively). Serious adverse drug reactions in the phase 2 and the phase 3 population were: pneumonia, acute respiratory distress syndrome, headache, neutropenia, thrombocytopenia, constipation, diarrhoea, vomiting, nausea, pyrexia, peripheral motor neuropathy and peripheral sensory neuropathy, hyperglycaemia, demyelinating polyneuropathy, tumour lysis syndrome and Stevens-Johnson syndrome.

Adverse reactions led to treatment discontinuation in 19% and 32% of patients receiving brentuximab vedotin in the phase 2 and the phase 3 population, respectively. Serious adverse reactions that led to treatment discontinuation in two or more patients in either the phase 2 or the phase 3 population were peripheral sensory neuropathy, peripheral motor neuropathy, vomiting, and acute respiratory distress syndrome. Paresthesia also led to discontinuation in two or more patients in either the phase 2 or the phase 3 population.

The total number of deaths was similar in both arms (16%*).* Slightly more patients in the brentuximab vedotin arm (n=5: 2 ARDS; MDS, cardiac arrest and bladder cancer 1 each) compared with placebo (n=3: MDS, aplastic anaemia and fungal pneumonia) died before they experienced disease progression. In the two cases with ARDS reported as the cause of death, one (pneumonitis) was considered treatment-related.

Among the AEs of special interest, no new safety signals were observed.

Peripheral neuropathy

The frequency of peripheral sensory (56%) and motor neuropathy (23%) were higher compared with previously observed frequencies (44% and <10%, respectively). Peripheral neuropathy was typically Grade 1 or Grade 2 in severity and managed with dose reductions and delays, and complete resolution or improvement occurred in 73% of patients. In the phase 3 population, at the time of last evaluation, the majority of patients in the brentuximab vedotin arm (85%) had improvement or resolution of their peripheral neuropathy symptoms. For patients who reported peripheral neuropathy, brentuximab vedotin treatment discontinuation occurred in 23%, dose reductions were reported in 29%, and dose delays occurred in 22% of patients compared with known safety data from the phase II HL and sALCL patient population (8%, 13% and 9% respectively), again likely due to a difference in treatment duration.

Pulmonary toxicity

Data from non-clinical single- and repeat-dose toxicology studies demonstrate that the lung is not a primary target organ of toxicity of brentuximab vedotin. The risk of pulmonary toxicity associated with the concomitant use of brentuximab vedotin and bleomycin was identified in clinical studies, and the combination is listed as a Contraindication in the SmPC and as an Identified Risk in the EU-RMP. However, cases of pulmonary toxicity in patients not receiving concomitant bleomycin have been reported in patients receiving brentuximab vedotin as well. Cases of pulmonary toxicity including acute respiratory distress syndrome (ADRS) and pneumonitis some with fatal outcomes, have been reported (SmPC section 4.4)

Haematological cell toxicity

Infections

Overall the frequency of infections was similar as previously reported (60% brentuximab vedotin arm phase III AETHERA study, 58% in previous phase II studies). As expected with brentuximab vedotin treatment, upper respiratory tract infection was the most common reported TEAE in the infection SOC. No events of bacteraemia, sepsis, or septic shock were reported in the brentuximab vedotin arm. Serious infections and opportunistic infections were very common in patients treated with this medicine (see section 4.4). In the phase 2 and the phase 3 population, the most commonly reported opportunistic infections were herpes zoster and herpes simplex.

The imbalance in opportunistic infections is mostly caused by herpes zoster and simplex infections. Herpes Zoster is a known common AE of brentuximab vedotin. SmPC section 4.8 has been updated to include herpes simplex infections. The majority of opportunistic infections reported in patients treated with brentuximab vedotin have been non-serious and considered manageable.

Neutropenia and thrombocytopenia

Microscopic effects in bone marrow correlated with anaemia and leukopenia (primarily neutropenia) and thrombocytopenia in repeat-dose toxicology studies in monkeys and rats dosed with brentuximab vedotin (see EPAR). Consistent with the nonclinical toxicology results, neutropenia is a common ADR (35% brentuximab vedotin vs 12% placebo). Frequencies were higher compared with the phase II HL and sALCL population (TEAE in 21%, grade 3 in 7-13%), likely explained by the higher number of treatment cycles in the pivotal AETHERA trial. Nevertheless, neutropenia appeared to be well managed with the protocol-specified recommendations for haematologic toxicity (i.e., dose delay, growth factor support). Thromboctypenia and anaemia occurred less frequently (7% and 8% in the brentuximab vedotin arm) than neutropenia. Grade $\geqslant$3 thrombocytopenia was not shown to be associated with bleeding events.

Thrombocytopenia is the only hematologic AE resulting in treatment discontinuation in this study, and occurred in 1 patient from each treatment group. None of the hematologic AEs led to dose reduction.

ADA and immunological events

Similar percentages of patients were ADA positive at any post-baseline visit in the two treatment arms (32-35%), although higher titers were observed with brentuximab vedotin treatment as compared to placebo. It is reassuring that lower percentages of patients in the brentuximab vedotin arm were persistently positive post-baseline (8%) as compared to the placebo arm (12%), and that the overall incidence of (more severe) AEs did not appear to be higher in persistently ADA-positive patients relative to transiently ADA-positive or never positive patients. However, IRRs were observed more frequently and were more severe in patients with ADAs (90% (9/10) of persistently ADA positive patients).

IRRs occur very commonly in patients treated with brentuximab vedotin, and frequencies in the AETHERA study (15%) were in line with known frequencies in the phase II HL and sALCL populations (11%). Currently premedication is only administered in patients with prior infusion-related reactions. The

majority of events have been non-serious and the included safety information in the SmPC section 4.4 is considered sufficient.

Additional expert consultations

See clinical discussion.

Assessment of paediatric data on clinical safety

No paediatric data are available.

2.5.2. Conclusions on clinical safety

Overall, no new safety concerns have been identified with brentuximab vedotin treatment of HL patients at increased risk of relapse or progression following ASCT. Frequencies of several known ADRs, as well as of treatment discontinuation due to AEs, dose delays and dose reductions appeared higher than what is previously known from brentuximab vedotin treatment, likely attributed to the longer treatment duration. Among the separate risk groups, the incidence of adverse events was comparable. The safety profile was consistent with the known safety information from brentuximab vedotin in the previous approved HL and sALCL indications.

2.5.3. PSUR cycle

The PSUR cycle remains unchanged.

The next data lock point will be 19/02/2016.

The Annex II related to the PSUR, refers to the EURD list which remains unchanged.

2.6. Risk management plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan (RMP):

The PRAC considered that the RMP version 5.2 (dated 23 February 2015) is acceptable. However, the applicant was requested to remove “safety in patients with hepatic and renal impairment” from the list of missing information, based on the results of study SGN35-008, submitted under variation EMEA/H/C/002455/II/0012. Furthermore, the applicant was required to provide a justification for postponing the submission date of interim or final reports for trial SGN35-014. The CHMP endorsed this advice without changes.

The applicant implemented the changes in the RMP as requested by PRAC and CHMP and it also confirmed that there has been no postponement to any interim or final reports including SGN35-014 (MEA 015) for which the final CSR is due on 30 September 2019.

The CHMP endorsed the RMP version 6.3 (dated 19 May 2016) with the following content:

Safety concerns

Table 34: Summary of the Safety concerns

Important identified risks	• Progressive multifocal leukoencephalopathy • Pulmonary toxicity associated with combination use of bleomycin and brentuximab vedotin • Peripheral neuropathy (sensory and motor) • Neutropenia • Febrile neutropenia • Thrombocytopenia • Anaemia • Infection including bacteraemia/sepsis/septic shock • Opportunistic infection • Infusion-related reactions • Hyperglycaemia • Stevens-Johnson syndrome / Toxic epidermal necrolysis (TEN) • Tumour lysis syndrome • 1Antitherapeutic antibodies
Important potential risks	• Pancreatitis acute • Hepatotoxicity • Pulmonary toxicity • Gastrointestinal complications • Reproductive toxicity • Thymus depletion (paediatric) • Interaction with drugs modifying CYP3A4 activity
Missing information	• Safety in paediatrics • Safety in elderly • Safety in patients with cardiac impairment • Long term safety

Pharmacovigilance plan

Table 35: Ongoing and Planned Additional PhV Studies/Activities in the Pharmacovigilance Plan

Study/Activity Type, Title and Category (1-3)	**Objectives**	**Safety Concerns Addressed**	**Status (Planned, Started)**	**Submission Date of Interim / Final Report (Planned / Actual)**
SG035-0004: Phase 2 study of SGN-35 in treatment of patients with r/r sALCL (Category 2)	Single-agent efficacy, safety, PK	Peripheral neuropathy (sensory & motor)	CSR finalized: Dec 2011	Jan 2012 (actual)
			LTFU ongoing	Annual reports: Until 2016 or until OS data are sufficiently mature (≥ 50% OS events observed), whichever occurs earlier
SGN35-014: Randomized, double-blind, placebo-controlled, phase 3 study of brentuximab vedotin and CHP (A+CHP) versus CHOP in frontline treatment of patients with CD30-positive mature T-cell lymphomas	Multi-agent efficacy (PFS, OS, CR); safety	Peripheral neuropathy (sensory & motor); IRRs; ATAs	Ongoing	CSR (primary endpoint): Sep 2018 (estimated) Sep 2019 (due)

Study / Activity Type, Title and Category (1-3)	Objectives	Safety Concerns Addressed	Status (Planned, Started)	Submission Date of Interim / Final Report (Planned / Actual)
(MTCLs) (Category 3)				
C25001: Randomized, open-label, phase 3 trial of brentuximab vedotin versus physician's choice (methotrexate or bexarotene) in patients with CD30-positive cutaneous T-cell lymphoma (Category 3)	Comparison with physician's choice; efficacy (ORR, PFS, CR, OS); safety	Peripheral neuropathy (sensory & motor); IRRs (baseline & safety); ATAs (baseline & safety)	Ongoing	CSR (Registration): Jan 2017
C25002: Phase 1/2 PIP study of brentuximab vedotin in pediatric patients with r/r sALCL or HL (Category 3)	Safety; PK; paediatric maximum tolerated dose (MTD) and/or RP2D Immunogenicity, antitumor activity	Safety in paediatrics; thymus depletion (paediatric); ATAs	Ongoing	CSR (primary analysis): Dec 2016 CSR addendum (LTFU): Aug 2017
C25004: Phase 1, open–label, PIP study of OEPA followed by SGN-35 and COPDAC in paediatric patients with high-risk, newly diagnosed HL (Category 3)	Safety; determination of MTD or highest HPD in combination Evaluation of PK, immunogenicity, activity of combination therapy, and mobilization of peripheral blood stem cells for ASCT	Safety in paediatrics; thymus depletion (paediatric)	Planned	LPO: On/before Dec 2018
C25005: Phase 1 study to estimate MMAE metabolites in human plasma and urine in patients with r/r classical HL or r/r sALCL receiving brentuximab vedotin (Category 3)	Estimation of MMAE and metabolites; concentration of antibody-drug conjugate (ADC) and total antibody (TAb) in serum; ATAs; safety	ATAs	Ongoing	Primary endpoint CSR: Oct 2015 Final CSR (safety): Feb 2016
C25006: Phase 4, open-label, single-arm study of brentuximab vedotin in patients with r/r sALCL (Category 2)	Single-agent efficacy (ORR, duration of tumour control, including duration of response, PFS, and CR; proportion of patients proceeding to SCT; OS), safety and tolerability, PK, immunogenicity	ATAs	Ongoing	Primary CSR: Q1 2016
C25007: Phase 4, open-label, single-arm study of brentuximab vedotin in patients with r/r HL who are not suitable for SCT or multiagent chemotherapy (Category 2)	Single-agent efficacy (ORR, duration of tumour control, including duration of response, PFS, and CR; proportion of patients proceeding to SCT, OS), safety and tolerability, PK, immunogenicity	Peripheral neuropathy (sensory & motor); IRRs; ATAs	Ongoing	Primary CSR: Q2 2016
MA25101 (PASS): Observational cohort study	Safety: identification of potential risk	Peripheral neuropathy (sensory & motor);	Ongoing	Interim CSR: Apr 2016

Study / Activity Type, Title and Category (1-3)	Objectives	Safety Concerns Addressed	Status (Planned, Started)	Submission Date of Interim / Final Report (Planned / Actual)
of the safety of brentuximab vedotin in the treatment of r/r CD30+ HL and r/r sALCL Category 2	factors for peripheral neuropathy	neutropenia; infection including bacteremia/sepsis/ septic shock; opportunistic infection; IRRs; hyperglycemia; febrile neutropenia; pulmonary toxicity (devoid of concomitant bleomycin); safety in elderly; longer-term safety		Final CSR: Dec 2018

The PRAC agreed by consensus decision that routine PV is sufficient to assess the effectiveness of the RMMs.

Risk minimisation measures

Table 36: Summary table of the Risk Minimisation Measures

Safety Concern	Routine Risk Minimization Measures	Additional Measures
IMPORTANT IDENTIFIED RISKS		
Progressive multifocal leukoencephalopathy (PML)	Wording in SmPC Section 4.4, 4.8.	Not applicable
Pulmonary toxicity associated with combination use of bleomycin and brentuximab vedotin	Wording in SmPC Section 4.3, 4.4.	Not applicable
Peripheral neuropathy (sensory and motor)	Wording in SmPC Section 4.2, 4.4, 4.8.	Not applicable
Neutropenia	Wording in SmPC Section 4.2, 4.4, 4.8.	Not applicable
Febrile neutropenia	Wording in SmPC Section 4.2, 4.4, 4.8.	Not applicable
Thrombocytopenia	Wording in SmPC Section 4.4, 4.8.	Not applicable
Anaemia	Wording in SmPC Section 4.4, 4.8.	Not applicable
Infection including bacteraemia / sepsis / septic shock	Wording in SmPC Section 4.4, 4.8.	Not applicable
Opportunistic infection	Wording in SmPC Section 4.4, 4.8.	Not applicable
Infusion-related reactions (IRRs)	Wording in SmPC Section 4.4, 4.8.	Not applicable
Hyperglycaemia	Wording in SmPC Section 4.4, 4.8.	Not applicable
Stevens-Johnson syndrome (SJS) / Toxic epidermal necrolysis (TEN)	Wording in SmPC Section 4.4, 4.8.	Not applicable

Safety Concern	Routine Risk Minimization Measures	Additional Measures
Tumour lysis syndrome (TLS)	Wording in SmPC Section 4.4, 4.8.	Not applicable
Antitherapeutic antibodies (ATAs)	Wording in SmPC Section 4.4, 4.8.	Not applicable
IMPORTANT POTENTIAL RISKS		
Pancreatitis acute	Wording in SmPC Section 4.4, 4.8.	Not applicable
Hepatotoxicity	Wording in SmPC Section 4.2, 4.4, 4.8, 5.2.	Not applicable
Pulmonary toxicity	Wording in SmPC Section 4.3, 4.4, 4.8.	Not applicable
Gastrointestinal complications	Wording in SmPC Section 4.4, 4.8.	
Reproductive toxicity	Wording in SmPC Section 4.6, 5.3.	Not applicable
Thymus depletion (paediatric)	Wording in SmPC Section 4.2, 5.3.	Not applicable
Interaction with drugs modifying CYP3A4 activity	Wording in SmPC Section 4.2, 4.5, 5.2.	Not applicable
MISSING INFORMATION		
Safety in paediatrics	Wording in SmPC Section 4.2, 5.2.	Not applicable
Safety in elderly	Wording in SmPC Section 4.2, 5.2.	Not applicable
Safety in patients with cardiac impairment	Wording in SmPC Section 5.1.	Not applicable
Long-term safety	Wording in SmPC Section 4.2., 5.1.	Not applicable

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1. 4.2, 4.4, 4.8 and 5.1 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the applicant and has been found acceptable for the following reasons: the new indication has not resulted in significant changes to the Patient Information Leaflet (PIL).

3. Benefit-Risk Balance

Benefits

Beneficial effects

To support the current variation, one phase III, randomised, double blind, and placebo-controlled pivotal study, the AETHERA trial, was submitted. The primary endpoint of the pivotal study was met, i.e. a statistically significant PFS improvement of median 18.8 months (42.9 months vs. 24.1 months placebo; HR 0.57, 95% CI 0.4, 0.8, IRF analysis) for patients in the brentuximab vedotin arm compared with placebo. The primary efficacy results were supported by several PFS sensitivity and subgroup analyses, all showing benefit of brentuximab vedotin treatment, except for a small subgroup of patients ≥65 years of age (n=8). The observation that 94% of PFS events occurred within 25 months after randomization suggests that the majority of patients in the brentuximab vedotin arm in whom no PFS event has occurred are cured.

The PFS subgroup analyses indicated efficacy of brentuximab vedotin in patients with CR as well as active disease, and in patients with ≥1, ≥2, and ≥3 risk factors for progressive disease, which is reassuring. PFS benefit at fixed time points is observed in the group of brentuximab vedotin-treated patients with ≥2 risk factors (in particular at the plateau phase of the KM curves), whereas no benefit was observed in patients with only 1 risk factor group. These observations are supported by the results from the PFS HR analyses.

In the analysis of the secondary OS endpoint, no beneficial effect of brentuximab vedotin compared with placebo was observed, where the median OS was not reached; the estimated 24 month OS rate was 88% with brentuximab vedotin vs 89% with placebo; HR 1.15. OS did not show a difference between the treatment arms for the patient groups with 2 or ⩾3 risk factors.

The exploratory endpoints for QoL generally did not exceed the minimally important difference. However, data for medical resource utilisation (MRU) seems to show lower values for brentuximab vedotin compared to placebo.

The data from time-to-next-treatment (TTNT) analyses showed that brentuximab vedotin can postpone the time to first subsequent treatment in the ITT population (~3.7 months) and cause a small decrease in number of subsequent treatments in patients with 2 or more risk factors (~12%).

The results of the variants of the time to treatment failure analyses strengthen the conclusion that brentuximab vedotin brings clinical benefit.

Uncertainty in the knowledge about the beneficial effects

The substantial gain in PFS in the brentuximab vedotin treatment arm over the placebo group did not result in a gain in OS, as it would have been expected. The reason for this discrepancy in unknown, but a possibility could be that it is due to the cross-over of placebo patients once they progressed. The mature OS results are expected in 2020 and hence, the CHMP has recommended the MAH to submit the final OS data in 2020. Furthermore, no improvement in QoL in the overall population and in patients with 2 or ≥3 risk factors was observed.

The PFS improvement is supported by several sensitivity and subgroup analyses. However, it seems as if most PFS benefit is obtained in approximately the first 6 months after start of treatment, considering the rapid increase in events in the placebo arm in this period and the less steep part of the PFS KM curve/plateau phase in both study arms thereafter. This may indicate the existence of a subgroup of patients, likely those at risk for early disease relapse, that experience a larger treatment effect on PFS of brentuximab vedotin treatment. During the assessment, post hoc subset analyses using 5 risk factors showed that there was no benefit observed in patients with 1 risk factor compared with patients with 2 and 3 risk factors. The reason for this finding is unclear, but it is plausible that the number of patients in

the 1 risk factor group was limited, i.e. 21 patients vs. 28 patients on placebo, hampering any definitive conclusion.

The PFS analyses showed a consistent trend towards benefit for patients who received brentuximab vedotin compared with patients who received placebo with the exception of patients ⩾ 65 years of age (n=8). Few patients ≥ 65 years of age (n=8) were included, hence, no final conclusions regarding efficacy of brentuximab vedotin in this subgroup.

Risks

Unfavourable effects

No new safety signals have been observed. A higher percentages of AEs (98% vs 89%), treatment related AEs (88% vs 49%), SAEs (25% vs 13%) and discontinuation due to AEs (32% vs 6%) were observed in the brentuximab vedotin arm compared with the placebo study group.

The most frequent observed treatment related AEs occurring more frequently with brentuximab vedotin treatment compared with placebo were: peripheral sensory (54% vs 14% placebo) and motor (23% vs 2%) neuropathy, neutropenia (32% vs 9%), nausea (16% vs 4%), fatigue (13% vs 9%), diarrhoea (10% vs 3%), arthralgia and vomiting (both 10% vs 1%).

The frequency of SAEs with brentuximab vedotin treatment was also higher compared with placebo (25% vs 13%). Only pyrexia and vomiting were observed with >2% difference between the brentuximab vedotin and placebo arm, although the frequency in the brentuximab vedotin arm was still low (4% and 3%, respectively).

Treatment discontinuation (primarily due to peripheral neuropathy) (32% brentuximab vedotin vs 6% placebo), dose delays (54% vs 25%) and dose reductions (32% vs 3%) due to AEs all occurred more frequently in the in the brentuximab vedotin arm.

Among the separate risk groups, i.e. 1 risk factor, 2 risk factor or ≥3 risk factors, the incidence of adverse events was comparable.

The total number of deaths was similar in both arms (16%).

Uncertainty in the knowledge about the unfavourable effects

In the pivotal trial, a slight imbalance in pulmonary toxicity events (5% brentuximab vedotin vs 3% placebo) has been observed, with pneumonitis being the most common observed event in the brentuximab vedotin arm (2%). In addition, two deaths due to ARDS have been observed in the pivotal trial, one of which was considered treatment-related. Similar to previous evaluations of brentuximab vedotin, the risk of pulmonary toxicity due to brentuximab vedotin treatment could not be ruled out, although additional measures are not deemed necessary at this time. The risk of pulmonary toxicity is included in the RMP as an important identified risk.

Effects Table

Table 37. Effects table for brentuximab vedotin in HL– AETHERA study

Effect	Short Description	Unit	Brentuximab vedotin Treatment n=164	Placebo Control n=165	Uncertainties/ Strength of evidence	References
Favourable Effects						
PFS	Time from randomization until	Months (KM median;	42.9 (30.4, 42.9)	24.1 (11.5, -)	Substantial PFS improvement. Uncertainty regarding plateau phase of KM curves and	

	objective tumour progression per IRF or death in ITT population	95% CI)			difference in KM curves of IRF primary analysis and INV sensitivity analysis based on clinical assessments. In addition, patients with 2 or ≥3 risk factors for relapse in the first 6 months of treatment seem to have most benefit of brentuximab vedotin treatment, influencing overall PFS results.	
OS	Time from randomization to death due to any cause	Months (KM median; 95% CI)	Median OS not reached. Estimated 24 month OS rate 88%	Median OS not reached. Estimated 24 month OS rate 89%	Immature data, no difference between treatment arms. Results confounded by large crossover. Results not influenced by subgroup analyses based on presence of 1, 2 or ≥3 risk factors.	
QoL	Measured with patient reported outcome instrument: EQ-5D, summarized every 3 months	TTO US index value (1= perfect health)	Mean decrease in 24 months: 0.897 to 0.757	Mean decrease in 24 months: 0.907 to 0.787	Differences between arms did not exceed minimally important difference of 0.06.	
		Visual analog score (scale 0-100; 100= best possible health state)	Mean increase in 24 months: ~77 to ~85	Mean increase in 24 months: ~77 to 85	Differences between arms did not exceed minimally important difference of 7.	
Unfavourable Effects						
AEs	Incidence as percentage of patients involved	Percentage	All grades 98% ≥grade 3 AE: 56% Treatment related: 88% *(primarily: peripheral sensory neuropathy, neutropenia, nausea, fatigue, diarrhoea, arthralgia and vomiting)*	All grades 89% ≥grade 3 AE: 32% Treatment related: 49% *(primarily: peripheral sensory neuropathy, neutropenia and fatigue)*	High frequency of AEs, also higher grades compared with placebo and known safety information. This is related to the increased exposure in this pivotal study as compared to the registration studies. Overall, there was no difference in (S)AEs occurrence in the subgroups based on presence of 1, 2 or ≥3 risk factors.	
SAEs	Incidence as percentage of patients	Percentage	25% *(primarily pneumonia,*	13% *(primarily pneumoni*	High frequency of SAEs compared with placebo, although similar to known	

	involved		*pyrexia and vomiting)* Treatment related: 11%	*a)* Treatment related: 4%	safety information. This is related to the increased exposure in this pivotal study as compared to the registration studies.	
Dis-continuation and dose modification	Incidence as percentage of patients involved	Percentage	Discontinuation 32%, Dose delay 54% and Dose reduction 32%	Discontinuation 6%, Dose delay 25% and Dose reduction 3%	High frequencies compared with placebo and known safety information. This is related to the increased exposure in this pivotal study as compared to the registration studies.	

Data cut off primary analyses: 18 Aug 2014

Abbreviations: AE: adverse event, EQ-5D: European Quality of Life 5-dimensional, INV: investigator, ITT: intention to treat, KM: Kaplan Meier, OS: overall survival, PFS: progression free survival, SAE: serious adverse events, TTO: time trade off, US: United States,

Benefit-Risk Balance

Importance of favourable and unfavourable effects

For patients at increased risk of relapse or progression following ASCT, a PFS difference (~30%) between the study arms at 24 and 36 months represent a clinically relevant difference. Sensitivity analyses support the primary endpoint. Most of the improvement is observed within the first 6 months which then plateaus in both study arms. The presence of 2 or ≥3 risk factors conferred the population which benefited the most. Patients with 1 risk factor showed no benefit from the treatment. There is also evidence that brentuximab vedotin slightly reduces the number of subsequent therapies, delays the first and perhaps the second next line of treatment and reduces the need for allogeneic SCT, although it should be considered that this is in relation to the placebo group where no active treatment has been given yet. .

However, it is of concern is that despite this substantial improvement in PFS, a clinical benefit in terms of increased OS in the early treatment following ASCT for patients at increased risk of relapse or progression was not demonstrated neither for the total study population, nor for the patient groups with 2 or ⩾3 risk factors. The same applies to the effect on QoL. This would suggest that there is a lack of sustained clinical benefit for patients who start brentuximab vedotin treatment before disease progression or relapse compared to observation.

No new safety concerns were raised. Most adverse events were non-serious and manageable, but still a high frequency of treatment related AEs (88%, including 54% peripheral neuropathy), SAEs (25%), and even a (very small) risk of death in the brentuximab vedotin treatment arm was observed. The majority of patients had improvement or resolution of the peripheral neuropathy symptoms. The longer duration of the brentuximab vedotin treatment as compared to the indication of treatment of patients following relapse is likely to explain the higher frequencies of several known AEs, as well as of treatment discontinuation due to AEs, dose delays and dose reductions. Therefore, the risks are known and manageable by recommendations in the SmPC and risk minimisation activities in the RMP.

Benefit-risk balance

The CHMP considers that the benefits of brentuximab vedotin in terms of increase in PFS in patients with HL at increased risk of relapse or progression following ASCT outweighs the risk, at least in patients with at least two risk factors. This will be further discussed below. The side-effects are considered acceptable. Therefore, the CHMP considers that the benefit-risk balance is positive.

Discussion on the Benefit-Risk Balance

The current standard of care for patients with HL at increased risk of relapse or progression following ASCT is the "watchful waiting" approach where patients are treated once they have disease progression or relapse. Most patients with relapsed or refractory HL who are not cured by ASCT will eventually die of their lymphoma. For patients who relapse or progress after ASCT generally occurs early; approximately 71% of relapse/progression events occur within 1 year post-ASCT and 90% within 2 years post ASCT. Historical outcomes for the approximately 50% of patients experiencing progressive disease post-ASCT are extremely poor, with a median post-progression survival of 1.3 years, and a 5-year survival rate of 20% or less. No established system of risk factors systematically guides clinicians to identify patients at risk of relapse or progression post-ASCT. It is accepted that multiple risk factors are considered when treating physicians evaluate HL patients following ASCT for the risk of relapse, comparable to those criteria identified in the pivotal trial. Hence, there is a need for new therapies for patients with relapsed or refractory HL and for those who may be at risk of disease progression post-ASCT.

Brentuximab vedotin current indication includes patients that have relapsed/progressed after ASCT. The MAH proposes to extend this indication to treatment of patients at an earlier stage post-ASCT treatment for patients at increased risk of progression. This approach may offer a chance of eradicating any residual lymphoma after ASCT. A clear and relevant clinical benefit in terms of PFS was observed in patients with at least 2 risk factors. This patient population is at an increased risk of progression and early treatment with brentuximab has shown that it delayed subsequent more aggressive treatments with higher toxicity, with a small decrease in the number of subsequent treatments. This in itself, as suggested by the SAG-O experts, is considered a relevant clinical benefit for patients. It is somewhat of a concern that the observed PFS improvement did not translate into an improvement in OS, an objective and undisputable clinical benefit for patients. The lack of OS benefit could be explained by the limited number of events that have occurred thus far and the high frequency of cross-over to brentuximab vedotin (44% of patients) in the placebo arm. The high OS rate at 24 months (88%, although similar between treatment arms) does indicate that next line therapy is still successful with no detrimental effect after brentuximab vedotin treatment, which is reassuring. Moreover, the data seems also to suggest that those patients who experience prolonged remissions in the experimental arm could potentially be cured in the long term. Although QoL was not affected, a trend towards lower medical resource utilisation was also observed. Considering the poor prognosis in patients with high risk factors, the CHMP considers that a positive benefit risk balance for maintenance treatment with brentixumab vedotin in the high risk patient subgroup has been established.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of Indication to include the treatment of adult patients with Hodgkin Lymphona (HL) at increased risk of relapse or progression following autologous stem cell transplantation (ASCT). As a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet and the RMP (v.6.3) are updated in accordance.

In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet.

The variation leads to amendments to the Summary of Product Characteristics, Package Leaflet and to the Risk Management Plan (RMP).

Moreover, on the basis of the assessment performed by the CHMP concerning the extension of indication of Adcetris for the treatment of adult patients with Hodgkin Lymphona at increased risk of relapse or progression following autologous stem cell transplantation, contained in Annex IV, the CHMP is of the opinion that the extension of indication presents a significant clinical benefit as referred to in Article 14 (11) of Regulation (EC) No 726/2004

This CHMP recommendation is subject to the following conditions:

Conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list)) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk management plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

When the submission of a PSUR and the update of a RMP coincide, they should be submitted at the same time.

In addition, an updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- ***Specific Obligation to complete post-authorisation measures for the conditional marketing authorisation***

This being a conditional marketing authorisation and pursuant to Article 14(7) of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Description	Due date
Further Overall Survival follow up of the patients included in study	SG035-004 annual reports until

Description	Due date
SG035-004 should be provided, including sub-analysis of patients ≥100kg. The data should be presented in the context of historical controls.	2016 or when the overall survival data is sufficiently mature (at least 50% OS events observed), whichever occurs earlier
A Non-interventional Post-Authorisation Safety Study (PASS) in both studied HL and sALCL patient populations (n=500) should be performed including a sufficient number of sALCL patients (i.e. at least n=50, Study MA25101).	Final study report: 31/12/2018
To perform a single-arm study in a similar patient population as the sALCL population investigating response rate, duration of response, rate of (second) ASCT and data in subpopulations (including but not necessarily restricted to ALK status and age) based on a CHMP agreed protocol (Study C25006).	Final Study Report by: Q1 2021
To perform a single-arm studying r/r HL population not eligible for ASCT investigating response rate, PFS, OS, proportion of patients proceeding to transplant and safety (n=approx 60 pts) based on a CHMP agreed protocol.	Final study report by: Q2 2017