NAME OF THE MEDICINAL PRODUCT
Adcetris 50mg, powder for concentrate for solution for infusion.

NAME AND STRENGTH OF ACTIVE SUBSTANCES
Each single-use vial contains 50 mg of brentuximab vedotin.
Each mL contains 5 mg of brentuximab vedotin, after reconstitution.
Excipients: *Citric acid monohydrate, sodium citrate dihydrate,* α,α*-Trehalose dihydrate, polysorbate 80.*

PRODUCT DESCRIPTION
Adcetris powder for concentrate for solution for infusion is supplied as white to off-white lyophilized cake or powder.

Brentuximab vedotin is an antibody-drug conjugate composed of a CD30-directed monoclonal antibody (recombinant chimeric immunoglobulin G1 (IgG1), produced by recombinant DNA technology in Chinese Hamster ovary cells) that is covalently linked to the antimicrotubule agent monomethyl auristatin E (MMAE).

CLINICAL PHARMACOLOGY
Pharmacologic class: CD30-directed antibody-drug conjugate
ATC code: L01XC12
Pharmacotherapeutic group: monoclonal antibodies

Mechanism of Action
Adcetris is an Antibody Drug Conjugate (ADC) that delivers an antineoplastic agent that result in apoptotic cell death selectively in CD30-expressing tumor cells. Nonclinical data suggest that the biological activity of Adcetris results from a multi-step process. Binding of the ADC to CD30 on the cell surface initiates internalization of the ADC-CD30 complex, which then trafficks to the lysosomal compartment. Within the cell, a single defined active species, MMAE, is released via proteolytic cleavage. Binding of MMAE to tubulin disrupts the microtubule network within the cell, induces cell cycle arrest and results in apoptotic death of the CD30-expressing tumor cell.
Contributions to the mechanism of action by other antibody associated functions have not been excluded.

Pharmacodynamics Effects (e.g. subsections: Resistance, In vitro Susceptibility Data)
General
No primary pharmacodynamic relationships have been identified.

Cardiac Electrophysiology
Forty-six (46) patients with CD30-expressing hematologic malignancies were evaluable of the 52 patients who received 1.8 mg/kg of Adcetris every 3 weeks as part of a phase 1, single-arm, open-label, multicenter cardiac safety study. The primary objective was to evaluate the effect of Adcetris on cardiac ventricular repolarization and the predefined primary analysis was the change in QTc from baseline to multiple time points in Cycle 1.
The upper 90% confidence interval (CI) was <10 msec at each of the Cycle 1 post-baseline time-points. These data indicate the absence of clinically relevant QT prolongation due to Adcetris administered at a dose of 1.8 mg/kg in patients with CD30-expressing malignancies.

Pharmacokinetic Properties
General Introduction
The pharmacokinetics of Adcetris were evaluated in phase 1 studies and in a population pharmacokinetic analysis of data from 314 patients.

Absorption and Bioavailability
Monotherapy
The serum pharmacokinetics of ADC following an intravenous dose of Adcetris were similar to other antibody products. Maximum concentrations were typically observed at the end of infusion or the sampling time point closest to the end of infusion. A multiexponential decline in ADC serum concentrations was observed with a terminal half-life

of approximately 4 to 6 days. Exposures were approximately dose proportional. After multiple-dose administration of Adcetris, ADC steady-state was achieved by 21 days, consistent with the terminal half-life estimate. Minimal to no accumulation of ADC was observed with multiple doses at the every 3-week schedule.
The elimination of MMAE was limited by its rate of release from ADC. The time to maximum concentration ranged from approximately 1 to 3 days after each infusion. MMAE exposures decreased after multiple doses of Adcetris with approximately 50% to 80% of the exposure of the first dose being observed at subsequent doses.

Combination Therapy
The pharmacokinetics of Adcetris in combination with doxorubicin, vinblastine, and dacarbazine (AVD) were evaluated in a single phase 3 study in 661 patients (C25003). Population pharmacokinetic analysis indicated that the pharmacokinetics of Adcetris in combination with AVD were consistent with that in monotherapy.
After multiple-dose, IV infusion of 1.2 mg/kg Adcetris every two weeks, maximal serum concentrations of ADC were observed near the end of the infusion and elimination exhibited a multiexponential decline with a $t_{1/2z}$ of approximately 4 to 5 days. Maximal plasma concentrations of MMAE were observed approximately 2 days after the end of infusion, and exhibited a mono-exponential decline with a $t_{1/2z}$ of approximately 3 to 4 days.
After multiple-dose, IV infusion of 1.2 mg/kg Adcetris every two weeks, steady-state trough concentrations of ADC and MMAE were achieved by Cycle 3. Once steady-state was achieved, the pharmacokinetics (PK) of ADC did not appear to change with time. ADC accumulation (as assessed by AUC_{14D} between Cycle 1 and Cycle 3) was 1.27-fold. The exposure of MMAE (as assessed by AUC_{14D} between Cycle 1 and Cycle 3) appeared to decrease with time by approximately 50%.
The pharmacokinetics of Adcetris in combination with CHP were evaluated in a single phase 3 study in 223 patients (SGN35-014). After multiple-dose IV infusion of 1.8 mg/kg Adcetris every 3 weeks, the pharmacokinetics of ADC and MMAE were similar to those of monotherapy.

Distribution
In vitro, the binding of MMAE to human serum plasma proteins ranged from 68-82%. MMAE is not likely to displace or to be displaced by highly protein-bound drugs. In vitro, MMAE was a substrate of P-gp and was not a potent inhibitor of P-gp.
In humans, the mean steady state volume of distribution was approximately 6-10 L for ADC.

Metabolism
In vivo data in animals and humans suggests that only a small fraction of MMAE released from Adcetris is metabolized. In vitro data indicate that the MMAE metabolism that occurs is primarily via oxidation by CYP3A4/5. In vitro studies using human liver microsomes indicate that MMAE inhibits CYP3A4/5 but not other isoforms. MMAE did not induce any major CYP450 enzymes in primary cultures of human hepatocytes.

Elimination
An excretion study was undertaken in patients who received a dose of 1.8 mg/kg of Adcetris (brentuximab vedotin). Approximately 24% of the total MMAE administered as part of the ADC during an Adcetris infusion was recovered in both urine and feces over a 1-week period. Of the recovered MMAE, approximately 72% was recovered in the feces and the majority of the excreted MMAE was unchanged. A lesser amount of MMAE (28%) was excreted in the urine and the majority was excreted unchanged.

Special Populations
Pediatric
Clinical studies of Adcetris did not include sufficient numbers of subjects below 18 years of age to determine whether they respond differently from older subjects. Safety and efficacy have not been established.

Geriatric
The population pharmacokinetics of brentuximab vedotin as monotherapy were examined from several monotherapy studies, including data from 380 patients up to 87 years old (34 patients ≥65-<75 and 17 patients ≥75 years of age). Additionally, the population pharmacokinetics of brentuximab vedotin in combination with AVD were examined, including data from 661 patients up to 82 years old (42 patients ≥65-<75 and 17 patients ≥75 years of age). The influence of age on pharmacokinetics was investigated in each analysis and it was not a significant covariate.

Renal impairment
A study evaluated the pharmacokinetics of Adcetris and MMAE after the administration of 1.2 mg/kg of Adcetris to patients with mild (n=4), moderate (n=3) and severe (n=3) renal impairment. Compared to patients with normal renal function, MMAE exposure increased approximately 1.9-fold in patients with severe renal impairment.

Hepatic impairment
A study evaluated the pharmacokinetics of Adcetris and MMAE after the administration of 1.2 mg/kg of Adcetris to patients with mild (Child-Pugh A; n=1), moderate (Child-Pugh B; n=5) and severe (Child-Pugh C; n=1) hepatic impairment. Compared to patients with normal hepatic function, MMAE exposure increased approximately 2.3-fold in patients with hepatic impairment.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity
Carcinogenicity studies with Adcetris (brentuximab vedotin) or MMAE have not been conducted.

Mutagenicity
MMAE was negative for mutagenicity in the bacterial reverse mutation assay (Ames test) and the mouse lymphoma forward mutation assay. The in vivo rat bone marrow micronucleus study revealed aneugenic rather than clastogenic micronuclear formation. These results were consistent with the pharmacological effect of MMAE on the mitotic apparatus (disruption of the microtubule network) in cells.

Impairment of Fertility
The effects of Adcetris on human male and female fertility have not been studied. However, results of repeat-dose toxicity studies in rats indicate the potential for Adcetris to impair male reproductive function and fertility. Testicular atrophy and degeneration were observed in a 4-week rat study when Adcetris was given weekly at intravenous doses of 5 or 10 mg/kg.
These changes were partially reversible following a 16-week treatment-free period.
While not observed with ADCETRIS, ovarian effects were observed in repeat dose toxicity studies of other MMAE-containing ADCs. A mild to moderate decrease in, or absence of, secondary and tertiary ovarian follicles was observed in young female cynomolgus monkeys at doses ≥ 3 mg/kg weekly for 4 weeks. These effects showed evidence of recovery 6 weeks after the end of dosing and no changes were observed in primordial follicles.

CLINICAL STUDIES

Hodgkin Lymphoma
Study SG035-0003
The efficacy and safety of Adcetris as a single agent was evaluated in an open-label, single-arm, multicenter study in 102 patients with relapsed or refractory Hodgkin Lymphoma (HL).

Table 1: Summary of Baseline Patient and Disease Characteristics in the Phase 2 Relapsed or Refractory HL Study

Patient Characteristics	**N = 102**
Age (median)	31 years (15 – 77)
Gender	48M (47%) / 54F (53%)
ECOG status 0 1 Prior ASCT Prior chemotherapy regimens Time from ASCT to first post-transplant relapse	 42 (41%) 60 (59%) 102 (100%) 3.5 (1 – 13) 6.7 mo (0 – 131)
Disease Characteristics	
Primary Refractory to frontline therapy	72 (71%)
Refractory to most recent therapy	43 (42%)
Relapsed to most recent therapy	59 (58%)

All patients had a histologically confirmed CD30- expressing disease and had at least one prior autologous stem cell transplant (ASCT). Seventy-two patients (71%) had primary refractory HL, defined as a failure to achieve a complete response to, or progressed within 3 months of completing frontline therapy; 43 patients (42%) were refractory and 59 patients (58%) had relapsed following their most recent prior therapy. Patients had received a median of 3.5 prior systemic chemotherapies. The median time from ASCT to first post-transplant relapse was 6.7 months. Patients

received up to 16 cycles of therapy; the median number of cycles received was 9 (ranging from 1 to 16). The primary endpoint, Objective Response Rate, was 74.5%. See Table 2 below for other pre-specified endpoints**.**

Table 2: Efficacy Results in Relapsed or Refractory Hodgkin Lymphoma Patients Treated with 1.8 mg/kg of Adcetris Every 3 Weeks

Best Clinical Response[a] (N=102[b])	**IRF N (%)**	**95% CI**	**Investigator N (%)**	**95 % CI**
Objective response rate (CR + PR)	76 (75)	64.9, 82.6	73 (72)	61.8, 80.1
Complete response (CR)	34 (33)	24.3, 43.4	34 (33)	24.3, 43.4
Partial response (PR)	42 (41)	N/A	39 (38)	N/A
Disease control rate (CR + PR + SD)	98 (96)	90.3, 98.9	101 (99)	94.7, 100
Duration of Response[c]	**Median per IRF**	**95% CI**	**Median per Investigator**	**95% CI**
Objective response rate (CR + PR)	6.7 months	3.6, 14.8	11.2 months	7.7, 18.7
Complete response (CR)	Not reached	10.8, NE[d]	Not reached	20.5, NE
Progression free survival (PFS)[e]	**Median per IRF**	**95% CI**	**Median per Investigator**	**95 % CI**
-	5.6 months	5.0, 9.0	9.3 months	7.1, 12.2
Overall Survival (OS)[f]	**Median**	**95% CI**	**-**	**-**
Median	40.5 months	28.7, NE	-	-

[a] *Independent review facility (IRF) and investigator assessments per Revised Response Criteria for Malignant Lymphoma (Cheson, B., Pfistner, B., Juweid, M., Gascoyne, R., & Specht, L., Horning, S., …Diehl, V. (2007). Revised response criteria for malignant lymphoma. Journal of Clinical Oncology, 25104, 579-586. doi:10.1200/JCO.2006.09.2403). Treatment response was assessed by spiral CT of chest, neck, abdomen and pelvis; PET scans and clinical data. Response assessments were performed at cycles 2, 4, 7, 10, 13 and 16 with PET at cycles 4 and 7.*

[b] *Patients ranged in age from 15 to 77 years (overall median, 31 years), 53% were female and 87% white, 34% of patients had B-symptoms at baseline.*

[c] *Duration of response is calculated from date of response to date of progression. The median follow-up time from first dose for patients who achieved objective response (OR) per IRF was 9.0 months.*

[d] *Not estimable*

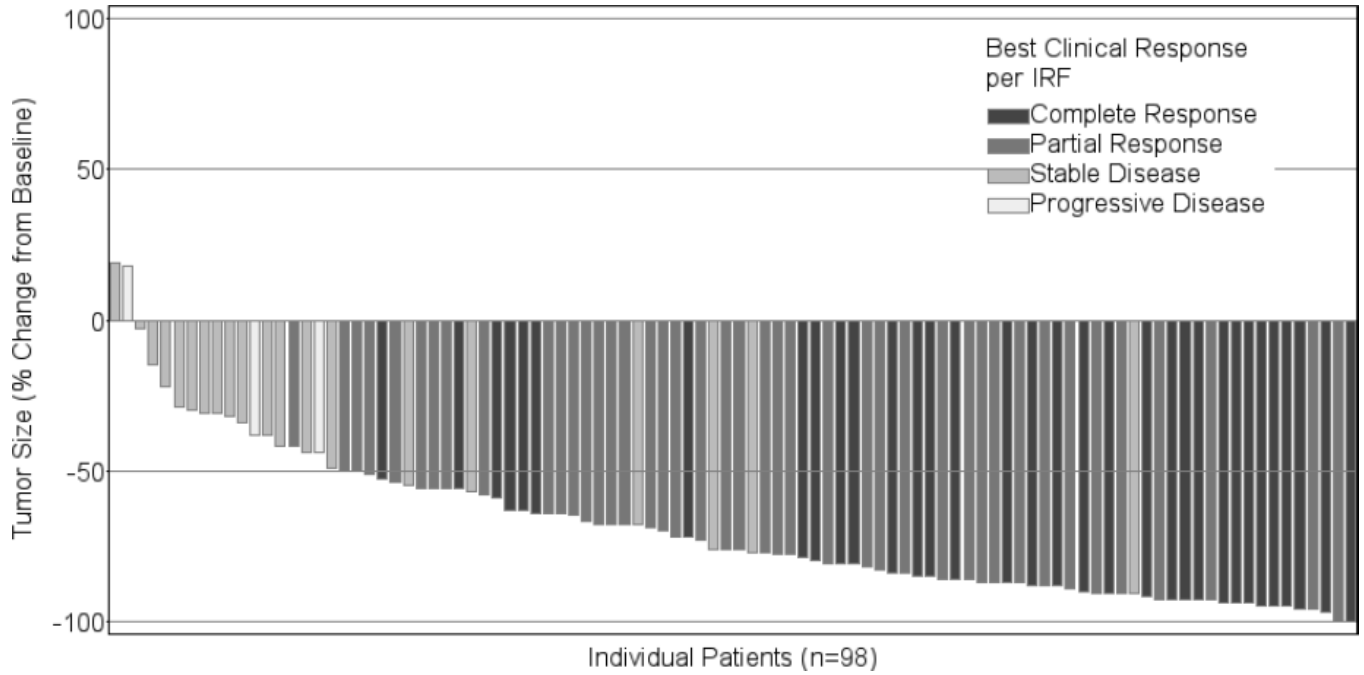
[e] *The median follow-up time (time to earliest of progressive disease, death or last contact) from first dose was 5.8 months.*

[f] *The median observation time (time to death or last contact) from first dose was 32.7 months.*

No clinically meaningful differences in the objective response rate were observed within the subgroups analyzed among the following subgroups analyzed: gender, baseline weight (≤100 kg versus >100 kg), baseline B symptoms, number of treatments prior to ASCT (≤2 versus >2), number of treatments post-ASCT (0 versus ≥1), relapsed versus refractory to last therapy, primary refractory disease, and time from ASCT to relapse post-ASCT (≤1 year versus >1 year).

Tumor reduction was achieved in 94% of patients. See Figure 1 for waterfall chart of tumor reduction, ORR and CR.

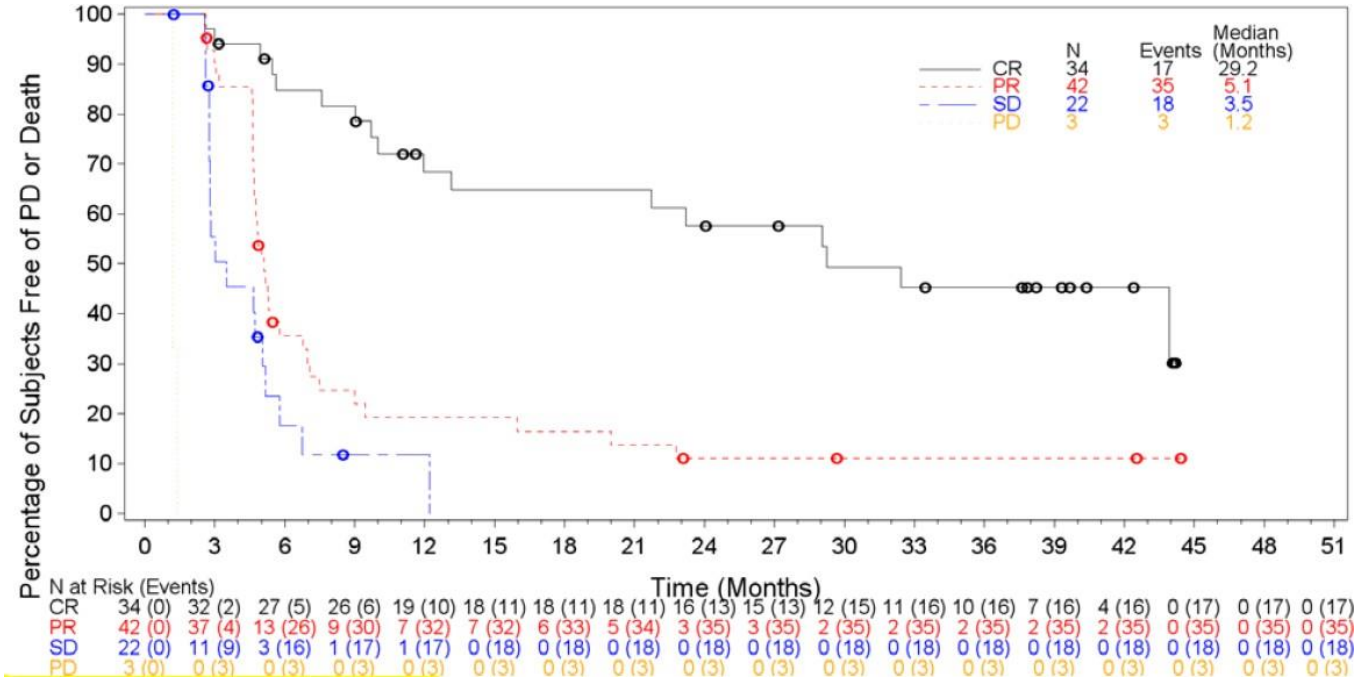
Figure 1: Best Clinical Response per Patient by Independent Review Facility (IRF) Determination



In the designation of CR per Revised Response Criteria for Malignant Lymphoma (Cheson et al., 2007), a post-treatment residual mass of any size is permitted as long as it is PET negative

Per IRF, median time to first response was 1.3 months, and median time to CR was 2.8 months. Median duration of objective response was 6.7 months (95% CI [3.6, 14.8]) with a range of 1.2+ to 26.1+ months. Of the patients treated, 7 responding patients went on to receive an allogeneic stem cell transplant.
Of the 35 patients who had B symptoms at baseline, 27 patients (77%) experienced resolution of all B symptoms at a median time from initiation of Adcetris of 0.7 months.
Per IRF, the median PFS for patients treated with Adcetris was 5.6 months (95% CI [5.0, 9.0]) (the median follow-up time from first dose for patients who were censored on PFS was 5.8 months). Patients who attained a CR achieved a median PFS of 29.2 months while those who attained a PR achieved a median PFS of 5.1 months and those who attained SD achieved a median PFS of 3.5 months. See Figure 2 for median PFS by best clinical response.

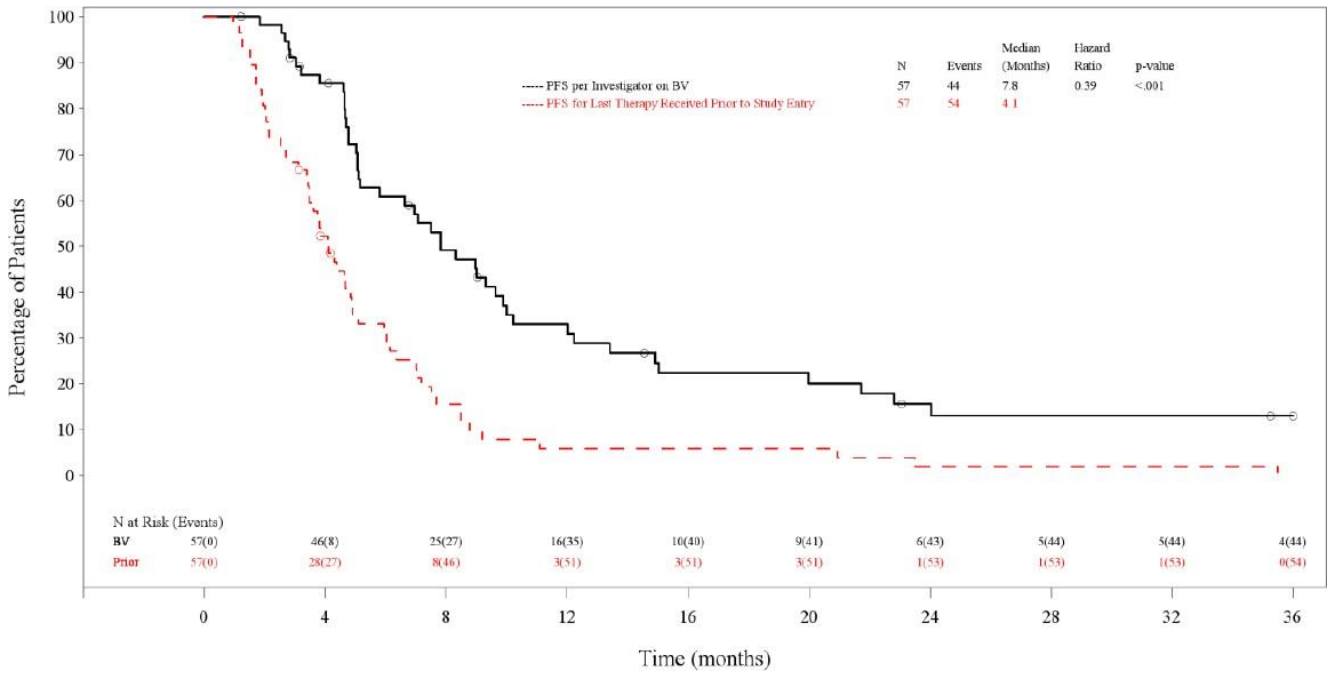
Figure 2: Progression-free survival by best clinical response per IRF



Symbols on the plot indicate censored patients

Patients who received Adcetris achieved a PFS improvement versus their most recent post ASCT therapy (7.8 months [5.2, 9.9] versus 4.1 months [3.4, 4.9] as assessed by investigator). See Figure 3 for a KM plot of PFS with Adcetris compared to PFS from most recent post-ASCT therapy.

Figure 3: Comparison of current PFS per investigator and PFS achieved with the last therapy received prior to study entry - subset of patients who received systemic therapy post-ASCT and prior to Adcetris



Symbols on the plot indicate censored patients. BV is Brentuximab Vedotin.

In addition, patients experienced a greater overall and complete response rate compared to their most recent post-ASCT therapy. The median overall survival was 40.5 months.
An exploratory intra-patient analysis showed that approximately 64% of the HL patients treated with brentuximab vedotin as part of the SG035-0003 clinical study experienced an improvement in clinical benefit as measured by longer progression free survival (PFS) compared with their most recent prior line of therapy.
Data were collected from patients (n=15) in phase 1 dose escalation and clinical pharmacology studies, and from patients (n=26) in a Named-Patient Program (NPP), with relapsed or refractory HL who had not received an ASCT, and who were treated with 1.8 mg/kg of Adcetris every 3 weeks.
Baseline patient characteristics showed failure from multiple prior chemotherapy regimens (median of 3 with a range of 1 to 7) before first administration with brentuximab vedotin. Fifty nine percent (59%) of patients had advanced stage disease (stage III or IV) at initial diagnosis.
Results from these phase 1 studies and from the NPP experience showed, that in patients with relapsed or refractory HL without prior ASCT, clinically meaningful responses can be achieved as evidenced by an investigator-assessed, objective response rate of 54% and a complete remission rate of 22% after a median of 5 cycles of brentuximab vedotin.

Study SGN35-005
The efficacy and safety of brentuximab vedotin were evaluated in a randomized, double-blinded, placebo-controlled, 2-arm multicenter trial in 329 patients with HL at risk of relapse or progression following ASCT. Of the 329 patients, 165 patients were randomized to the treatment arm and 164 patients were randomized to the placebo arm. The safety population in the Adcetris arm (N=167) included two additional patients who received at least one dose of Adcetris but were not randomized to the treatment arm. In the study, patients were to receive their first dose after recovery from ASCT (between days 30-45 following ASCT). Patients were treated with 1.8 mg/kg of Adcetris or matching placebo intravenously over 30 minutes every 3 weeks for up to 16 cycles. The median number of cycles received in both arms was 15 cycles. Eligible patients were required to have at least one of the following risk factors:
• HL that was refractory to frontline treatment
• Relapsed or progressive HL that occurred <12 months from the end of frontline treatment

• Extranodal involvement at time of pre-ASCT relapse, including extranodal extension of nodal masses into adjacent vital organs

Table 3: Summary of Baseline Patient and Disease Characteristics in the Phase 3 HL post-ASCT Study

Patient Characteristics	**Adcetris N=165**	**Placebo N=164**
Age (median)	33 years (18-71)	32 years (18-76)
Gender	76M (46%)/ 89F (54%)	97M (59%)/ 67F (41%)
ECOG status 0 1 2	 87 (53%) 77 (47%) 1 (1%)	 97 (59%) 67 (41%) 0
Disease Characteristics		
Number of prior chemotherapy regimens (median)	2 (2 - 8)	2 (2 - 7)
Time from HL diagnosis to first dose (median)	18.7 mo (6.1 - 204.0)	18.8 mo (7.4 – 180.8)
Disease stage at initial diagnosis of HL		
Stage I	1 (1%)	5 (3%)
Stage II	73 (44%)	61 (37%)
Stage III	48 (29%)	45 (27%)
Stage IV	43 (26%)	51 (31%)
Unknown	0	2 (1%)
PET scan Status prior to ASCT		
FDG-AVID	64 (39%)	51 (31%)
FDG-Negative	56 (34%)	57 (35%)
Not Done	45 (27%)	56 (34%)
Extranodal involvement at time of pre-ASCT relapse	54 (33%)	53 (32%)
B symptoms[a]	47 (28%)	40 (24%)
Best response to salvage therapy pre-ASCT[b]		
Complete Response	61 (37%)	62 (38%)
Partial Response	57 (35%)	56 (34%)
Stable Response	47 (28%)	46 (28%)
HL Status after the end of frontline standard chemotherapy[b]		
Refractory	99 (60%)	97 (59%)
Relapsed occurred <12 months	53 (32%)	54 (33%)
Relapsed occurred > = 12	13 (8%)	13 (8%)

[a] For refractory disease, or upon progression or relapse after frontline therapy

[b] Stratification factors at randomization

Table 4: Efficacy Results in HL patients at Risk of Relapse or Progression Following ASCT Treated with 1.8mg/kg of Adcetris Every 3 Weeks

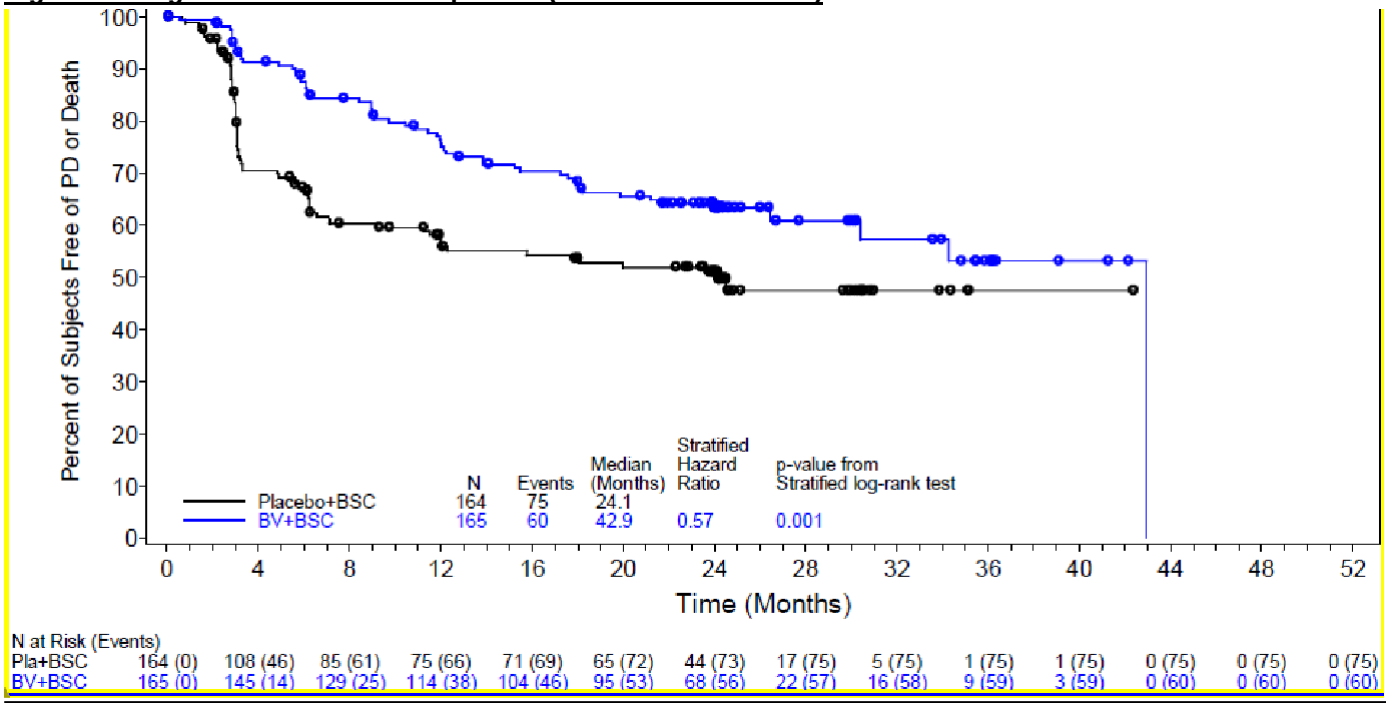
	Adcetris N=165	**Placebo N=164**	**Stratified Hazard Ratio**
	Median per IRF		
Progression Free Survival (PFS)[a]	42.9 months (95% CI [30.4, 42.9])	24.1 months (95% CI [11.5, -])	0.57 (95% CI [0.40, 0.81]) Stratified log-rank test P=0.001
	Median per Investigator using radiographic, biopsy, and clinical lymphoma assessments		
	Not reached	**15.8 months**	**0.50**

	(95% CI [-,-])	**(95% CI [8.5, -])**	**(95% CI [0.36, 0.70])[b]**

[a] At the time of analysis, the median follow-up time for both arms was 30 months [range, 0 to 50]

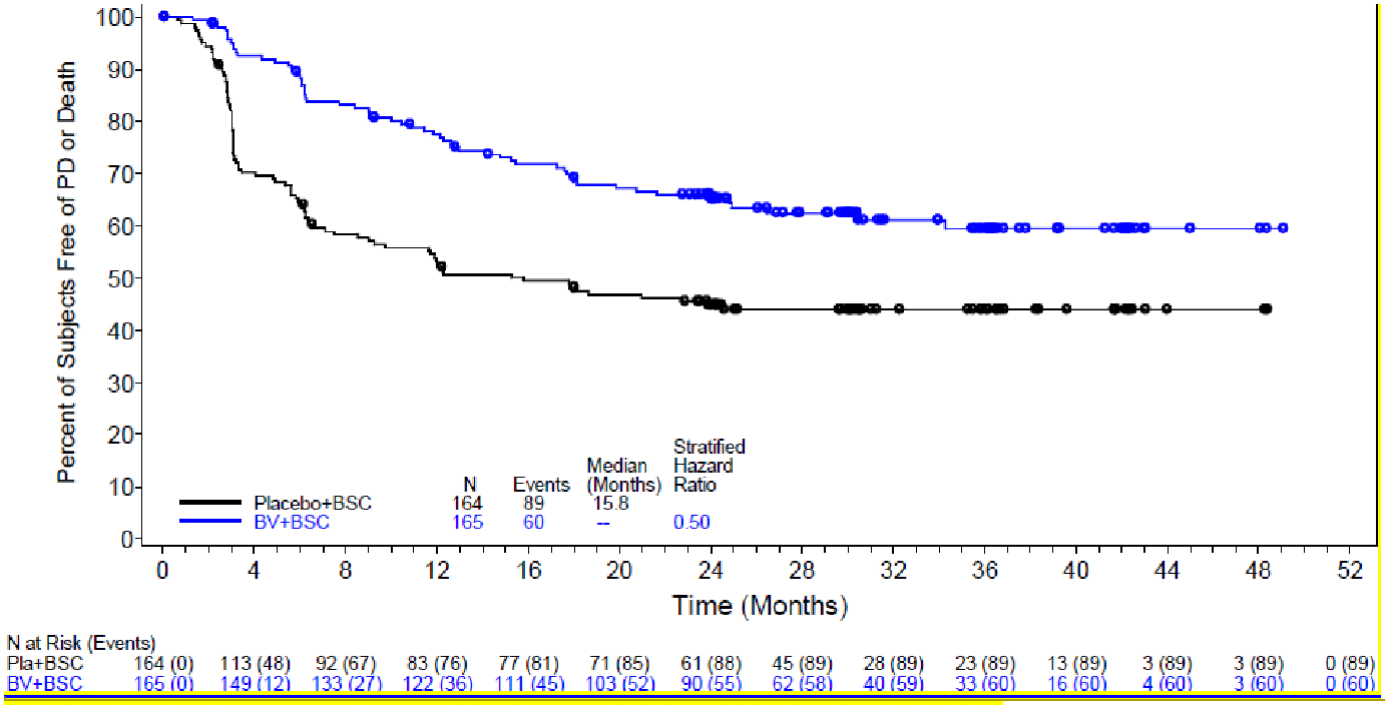
[b] Stratified log-rank test was not performed for PFS per Investigator

Figure 4: Progression-free survival per IRF (Adcetris vs. Placebo)



Symbols on the plot indicate censored patients. BV is Brentuximab Vedotin. BSC is Best Standard of Care.

Figure 5: Progression-free survival per Investigator using radiographic, biopsy and clinical lymphoma assessments (Adcetris vs. Placebo).



Symbols on the plot indicate censored patients. BV is Brentuximab Vedotin. BSC is Best Standard of Care.

Pre-specified subgroup analyses of PFS per IRF were performed by patients' best response to pre-ASCT salvage therapy, HL status after frontline therapy, age, gender, baseline weight, baseline ECOG performance status, number of treatments pre-ASCT, geographic region, pre-ASCT PET status, B symptom status after failure of frontline therapy, and pre-ASCT extranodal disease status. The analyses showed a consistent trend towards benefit for patients who received placebo with the exception of patients ≥ 65 years of age (n=8).

At the time of primary PFS analysis, an interim OS analysis was performed and there was no significant difference in OS between the treatment and placebo arms. Fifty-three patients had died; 28/165 patients in the brentuximab vedotin arm versus 25/164 patients in the placebo arm.

Quality of life was assessed using the EQ-5D instrument. No clinically meaningful differences were observed between the treatment and placebo arms.

Systemic Anaplastic Large Cell Lymphoma (sALCL)

Study SG035-0004

The efficacy and safety of Adcetris as a single agent was evaluated in an open-label, single-arm, multicenter study in 58 patients with relapsed or refractory sALCL.

Table 5: Summary of Baseline Patient and Disease Characteristics in the Phase 2 Relapsed or Refractory sALCL Study

Patient Characteristics	**N = 58**
Age (median)	52 years (14 – 76)
Gender	33M (57%) / 25F (43%)
ECOG status[a] 0 1 Prior ASCT Prior chemotherapy regimens	 19 (33%) 38 (66%) 15 (26%) 2 (1 – 6)
Disease Characteristics	
Primary Refractory to frontline therapy	36 (62%)
Refractory to most recent therapy	29 (50%)
Relapsed to most recent therapy	29 (50%)

[a] *One patient had a baseline ECOG status of 2, which was prohibited by protocol and is captured as Inclusion Criteria Not Met*

All patients had a histologically confirmed CD30-expressing disease and had received front-line chemotherapy with curative intent. A total of 58 patients were treated: 36 patients (62%) had primary refractory sALCL, defined as a failure to achieve a complete response to, or progressed within 3 months of completing frontline therapy; 29 patients (50%) were relapsed and 29 patients (50%) were refractory to most recent prior therapy; 42 patients (72%) had anaplastic lymphoma kinase (ALK)-negative disease. Patients had received a median of 2 prior systemic chemotherapies. Fifteen patients (26%) had received a prior ASCT. The median time from initial sALCL diagnosis to first dose with Adcetris was 16.8 months. Patients received up to 16 cycles of therapy; the median number of cycles received was 7 (range, 1 to 16). The primary endpoint, Objective Response Rate, was 86.2%. See Table 7 below for other pre-specified endpoints.

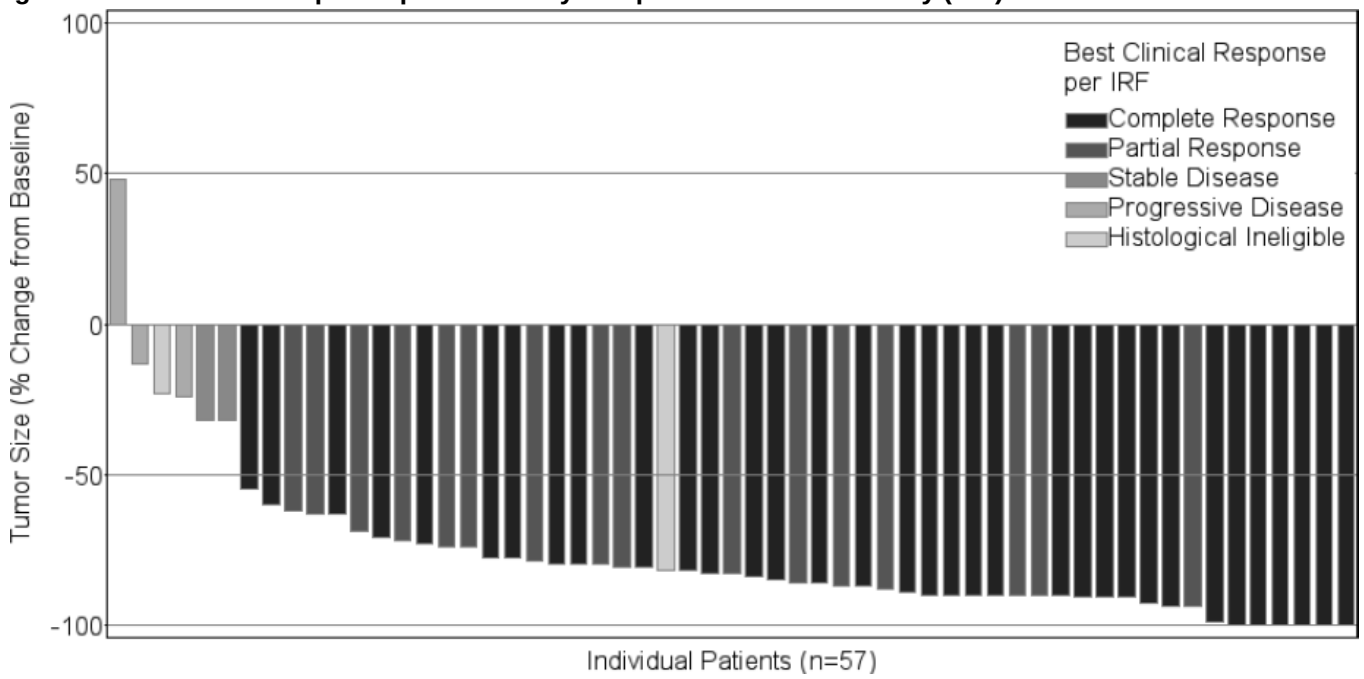
Table 6: Efficacy Results in Relapsed or Refractory sALCL Patients Treated with 1.8 mg/kg of Adcetris Every 3 Weeks

Best Clinical Response[a] (N=58[b])	**IRF N (%)**	**95% CI**	**Investigator N (%)**	**95 % CI**
Objective response rate (CR + PR) Complete response (CR) Partial response (PR) Disease control rate (CR + PR + SD)	50 (86) 34 (59) 16 (28) 52 (90)	74.6, 93.9 44.9, 71.4 N/A 78.8, 96.1	48 (83) 35 (60) 13 (22) 52 (90)	70.6, 91.4 46.6, 73 N/A 78.8, 96.1
Duration of Response[c,d]	**Median per IRF**	**95% CI**	**Median per Investigator**	**95% CI**
Objective response rate (CR + PR) Complete response (CR)	13.2 Not reached	5.7, -NE[e] 13.0, -NE	18.7 months Not reached	11.5, NE 13.2, NE
Progression free survival (PFS)[f]	**Median per IRF**	**95% CI**	**Median per Investigator**	**95 % CI**
	14.6 months	6.9 – 20.6	20.0 months	9.4, NE
Overall Survival[g]	**Median**	**95% CI**	**-**	**-**
	Not reached	21.3, NE	-	-

[a] *Independent review facility (IRF) and investigator assessments per Revised Response Criteria for Malignant Lymphoma (Cheson et al., 2007). Treatment response was assessed by spiral CT of chest, neck, abdomen and pelvis; PET scans and clinical data. Response assessments were performed at cycles 2, 4, 7, 10, 13 and 16 with PET at cycles 4 and 7.*
[b] *Patients ranged in age from 14 to 76 years (overall median, 52 years), 57% were male and 83% white, 36% of patients were stage IV at initial diagnosis and 29% of patients had B-symptoms at baseline.*
[c] *Duration of response is calculated from date of response to date of progression.The median follow-up time from first dose for patients who achieved objective response (OR) per IRF was 11.8 months.*
[d] *At a median duration of treatment of 5.4 months and a current range of 0.7 to 17.3 months, 27 of 50 patients who had an objective response have had disease progression or have died and 13 of 34 patients who had a CR have had disease progression or have died.*
[e] *Not estimable*
[f] *The median follow-up time (time to earliest of progressive disease, death or last contact) from first dose was 14.2 months.*
[g] *The estimated 36 month overall survival was 63% (95% CI [51, 76]). The median observation time (time to death or last contact) from first dose was 33.4 months.*

No clinically meaningful differences in the objective response rate were observed among the following subgroups analyzed: gender, baseline weight (≤100 kg versus >100 kg), baseline B symptoms, prior autologus stem cell transplantation (ASCT), and post-treatment ASCT. The ORR for relapsed patients was higher than those who were refractory (97% vs. 76%).
Tumor reduction was achieved in 97% of patients. See Figure 4 for waterfall chart of tumor reduction, ORR and CR.

Figure 6: Best Clinical response per Patient by Independent Review Facility (IRF) Determination

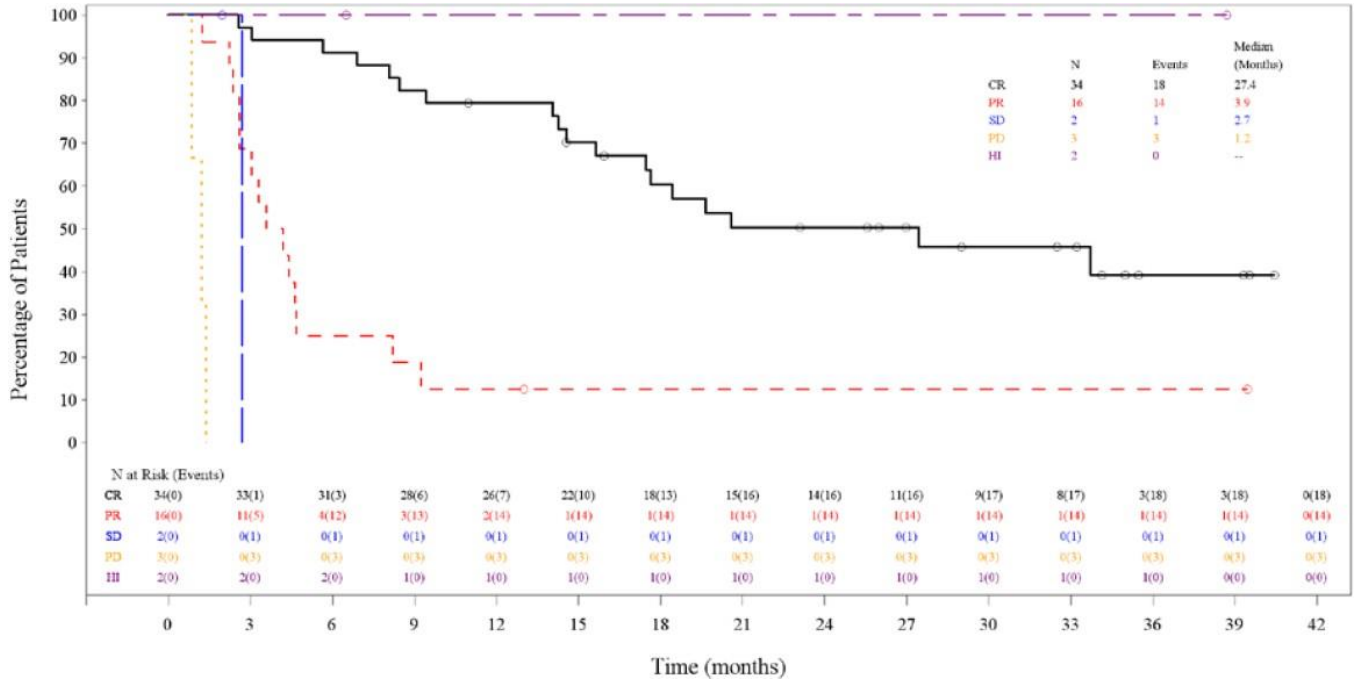


In the designation of CR per Revised Response Criteria for Malignant Lymphoma (Cheson et al., 2007), a post-treatment residual mass of any size is permitted as long as it is PET negative
Per IRF, median time to first objective response was 1.4 months (range, 1.0 – 3.2 months) and the median time to CR was 2.7 months (range, 1.2 – 11.6 months). Median duration of objective response was 13.2 months (95% CI [5.7, NE]) with a range of 0.1+ to 21.7+ months (the median follow-up time from first dose was 11.8 months). Of the patients treated, 9 responding patients went on to receive an allogeneic stem cell transplant (SCT) and 7 responding patients went onto autologous SCT.

Of the 17 patients who had B symptoms at baseline, 14 patients (82%) experienced resolution of all B symptoms in a median time from initiation of Adcetris of 0.7 months.

Per IRF, the median PFS for patients treated with Adcetris was 14.6 months (the median follow-up time from first dose was 14.2 months). Patients who attained a CR achieved a median PFS of 27.4 months while those who attained a PR achieved a PFS of 3.9 months. See Figure 7 for median PFS by best clinical response.

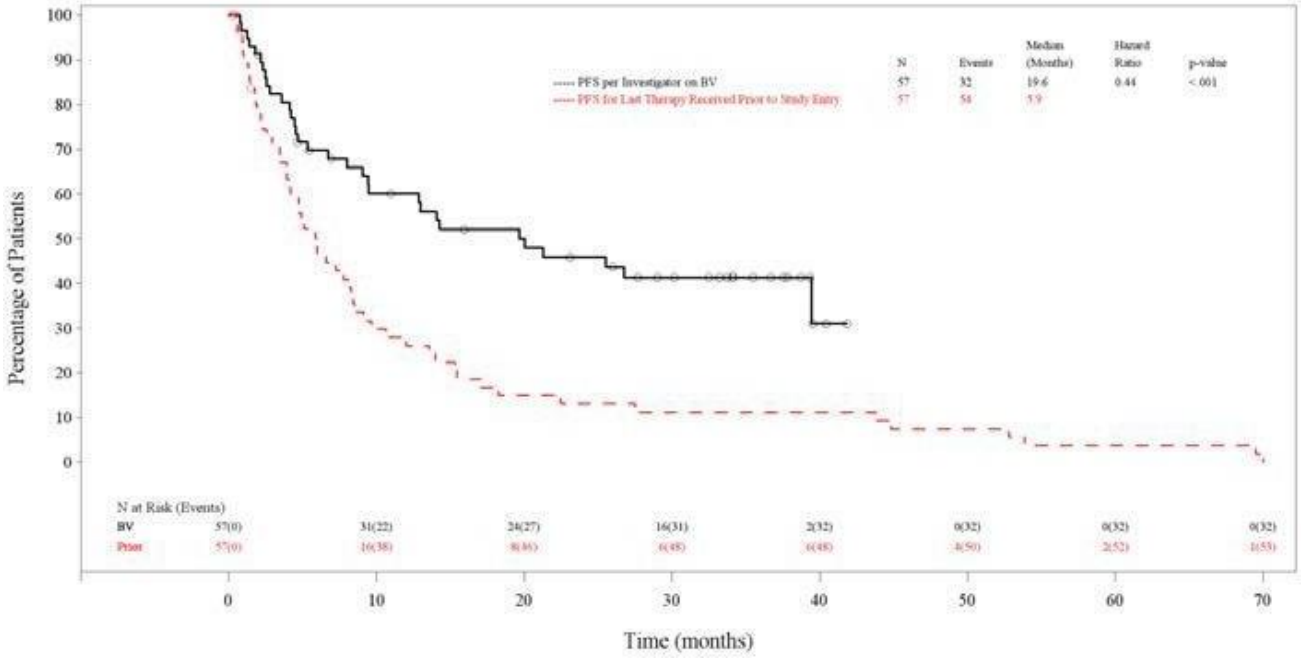
Figure 7: Progression-free survival by best clinical response per IRF



Symbols on the plot indicate censored patients

Patients who received Adcetris achieved a PFS improvement versus last therapy received prior to study entry (19.6 months [9.1, -NE] versus 5.9 months [3.9, 8.3] as assessed by investigator). See Figure 8 for a KM plot of PFS with Adcetris compared to PFS from last therapy received prior to study entry.

Figure 8: Comparison of current PFS per investigator and PFS achieved with the last therapy received prior to study entry



Symbols on the plot indicate censored patients BV is Brentuximab Vedotin.

In addition, patients experienced a greater overall and CR rate compared to their most recent therapy. The median overall survival was not reached. The estimated 36 months overall survival was 63% (95% CI [51, 76]).
An exploratory intra-patient analysis showed that approximately 69% of the sALCL patients treated with brentuximab vedotin as part of the SG035-0004 clinical study experienced an improvement in clinical benefit as measured by longer progression free survival (PFS) compared with their most recent prior line of therapy.

Cutaneous T-Cell Lymphoma (CTCL)

Study C25001

The efficacy and safety of Adcetris as a single agent was evaluated in a pivotal phase 3, open-label, randomized, multicenter study in 128 patients with histologically confirmed CD30-expressing CTCL.
Patients were stratified by disease subtype (mycosis fungoides [MF] or primary cutaneous anaplastic large cell lymphoma [pcALCL]) and randomized 1:1 to receive either Adcetris or the physician's choice of either methotrexate or bexarotene. Patients with pcALCL received either prior radiation therapy or at least 1 prior systemic therapy and patients with MF received at least 1 prior systemic therapy. Patients were treated with 1.8 mg/kg of Adcetris intravenously over 30 minutes every 3 weeks for up to 16 cycles or physician's choice for up to 48 weeks. The median number of cycles was approximately 12 cycles in the Adcetris arm. In the physician's choice arm, the median duration of treatment (number of cycles) for patients receiving bexarotene was approximately 16 weeks (5.5 cycles) and 11 weeks (3 cycles) for patients receiving methotrexate. Table 7 provides a summary of the baseline patient and disease characteristics.

Table 7: Summary of Baseline Patient and Disease Characteristics in the Phase 3 CTCL Study (Intention-to-Treat (ITT) Population)

	Adcetris N=64	**Physician's Choice (methotrexate or Bexarotene) N=64**
Patient Characteristics		
Median age (range)	62 years (22-83)	58.5 years (22-83)
Patients ≥ 65 years old n (%)	28 patients (44)	24 patients (38)
Gender n (%)	33M (52%)/ 31F (48%)	37M (58%)/ 27F (42%)
ECOG status n (%)		
0	43 (67)	46 (72)
1	18 (28)	416 (25)
2	3 (5)	2 (3)
Disease Characteristics		
Median number of prior therapies (range)	4 (0-13)	3.5 (1-15)
Median number of skin-directed therapy (range)	1 (0-6)	1 (0-9)
Median number of systemic therapy (range)	2 (0-11)	2 (1-8)

The primary endpoint was objective response rate that lasts at least 4 months (ORR4) (duration from first response to last response ≥ 4 months), as determined by an independent review of the Global Response Score (GRS) consisting of skin evaluations (modified severity weighted assessment tool [mSWAT] assessment), nodal and visceral radiographic assessment, and detection of circulating Sézary cells. The ORR4 was significantly higher in the Adcetris arm compared to the physician's choice arm (56.3% vs 12.5%, p<0.0001). Table 8 includes the results for ORR4 and other key secondary endpoints.

Table 8: Efficacy Results in CTCL patients Treated with 1.8 mg/kg of Trade Name Every 3 Weeks (ITT Population)

	Adcetris N=64	Physician's Choice (Methotrexate or Bexarotene) N=64
Objective Response Rate 4 (ORR4) per IRF		
N (%)	36 (56.3)	8 (12.5)
Percent Difference (95% CI)	43.8 (29.1, 58.4)	
p-value	<0.0001	

Complete Response (CR) per IRF		
N (%)	10 (15.6)	1 (1.6)
Percent Difference (95% CI)	14.1 (+4.0, 31.5)	
Adjusted p-value[a]	0.0046	
Progression Free Survival (PFS) per IRF		
Median (months)	16.7	3.5
Hazard Ratio	0.270	
95% CI	(0.17, 0.43)	
Adjusted p-value[a]	<0.001	

[a] Calculated from a weighted Holm's procedure

Pre-specified subgroup analyses of ORR4 per IRF were performed by patients' CTCL subtype, physicians' choice of treatment, baseline ECOG status, age, gender, and geographic region. The analyses showed a consistent trend towards benefit for patients who received Adcetris compared with patients who received physician's choice. ORR4 was 50% and 75% in the Adcetris arm versus 10.2% and 20% in the physician's choice arm for MF and pcALCL, respectively.

No meaningful differences in quality of life (assessed by the EuroQol five dimensions questionnaire [EQ-5D] and Functional Assessment of Cancer Therapy-General [FACT-G]) were observed between the treatment arms.

The efficacy and safety of Adcetris were evaluated in two additional open-label studies in 108 patients with relapsed CD30+ CTCL (including patients with MF and pcALCL as well as SS, Lyp and mixed CTCL histology) regardless of CD30 expression level. Patients were treated with Adcetris 1.8 mg/kg intravenously over 30 minutes every 3 weeks for up to 16 cycles. The safety and efficacy results in these studies were consistent with results in Study C25001. Overall response rates for MF were 54-66%; pcALCL, 67%; SS, 50%; LyP, 92%; and mixed CTCL histology, 82-85%.

Hodgkin Lymphoma

Study C25003

The efficacy and safety of Adcetris were evaluated in a randomized, open-label, 2-arm, multicenter trial in 1334 patients with advanced frontline HL in combination with chemotherapy (doxorubicin [A], vinblastine [V] and dacarbazine [D] [AVD]). All patients had CD30-expressing HL. Sixty-two percent of patients had extranodal site involvement. Of the 1334 patients, 664 patients were randomized to the Adcetris + AVD arm and 670 patients were randomized to the ABVD (doxorubicin [A], bleomycin [B], vinblastine [V] and dacarbazine [D]) arm and stratified by the number of International Prognostic Factor Project (IPFP) risk factors and region. Patients were treated with 1.2 mg/kg of Adcetris administered as an intravenous infusion over 30 minutes on days 1 and 15 of each 28-day cycle + AVD. The median number of cycles received was 6 (range, 1 to 6 cycles). Table 9 provides a summary of the baseline patient and disease characteristics.

Table 9: Summary of Baseline Patient and Disease Characteristics in the Phase 3 Frontline HL Study

Patient Characteristics	**Adcetris + AVD N=664**	**ABVD N=670**
Median age (range)	35 years (18-82)	37 years (18-83)
Patients ≥ 65 years old n (%)	60 (9)	62 (9)
Gender, n (%)	378M (57)/ 286F (43)	398M (59)/ 272F (41)
ECOG status n (%) 0 1 2 Missing	 376 (57) 260 (39) 28 (4) 0	 378 (57%) 263 (39) 26 (4) 2
Disease Characteristics		
Median time from HL diagnosis to first dose (range)	0.92 mo (0.1 – 21.4)	0.89 mo (0.0 – 81.4)
Disease stage[a] at initial diagnosis of HL, n (%)		
Stage III	237 (36)	246 (37)
Stage IV	425 (64)	421 (63)
Not applicable	1 (<1)	1 (<1)
Missing	0	2 (<1)

Extranodal involvement at time of diagnosis, n (%)	411 (62)	416 (62)
IPFP[b] risk factors, n (%)		
0-1	141 (21)	141 (21)
2-3	354 (53)	351 (52)
4-7	169 (25)	178 (27)
Bone marrow involvement at time of diagnosis or study entry, n (%)	147 (22)	151 (23)
B symptoms[a] n (%)	400 (60)	381 (57)

[a] *Per Ann Arbor Staging*
[b] *IPFP = International Prognostic Factor Project*

The primary endpoint in Study C25003 was modified PFS per IRF, defined as time from randomization to progression, death, or evidence of non-CR after completion of frontline therapy per independent review facility (IRF) followed by subsequent anticancer therapy. *Timing of the modified event was the date of the first PET scan post completion of frontline therapy demonstrating the absence of CR, defined as Deauville score of ≥3.* The median mPFS by IRF assessment was not estimable for either treatment arm.
The results showed a statistically significant improvement in modified PFS for Adcetris+AVD, with a 2-sided p-value of 0.035 based on a stratified log-rank test. The stratified hazard ratio was 0.770 (95% CI, 0.603; 0.983), indicating a 23% reduction in the risk of modified PFS events for Adcetris+AVD versus ABVD. Table 10 provides the efficacy results for modified PFS and overall survival (OS).

Table 10: Efficacy Results in Advanced Frontline HL Patients Treated with 1.2 mg/kg of Adcetris + AVD on Days 1 and 15 of a 28-Day Cycle

	Adcetris + AVD N=664	ABVD N=670	Stratified Hazard Ratio
	Modified Progression Free Survival (mPFS) Per IRF[a]		
Number of events (%)	117 (18)	146 (22)	0.77 (95% CI [0.60, 0.98]) Stratified log-rank test p-value=0.035
Estimated mPFS[a] at 2 Year (%)	82.1 (95% CI [78.8, 85.0])	77.2 (95% CI [73.7, 80.4])	
	Modified Progression Free Survival (mPFS) Per Investigator		
Number of events (%)	123 (19)	164 (24)	0.72 (95% CI [0.57, 0.91])
Estimated mPFS[a] at 2 Year (%)	81 (95% CI [77.6, 83.9])	74.4 (95% CI [70.7, 77.7])	
	Overall Survival[b]		
Number of Deaths (%)	28 (4)	39 (6)	0.73 (95% CI [0.45, 1.18]) p-value=0.199

[a] *At the time of analysis, the median follow-up time for both arms was 24.6 months*
[b] *Data from an interim OS analysis*

Figure 9: Modified Progression-free Survival per IRF (Adcetris + AVD vs. ABVD)

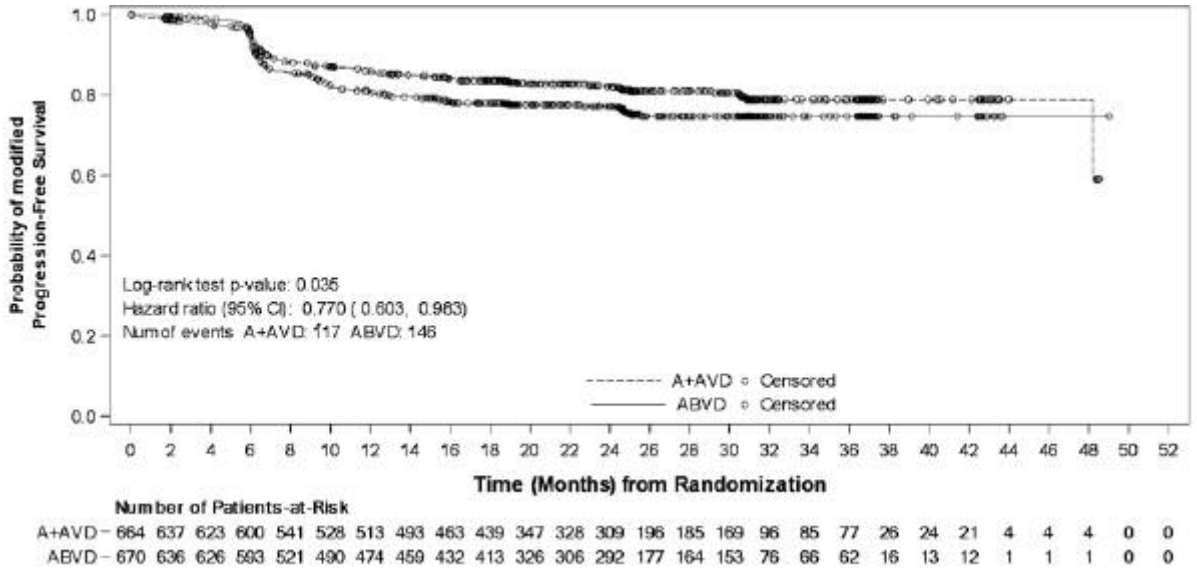
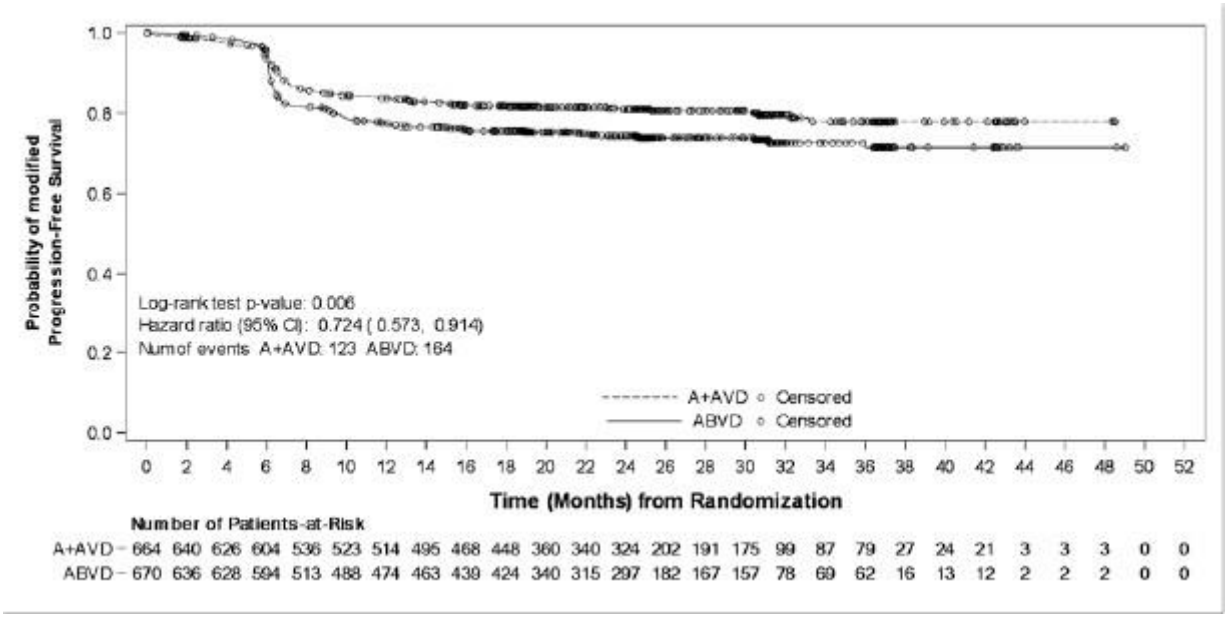


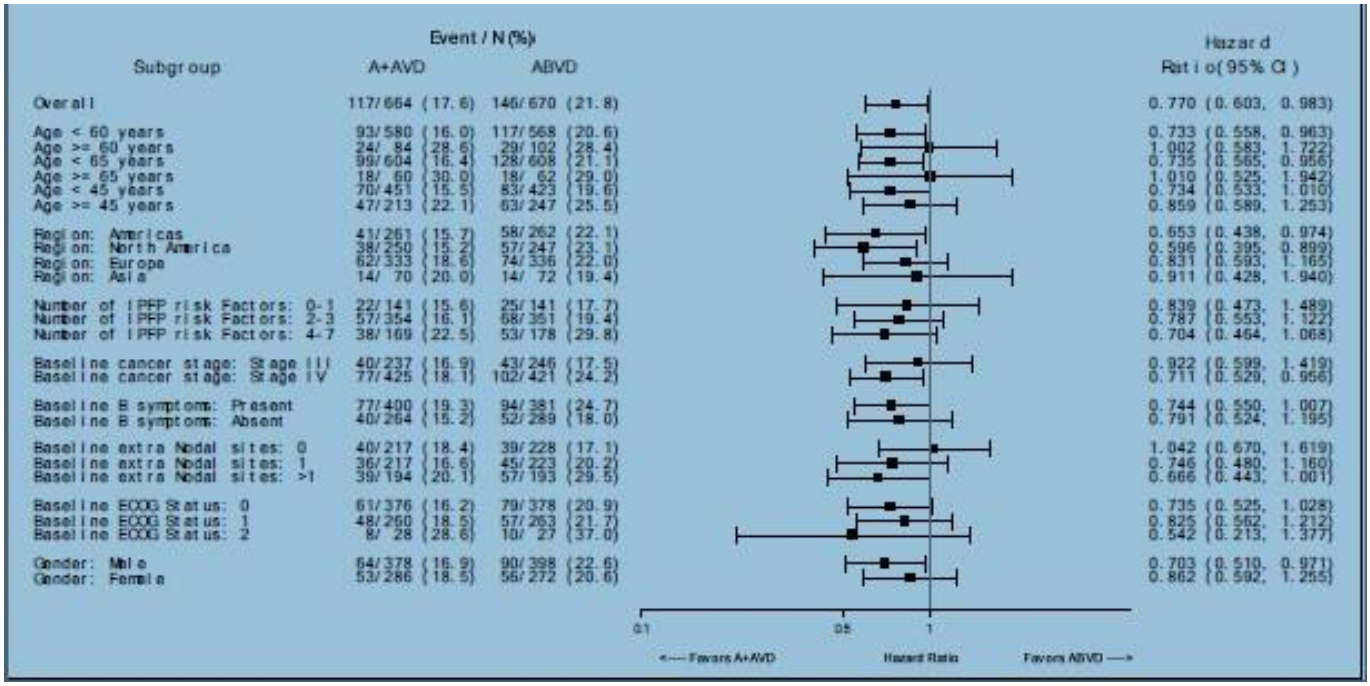
Figure 10: Modified Progression-free Survival per Investigator (Adcetris + AVD vs. ABVD)



Other secondary efficacy endpoints including CR rate and ORR at the end of randomization regimen, CR rate at the end of frontline therapy, and the rate of PET negativity at the end of Cycle 2, duration of response (DOR), duration of complete remission (DOCR), disease-free survival (DFS,) and event-free survival (EFS) all trended in favor of Adcetris+AVD.

Pre-specified subgroup analyses of modified PFS per IRF were performed. The analyses showed that efficacy trended consistently in favor of patients who received Adcetris + AVD compared with patients who received ABVD for most subgroups, as summarized in Figure 11.

Figure 11: Forest Plot of Hazard Ratio in Modified Progression-Free Survival (mPFS) Per IRF for Subgroup Analyses



Approximately one-third fewer patients treated with Adcetris + AVD received subsequent salvage chemotherapy (n=66) and high-dose chemotherapy and transplant (n=36) compared with those treated with ABVD (n=99 and n=54, respectively).

The European Organization for Research and Treatment of Cancer Quality of Life 30-Item Questionnaire (EORTC-QLQ-C30) showed no clinically meaningful difference between the two arms.

Post-hoc Subgroup Analyses

Subgroups including patients with Stage IV disease and extranodal sites ≥ 1 experienced a greater clinical benefit based on mPFS compared with the overall ITT population. The results from post-hoc analyses in patients with Stage IV disease and extranodal involvement are shown in Table 11.

Table 11: Efficacy Results in Advanced Frontline HL Patients with Stage IV Disease and Extranodal Involvement

	Adcetris + AVD	**ABVD**	**Hazard Ratio (95% CI)[a]**
Patients with Stage IV FL HL			
Number of patients	425	421	
Number of events (%)	*77 (18)*	*102 (24)*	*0.712 (0.529, 0.956)*
Estimated Modified Progression Free Survival (mPFS) at 2 Year per IRF (%)	*82.0 (77.8, 85.5)*	*75.3 (70.6, 79.3)*	
Overall Survival (OS)[b] Number of deaths (%)	*14 (3)*	*26 (6)*	*0.507 (0.265, 0.971)*

Patients with Extranodal Sites ≥ 1			
Number of patients	*411*	*416*	
Number of events (%)	*75 (18)*	*102 (25)*	*0.699 (0.518, 0.943)*
Estimated Modified Progression Free Survival (mPFS) at 2 Year per IRF (%)	*82.4 (78.2, 85.9)*	*74.9 (70.2, 79.0)*	
OS Number of deaths (%)	*12 (3)*	*27 (6)*	*0.431 (0.218, 0.852)*

[a]*Hazard ratio and 95% CI are based on an unstratified Cox's proportional hazard regression model with treatment as the explanatory variable in the model.*

[b]*Data from an interim OS analysis*

Study SGN35-014

The efficacy of ADCETRIS in combination with chemotherapy for the treatment of adult patients with previously untreated, CD30-expressing PTCL was evaluated in a multicenter, randomized, double-blind, double-dummy, actively controlled trial. For enrollment, the trial required CD30 expression ≥10% per immunohistochemistry. The trial excluded patients with primary cutaneous CD30-positive T-cell lymphoproliferative disorders and lymphomas. The trial required hepatic transaminases ≤3 times ULN, total bilirubin ≤1.5 times ULN, and serum creatinine ≤2 times ULN.

Of the 452 total patients, 226 patients were randomized to the ADCETRIS + CHP arm and 226 patients were randomized to the CHOP arm. Patients in both treatment arms were treated intravenously on Day 1 of each 21-day cycle for 6 to 8 cycles; prednisone was administered orally on Days 1-5. Dosing in each treatment arm was administered according to the following:

- ADCETRIS + CHP arm: ADCETRIS 1.8 mg/kg over 30 minutes, cyclophosphamide 750 mg/m^2, doxorubicin 50 mg/m^2, and prednisone 100 mg orally
- CHOP arm: cyclophosphamide 750 mg/m^2, doxorubicin 50 mg/m^2, vincristine 1.4 mg/m^2, and prednisone 100 mg orally.

The median age was 58 years (range: 18 to 85), 63% were male, 62% were White, 22% were Asian, and 78% had an ECOG performance status of 0-1. Of the 452 patients enrolled, the disease subtypes included patients with systemic ALCL [70%; 48% anaplastic lymphoma kinase (ALK) negative and 22% ALK positive], PTCL not otherwise specified (16%), angioimmunoblastic T-cell lymphoma (12%), adult T-cell leukemia/lymphoma (2%), and enteropathy-associated T-cell lymphoma (<1%).

Most patients had Stage III or IV disease (81%) and a baseline international prognostic index of 2 or 3 (63%).

During randomized treatment, on the ADCETRIS + CHP arm, 70% of patients received 6 cycles and 18% of patients received 8 cycles. On the CHOP arm, 62% of patients received 6 cycles and 19% received 8 cycles.

Efficacy was based on IRF-assessed PFS, which was defined as time from randomization to progression, death due to any cause, or receipt of subsequent anticancer chemotherapy to treat residual or progressive disease. Other efficacy endpoints included PFS in patients with systemic ALCL, overall survival, complete response rate, and overall response rate. Efficacy results are summarized in Table 12: Kaplan-Meier curves for PFS and overall survival are presented in Figure 12 and Figure 13, respectively.

Table 12: Efficacy Results in Patients with Previously Untreated, CD30-Expressing PTCL

Outcomes per IRF[a]	ADCETRIS + CHP N=226	CHOP N=226
PFS		
Number of events, n (%)	95 (42)	124 (55)
Median PFS, months (95% CI)	48.2 (35.2, NE)	20.8 (12.7, 47.6)
Hazard ratio (95% CI)[b]	0.71 (0.54, 0.93)	
P-value[c]	0.011	
Reason leading to a PFS event, n (%)		
Progressive disease	71 (31)	86 (38)
Death	13 (6)	17 (8)
Receipt of subsequent anticancer chemotherapy to treat residual or progressive disease	11 (5)	21 (9)
PFS for patients with sALCL		
N	163	151
Number of patients with a PFS event, n (%)	56 (34)	73 (48)
Median PFS, months (95% CI)	55.7 (48.2, NE)	54.2 (13.4, NE)

Hazard ratio (95% CI)[b]	0.59 (0.42, 0.84)	
P-value[c]	0.003	
OS[d]		
Number of deaths	51 (23)	73 (32)
Median OS, months (95% CI)	NE (NE, NE)	NE (54.2, NE)
Hazard ratio (95% CI)[b]	0.66 (0.46, 0.95)	
P-value[c]	0.024	
CR Rate[e]		
% (95% CI)	68 (61, 74)	56 (49, 62)
P-value[f]	0.007	
ORR[e]		
% (95% CI)	83 (78, 88)	72 (66, 78)
P-value[f]	0.003	

NE: Not estimable

a Efficacy endpoints were tested at a two-sided alpha level 0.05 in the following order: PFS in ITT, PFS in the sALCL subgroup, complete remission rate, overall survival, and objective response rate in ITT.

b Hazard ratio (A+CHP/CHOP) and 95% confidence intervals are based on a stratified Cox's proportional hazard regression model with the following stratification factors (ALK-positive sALCL and International Prognostic Index [IPI] score at baseline).

c P-value is calculated using a stratified log-rank test.

d Median OS follow-up in the ADCETRIS+CHP arm was 41.9 months; in the CHOP arm was 42.2 months.

e Best response per 2007 International Working Group Criteria at end of treatment.

f P-value is calculated using a stratified Cochran-Mantel-Haenszel test

Figure 12: **Kaplan-Meier Curve of IRF-Assessed Progression-Free Survival** in Patients with Previously Untreated, CD30-Expressing PTCL (ITT population)

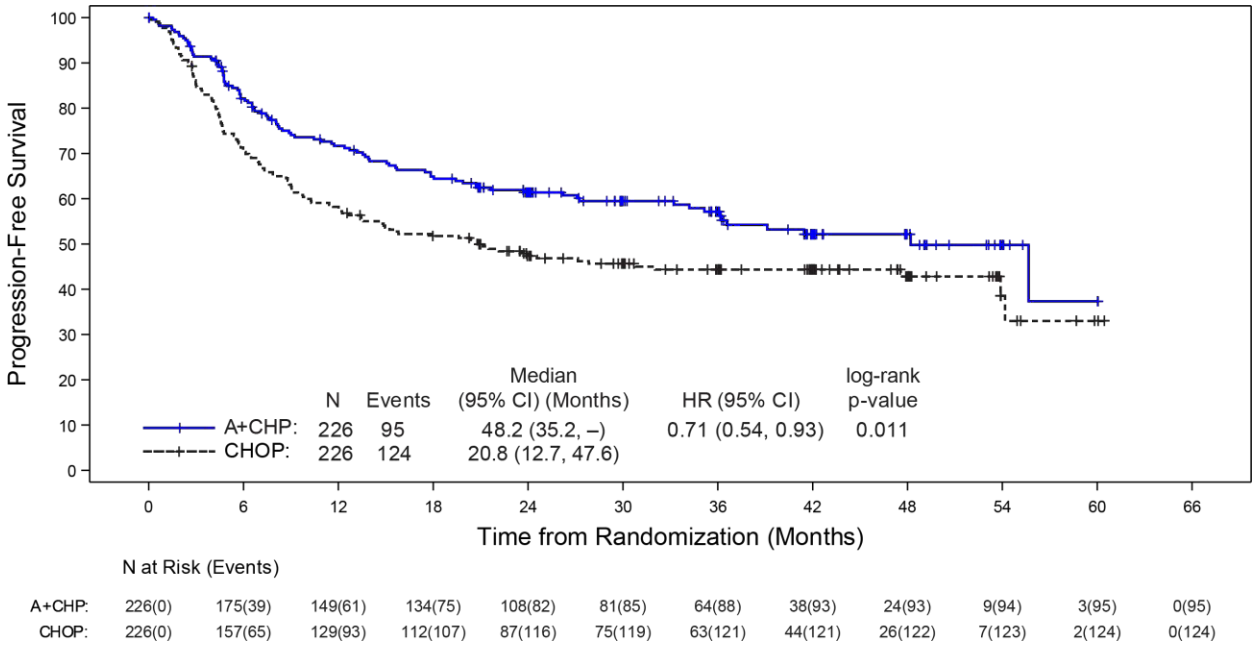
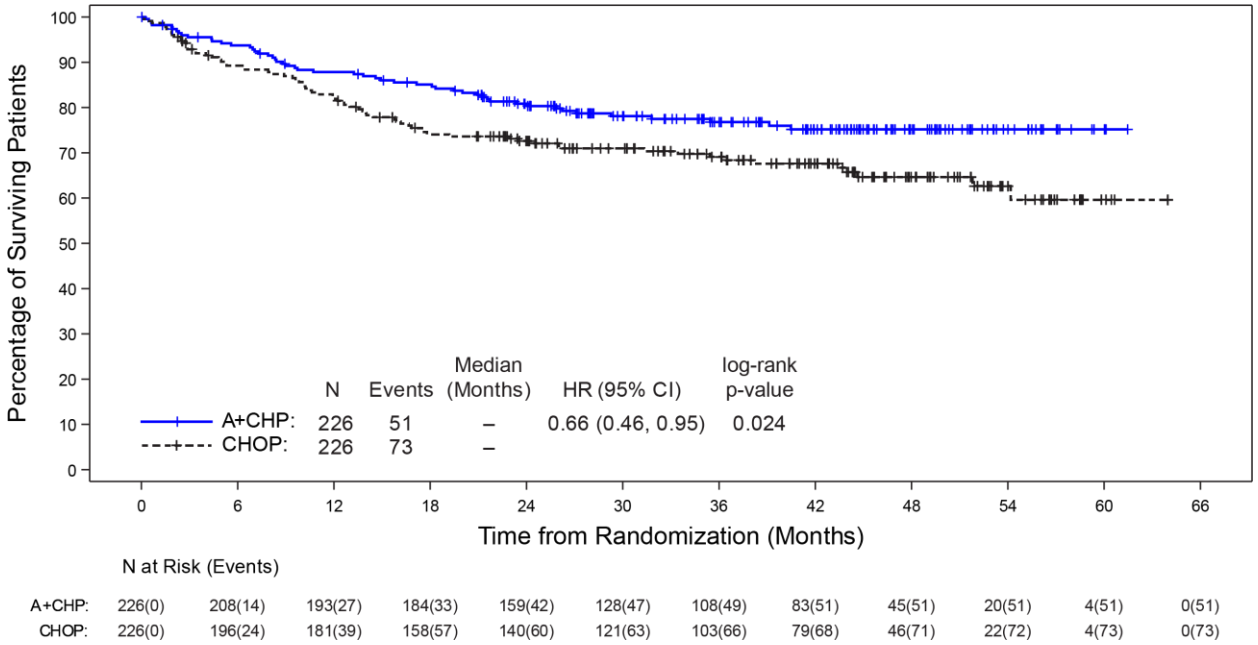


Figure 13: **Overall Survival** in Patients with Previously Untreated, CD30-Expressing PTCL (ITT population)



Median overall survival was not reached in either treatment arm.

INDICATION

Adcetris is indicated for the treatment of adult patients with previously untreated CD30+ Stage IV Hodgkin lymphoma (HL), in combination with doxorubicin, vinblastine, and dacarbazine.

Adcetris is indicated for the treatment of adult patients with CD30+ HL at increased risk of relapse or progression following ASCT.

Adcetris is indicated for the treatment of adult patients with relapsed or refractory CD30+ HL:

1. following autologous stem cell transplant (ASCT) or
2. following at least two prior therapies when ASCT or multi-agent chemotherapy is not a treatment option.

Adcetris is indicated for the treatment of adult patients with previously untreated sALCL or other CD30-expressing Peripheral T-Cell Lymphoma (PTCL), including angioimmunoblastic T-cell lymphoma and PTCL not otherwise specified, in combination with cyclophosphamide, doxorubicin and prednisone,

Adcetris is indicated for the treatment of adult patients with relapsed or refractory systemic anaplastic large cell lymphoma (sALCL).

Adcetris is indicated for the treatment of adult patients with CD30+ cutaneous T-cell lymphoma (CTCL) after at least 1 prior systemic therapy.

DOSAGE AND ADMINISTRATION

Previously Untreated HL

The recommended dose in combination with chemotherapy (doxorubicin [A], vinblastine [V] and dacarbazine [D] [AVD]) is 1.2 mg/kg administered as an intravenous infusion over 30 minutes on days 1 and 15 of each 28-day cycle for 6 cycles (see section CLINICAL STUDIES).

Primary prophylaxis with growth factor support (G-CSF) is recommended for all patients with previously untreated HL receiving combination therapy beginning with the first dose (see section Warnings and Precautions).

Refer to the package insert (PI) of chemotherapy agents given in combination with Adcetris for patients with previously untreated HL.

HL at increased risk of relapse or progression

The recommended dose is 1.8 mg/kg administered as an intravenous infusion over 30 minutes every 3 weeks. Adcetris treatment should start following recovery from ASCT based on clinical judgment. These patients should receive up to 16 cycles (see section CLINICAL STUDIES).

Relapsed or refractory HL
The recommended dose is 1.8 mg/kg administered as an intravenous infusion over 30 minutes every 3 weeks.
The recommended starting dose for the retreatment of patients who have previously responded to treatment with Adcetris is 1.8 mg/kg administered as an intravenous infusion over 30 minutes every 3 weeks. Alternatively, treatment may be started at the last tolerated dose (see section CLINICAL STUDIES).
Treatment should be continued until disease progression or unacceptable toxicity (see section Warnings and Precautions).
Patients who achieve stable disease or better should receive a minimum of 8 cycles and up to a maximum of 16 cycles (approximately 1 year) (see section CLINICAL STUDIES).

Previously untreated sALCL or other CD30-expressing PTCL
The recommended dose in combination with chemotherapy (cyclophosphamide [C], doxorubicin [H] and prednisone [P] [CHP]) is 1.8 mg/kg administered as an intravenous infusion over 30 minutes every 3 weeks for 6 to 8 cycles (see section CLINICAL STUDIES).
Primary prophylaxis with growth factor support (G-CSF) beginning with the first dose, is recommended for all patientswith previously untreated sALCL or other CD30-expressing PTCL, receiving combination therapy (See Warnings and Precautions).
Refer to the product information of chemotherapy agents given in combination with Adcetris for treatment of patients with previously untreated sALCL or other CD30-expressing PTCL.

Relapsed or refractory sALCL
The recommended dose is 1.8 mg/kg administered as an intravenous infusion over 30 minutes every 3 weeks.
The recommended starting dose for the retreatment of patients who have previously responded to treatment with ADCETRIS is 1.8 mg/kg administered as an intravenous infusion over 30 minutes every 3 weeks. Alternatively, treatment may be started at the last tolerated dose (see section CLINICAL STUDIES).
Treatment should be continued until disease progression or unacceptable toxicity (see section Warnings and Precautions).
Patients who achieve stable disease or better should receive a minimum of 8 cycles and up to a maximum of 16 cycles (approximately 1 year) (see section CLINICAL STUDIES).

CTCL
The recommended dose is 1.8 mg/kg administered as an intravenous infusion over 30 minutes every 3 weeks.
Patients with CTCL should receive up to 16 cycles (see section CLINICAL STUDIES).

General
If the patient's weight is more than 100 kg, the dose calculation should use 100 kg.
Complete blood counts should be monitored prior to administration of each dose of this treatment (see section Warnings and Precautions).
Patients should be monitored during and after infusion (see section Warnings and Precautions).

Dose adjustments
Neutropenia
If neutropenia develops during treatment it should be managed by dose delays. See Table 13 and Table 14 below for appropriate dosing recommendations for monotherapy and combination therapy, respectively.

Table 13: Dosing recommendations for New or Worsening Neutropenia with Monotherapy

	Monotherapy
Severity grade of neutropenia (signs and symptoms [abbreviated description of CTCAEa])	**Modification of dosing schedule**
Grade 1 (< LLN-1500/mm3 < LLN-1.5 x 109/L) or Grade 2 (< 1500-1000/mm3 < 1.5-1.0 x 109/L)	Continue with the same dose and schedule

Grade 3 (< 1,000-500/mm3 < 1.0-0.5 x 109/L) or Grade 4 (< 500/mm3 < 0.5 x 109/L)	Withhold dose until toxicity returns to ≤ Grade 2 or baseline then resume treatment at the same dose and schedule b. Consider G-CSF or GMCSF in subsequent cycles for patients who develop Grade 3 or Grade 4 neutropenia.

a. Grading based on National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v3.0; see Neutrophils/granulocytes; LLN = lower limit of normal
b. Patients who develop Grade 3 or Grade 4 lymphopenia may continue treatment without interruption.

Table 14: Dosing Recommendations for New or Worsening Neutropenia during Combination Therapy

Severity Grade of Neutropenia (Signs and Symptoms [abbreviated description of CTCAE[a]])	**Modification of Dosing Schedule**
Grade 1 (<LLN - 1500/mm3, <LLN - 1.5 × 109/L) or Grade 2 (<1500 - 1000/mm3, <1.5 - 1.0 × 109/L) Grade 3 (<1000 - 500/mm3, <1.0 - 0.5 × 109/L) or Grade 4 (<500/mm3, <0.5 × 109/L)	Primary prophylaxis with G-CSF is recommended for all patients receiving combination therapy beginning with the first dose. Continue with the same dose and schedule. *Administer G-CSF prophylaxis for subsequent cycles for patients not receiving primary G-CSF prophylaxis*.

G-CSF=granulocyte colony-stimulating factor; GM-CSF=granulocyte macrophage colony-stimulating factor; LLN= lower limit of normal; NCI
CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events
[a] Abbreviated description of CTCAE; grading based on NCI CTCAE v4.03

Peripheral neuropathy
If peripheral sensory or motor neuropathy emerges or worsens during treatment see Table 15 and Table 16 for appropriate recommendations for monotherapy and combination therapy, respectively.

Table 15: Dosing recommendations for new or worsening peripheral sensory or motor Neuropathy with Monotherapy

	Monotherapy
Severity of peripheral sensory or motor neuropathy (signs and symptoms [abbreviated description of CTCAEa])	**Modification of dose and schedule**
Grade 1 (paraesthesia and/or loss of reflexes, with no loss of function)	Continue with the same dose and schedule
Grade 2 (interfering with function but not with activities of daily living) or	Withhold dose until toxicity returns to ≤ Grade 1 or baseline, then restart treatment at a reduced dose of 1.2 mg/kg up to a maximum of 120 mg every 3 weeks
Grade 3 (interfering with activities of daily living)	Withhold dose until toxicity returns to ≤ Grade 1 or baseline, then restart treatment at a reduced dose of 1.2 mg/kg up to a maximum of 120mg every 3 weeks
Grade 4 (sensory neuropathy that is disabling or motor neuropathy that is life threatening or leads to paralysis)	Discontinue treatment

Grading based on National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v3.0; see neuropathy: motor; neuropathy: sensory; and neuropathic pain.

Table 16: Dosing recommendations for new or worsening peripheral sensory or motor Neuropathy during Combination Therapy

	Combination Therapy with AVD	**Combination Therapy with CHP**
Severity of Peripheral Sensory or Motor Neuropathy (Signs and Symptoms [abbreviated description of CTCAE*])	**Modification of Dose and Schedule**	
Grade 1 (paraesthesia and/or loss of reflexes, with no loss of function)	Continue with same dose and schedule	Continue with same dose and schedule
Grade 2 (interfering with function but not with activities of daily living)	Reduce dose to 0.9 mg/kg up to a maximum of 90 mg every 2 weeks	Sensory neuropathy: Continue treatment at same dose level Motor neuropathy: Reduce dose to 1.2 mg/kg up to a maximum of 120 mg every 3 weeks
Grade 3 (interfering with activities of daily living)	Withhold treatment with brentuximab vedotin until toxicity is ≤ Grade 2, then restart treatment at a reduced dose of 0.9 mg/kg up to a maximum of 90 mg every 2 weeks. Consider modifying the dose of other neurotoxic agents as per their product information	Sensory neuropathy: Reduce dose to 1.2 mg/kg up to a maximum of 120 mg every 3 weeks Motor neuropathy: Discontinue Treatment
Grade 4 (sensory neuropathy that is disabling or motor neuropathy that is life threatening or leads to paralysis)	Discontinue treatment	Discontinue treatment

a Abbreviated description of CTCAE; grading based on NCI CTCAE v4.03; see neuropathy: motor; neuropathy: sensory and neuropathic pain

Special patient populations

Renal and hepatic impairment

Combination therapy

Patients with renal impairment should be closely monitored for adverse events. There is no clinical trial experience using Adcetris in combination with chemotherapy in patients with renal impairment, where serum creatinine is ≥ 2.0 mg/dL and/or creatinine clearance or calculated creatinine clearance is ≤ 40 mL/minute. Use of Adcetris in combination with chemotherapy should be avoided in patients with severe renal impairment.

Patients with hepatic impairment should be closely monitored for adverse events. The recommended starting dose in patients with mild hepatic impairment receiving ADCETRIS in combination with AVD is 0.9 mg/kg administered as an intravenous infusion over 30 minutes every 2 weeks. The recommended starting dose in patients with mild hepatic impairment receiving ADCETRIS in combination with CHP is 1.2 mg/kg administered as an intravenous infusion over 30 minutes every 3 weeks. There is no clinical trial experience using Adcetris in combination with chemotherapy in patients with hepatic impairment, where total bilirubin is > 1.5 times the upper limit of normal (ULN) (unless due to Gilbert syndrome), or aspartate aminotransferase (AST) or alanine aminotransferase (ALT) are > 3 times the ULN, or > 5 times the ULN if their elevation may be reasonably ascribed to the presence of HL in the liver. Use of Adcetris in combination with chemotherapy should be avoided in patients with moderate and severe hepatic impairment.

Monotherapy

The recommended starting dose in patients with severe renal impairment is 1.2 mg/kg administered as an intravenous infusion over 30 minutes every 3 weeks. Patients with renal impairment should be closely monitored for adverse events (see section Pharmacokinetics).

The recommended starting dose in patients with hepatic impairment is 1.2 mg/kg administered as an intravenous infusion over 30 minutes every 3 weeks. Patients with hepatic impairment should be closely monitored for adverse events (see section Pharmacokinetics).

Elderly

The dosing recommendations for patients aged 65 and older are the same as for adults. Currently available data are described in sections ADVERSE EFFECTS/UNDESIRABLE EFFECTS, CLINICAL STUDIES and Pharmacokinetics Section.

Paediatric population
The safety and efficacy of Adcetris in children less than 18 years have not yet been established.
Currently available data are described in sections ADVERSE EFFECTS/UNDESIRABLE EFFECTS, CLINICAL STUDIES and Pharmacokinetic properties but no recommendation on a posology can be made.

Instructions for Reconstitution
General Precautions:
Follow proper aseptic technique throughout the handling of Adcetris.
Recommended safety measures for handling and preparation include protective clothing, gloves and vertical laminar airflow safety cabinets.
Adcetris vials are single-use containers. Any partially used vials or diluted dosing solutions are to be discarded using appropriate institutional drug disposal procedures.

Instructions for reconstitution
Each 50mg single use vial must be reconstituted with 10.5 ml of Water for Injection only. Direct the stream toward the wall of the vial and not directly at the cake. Gently swirl the vial to aid dissolution. DO NOT SHAKE. The reconstituted solution in the vial is a clear to slightly opalescent, colorless solution with a final pH of 6.6. The reconstituted solution should be inspected visually for any particulate matter or discoloration. If any discoloration or particulate matter is observed, the reconstituted solution must be discarded. If not used immediately, the reconstituted solution may be stored at 2 – 8˚C (DO NOT FREEZE) for no more than 24 hours. Adcetris contains no bacteriostatic preservatives. Discard any unused portion left in the vial.

Preparations of Infusion Solution
There are no known incompatibilities between Adcetris and polyvinylchloride bags, ethylene vinyl acetate (EVA), polyolefin, polyethylene (PE) or polypropylene (PP).
The appropriate amount of reconstituted Adcetris will be withdrawn from the vial(s) and added to an infusion bag containing 0.9% Sodium Chloride Injection in order to achieve a final concentration of 0.4-1.8 mg/mL Adcetris. The already reconstituted Adcetris can also be diluted into 5% dextrose in water (D5W), or Lactated Ringers Solution. Gently invert the bag to mix the solution containing Adcetris. DO NOT SHAKE. Excess agitation may cause aggregate formation.
Do not add other medications to the prepared Adcetris infusion solution or IV infusion set. Infusion line should be flushed following administration with 0.9% Sodium Chloride Injection, 5% dextrose in water (D5W), or Lactated Ringers Solution.
Following dilution, infuse the Adcetris solution immediately at the recommended infusion rate, or store the solution at 2 – 8˚C (DO NOT FREEZE) and use within 24 hours. Total storage time of the solution from reconstitution to infusion must not exceed 24 hours.

CONTRAINDICATION
Combination use of bleomycin and Adcetris due to pulmonary toxicity.
Hypersensitivity to the active substances or excipients.

WARNINGS AND PRECAUTIONS
Progressive Multifocal Leukoencephalopathy
John Cunningham virus (JCV) reactivation resulting in progressive multifocal leukoencephalopathy (PML) and death can occur in Adcetris-treated patients. PML has been reported in patients who received this treatment after receiving multiple prior chemotherapy regimens. PML is a rare demyelinating disease of the central nervous system that results from reactivation of latent JCV and is often fatal.
Patients should be closely monitored for new or worsening neurological, cognitive, or behavioral signs or symptoms which may be suggestive of PML. Adcetris dosing should be held for any suspected case of PML. Suggested evaluation of PML includes neurology consultation, gadolinium-enhanced magnetic resonance imaging of the brain and cerebrospinal fluid analysis for JCV DNA by polymerase chain reaction (PCR) or a brain biopsy for evidence of JCV. A negative JCV PCR does not exclude PML. Additional follow-up and evaluation may be warranted if no alternative diagnosis can be established. Adcetris dosing should be permanently discontinued if a diagnosis of PML is confirmed.
The physician should be particularly alert to symptoms suggestive of PML that the patient may not notice (e.g., cognitive, neurological, or psychiatric symptoms).

Pulmonary Toxicity

Cases of pulmonary toxicity, including pneumonitis, interstitial lung disease and acute respiratory distress syndrome (ADRS), some fatal outcomes, have been reported in patients receiving Adcetris. Although a causal association with Adcetris has not been established, the risk of pulmonary toxicity cannot be ruled out. In the event of new or worsening pulmonary symptoms (e.g., cough, dyspnea), a prompt diagnostic evaluation should be performed and patients should be treated appropriately. Consider holding Adcetris dosing during evaluation and until symptomatic improvement.

Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported with Adcetris. Fatal outcomes have been reported. If SJS or TEN occur, treatment with Adcetris should be discontinued and appropriate medical therapy should be administered.

Pancreatitis

Acute pancreatitis has been observed in patients treated with brentuximab vedotin. Fatal outcomes have been reported.

Patients should be closely monitored for new or worsening abdominal pain, which may be suggestive of acute pancreatitis. Patient evaluation may include physical examination, laboratory evaluation for serum amylase and serum lipase, and abdominal imaging, such as ultrasound and other appropriate diagnostic measures. Brentuximab vedotin should be held for any suspected case of acute pancreatitis. Brentuximab vedotin should be discontinued if a diagnosis of acute pancreatitis is confirmed.

Serious infections and opportunistic infections

Serious infections such as pneumonia, staphylococcal bacteraemia, sepsis/ septic shock (including fatal outcomes) and herpes zoster, and opportunistic infections such as Pneumocystis jiroveci pneumonia and oral candidiasis have been reported in patients treated with Adcetris. Patients should be carefully monitored during treatment for the emergence of possible serious and opportunistic infections.

Infusion-Related Reactions

Immediate and delayed infusion-related reactions (IRR), as well as anaphylactic reactions, have been reported. Patients should be carefully monitored during and after infusion. If an anaphylactic reaction occurs, administration of Adcetris should be immediately and permanently discontinued and appropriate medical therapy should be administered.

If an infusion-related reaction occurs, the infusion should be interrupted and appropriate medical management instituted. The infusion may be restarted at a slower rate after symptom resolution.

Patients who have experienced a prior infusion-related reaction should be premedicated for subsequent infusions. Premedication may include paracetamol, an antihistamine and a corticosteroid.

Infusion-related reactions are more frequent and more severe in patients with antibodies to Adcetris (see section ADVERSE EFFECTS/UNDESIRABLE EFFECTS)

Peripheral Neuropathy

ADCETRIS may cause peripheral neuropathy, both sensory and motor. ADCETRIS-induced peripheral neuropathy is typically an effect of cumulative exposure to this medicinal product and is reversible in most cases. In clinical trials, the majority of patients had resolution or improvement of their symptoms (see section ADVERSE EFFECTS/UNDESIRABLE EFFECTS). Patients should be monitored for symptoms of neuropathy, such as hypoesthesia, hyperesthesia, paraesthesia, discomfort, a burning sensation, neuropathic pain or weakness. Patients experiencing new or worsening peripheral neuropathy may require a delay and a dose reduction of ADCETRIS or discontinuation of treatment (see DOSAGE AND ADMINISTRATION).

Haematological toxicities

Grade 3 or Grade 4 anaemia, thrombocytopenia, and prolonged (≥1 week) Grade 3 or Grade 4 neutropenia can occur with Adcetris. Fatal and serious cases of febrile neutropenia have been reported with Adcetris. Complete blood counts should be monitored prior to administration of each dose of Adcetris. Patients should be monitored closely for fever. If Grade 3 or Grade 4 neutropenia develops, manage by dose modifications or discontinuations (refer to section Dosage and administration). In frontline treatment of patients with advanced HL, or in patients with previously untreated sALCL or other CD30-expressing PTCL, receiving combination therapy, primary prophylaxis with G-CSF is recommended for all patients beginning with the first dose.

Tumor Lysis Syndrome
Tumor lysis syndrome (TLS) has been reported with Adcetris. Patients with rapidly proliferating tumor and high tumor burden are at risk of tumor lysis syndrome. These patients should be monitored closely and managed according to best medical practice. Management of TLS may include aggressive hydration, monitoring of renal function, correction of electrolyte abnormalities, anti-hyperuricaemic therapy and supportive care.

Gastrointestinal Complications
Gastrointestinal (GI) complications including intestinal obstruction, ileus, enterocolitis, neutropenic colitis, erosion, ulcer, perforation and haemorrhage, some with fatal outcomes, have been reported in patients treated with Adcetris. Some cases of GI perforations were reported in patients with GI involvement of underlying lymphoma. In the event of new or worsening GI symptoms, perform a prompt diagnostic evaluation and treat appropriately.

Hepatotoxicity
Hepatotoxicity in the form of elevations in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) has been reported with Adcetris. Serious cases of hepatotoxicity, including fatal outcomes, have also occurred. Pre-existing liver disease, comorbidities, and concomitant medications may also increase the risk. Liver function should be routinely monitored in patients receiving Adcetris. Patients experiencing hepatotoxicity may require a delay, change in dose or discontinuation of Adcetris. (see ADVERSE EFFECTS/UNDESIRABLE EFFECTS)

Use in Pregnancy
Adcetris may cause fetal harm when administered to pregnant women.

Hyperglycaemia
Hyperglycaemia has been reported during clinical trials in patients with an elevated Body Mass Index (BMI) with or without a history of diabetes mellitus. However, any patient who experiences an event of hyperglycaemia should have their serum glucose closely monitored. Anti-diabetic treatment should be administered as appropriate.

Sodium content in excipients
This medicinal product contains a maximum of 2.1 mmol (or 47 mg) of sodium per dose. To be taken into consideration for patients on a controlled sodium diet.

INTERACTIONS WITH OTHER MEDICAMENTS
CYP3A4 Inhibitors, Inducers and Substrates
Co-administration of Adcetris with ketoconazole, a strong CYP3A4 inhibitor and P-gp inhibitor, did not alter exposure to Adcetris; however, a moderate increase to the exposure to MMAE was observed. Patients who are receiving strong CYP3A4 inhibitors and P-gp inhibitors concomitantly with Adcetris should be closely monitored for adverse events.
Co-administration of Adcetris with rifampicin, a strong CYP3A4 inducer, did not alter exposure to Adcetris; however, a moderate reduction to the exposure to MMAE was observed. Co-administration of Adcetris with CYP3A4 inducers is not expected to have an impact on safety or efficacy.
Co-administration of midazolam, a CYP3A4 substrate, with Adcetris did not alter the metabolism of midazolam; therefore Adcetris is not expected to alter the exposure to drugs that are metabolized by CYP3A4 enzymes (See Pharmacokinetics).

Doxorubicin, Vinblastine and Dacarbazine
The serum and plasma pharmacokinetic characteristics of ADC and MMAE respectively following administration of Adcetris in combination with doxorubicin, vinblastine and dacarbazine were similar to that in monotherapy. Co-administration of Adcetris did not affect the plasma exposure of doxorubicin, vinblastine or dacarbazine.

Cyclophosphamide, Doxorubicin, and Prednisone
The serum and plasma pharmacokinetic characteristics of ADC and MMAE, respectively, following administration of Adcetris in combination with cyclophosphamide, doxorubicin, and prednisone were similar to that in monotherapy.

USE IN SPECIFIC POPULATIONS
Pregnancy
There are no adequate and well-controlled studies with Adcetris in pregnant women. Adcetris may cause fetal harm when administered to pregnant women; therefore women who are pregnant should not begin treatment with Adcetris. Women of childbearing potential should be advised not to become pregnant while taking this medicine, and must use effective methods to prevent pregnancy from the start of treatment with Adcetris and must continue for 6 months

following the last dose of Adcetris. If the patient becomes pregnant while taking Adcetris, the patient should be apprised of the potential hazard to the fetus.
Adcetris was studied for effects on embryo-fetal development in pregnant female rats. The no-observed-adverse-effect-level of Adcetris when administered to pregnant rats was 1 mg/kg/dose.
It is not known if using Adcetris will affect human spermatogenesis. In nonclinical studies, Adcetris resulted in testicular toxicity which was partially resolved 16-weeks post last dose administration. Therefore, due to this potential risk, men should be advised not to impregnate their partner during treatment with Adcetris. Men of reproductive potential must use an appropriate method of barrier contraception throughout treatment with Adcetris and for at least 6 months following the last dose of Adcetris (See Warnings and Precautions).

Lactation (Breastfeeding)
It is not known whether Adcetris or MMAE are excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from Adcetris, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of Adcetris to the mother.

Fertility
In non-clinical studies, brentuximab vedotin treatment has resulted in testicular toxicity, and may alter male fertility. MMAE has been shown to have aneugenic properties. Therefore, men being treated with this medicine are advised to have sperm samples frozen and stored before treatment. Men being treated with this medicine are advised not to father a child during treatment and for up to 6 months following the last dose.
In non-clinical studies, treatment with MMAE containing ADCs other than Adcetris, have resulted in ovarian toxicity (see section NONCLINICAL TOXICOLOGY). See the Women of childbearing potential section above pertaining to advice for women on the use of methods of effective contraception.

ADVERSE EFFECTS/UNDESIRABLE EFFECTS

Summary of the safety profile
The safety profile of ADCETRIS is based on available clinical trial data, the Named Patient Program (NPP), and post-marketing experience to date. Frequencies of adverse reactions described below and in Table 5 have been determined based on data generated from clinical studies.

Monotherapy
In the pooled dataset of Adcetris as monotherapy across HL, sALCL and CTCL studies (SG035-0003, SG035-0004, SGN35-005, SGN35-006, C25001 and C25007, see section CLINICAL STUDIES), the most frequent adverse reactions (≥10%) were infections, peripheral sensory neuropathy, fatigue, nausea, diarrhea, pyrexia, upper respiratory tract infection, neutropenia, rash, cough, vomiting, arthralgia, peripheral motor neuropathy, infusion-related reactions, pruritus, constipation, dyspnea, weight decreased, myalgia and abdominal pain.

Serious adverse drug reactions occurred in 12% of patients. The frequency of unique serious adverse drug reactions was ≤ 1%.

Adverse events led to treatment discontinuation in 24% of patients receiving ADCETRIS.

The safety data in patients retreated with ADCETRIS (SGN35-006, see section CLINICAL STUDIES) were consistent with those observed in the combined pivotal phase 2 studies, with the exception of peripheral motor neuropathy, which had a higher incidence (28% vs. 9% in the pivotal phase 2 studies) and was primarily Grade 2. Patients also had a higher incidence of arthralgia, Grade 3 anaemia, and back pain compared to patients observed in the combined pivotal phase 2 studies.

The safety data in patients with relapsed or refractory HL who had not received an autologous stem cell transplant and were treated with the recommended dose of 1.8 mg/kg every three weeks in a single-arm phase 4 study (n = 60), the phase 1 dose escalation and clinical pharmacology studies (n = 15 patients) and in the NPP (n = 26 patients) (see section CLINICAL STUDIES) were consistent with the safety profile of the pivotal clinical studies.

Combination therapy

For safety information of chemotherapy agents given in combination with ADCETRIS (doxorubicin, vinblastine and dacarbazine (AVD) or cyclophosphamide, doxorubicin and prednisone (CHP)), refer to their summary of product characteristics.

In the studies of ADCETRIS as combination therapy in 662 patients with previously untreated advanced HL (C25003) and 223 patients with previously untreated CD30+ peripheral T-cell lymphoma (PTCL) (SGN35-014), the most common adverse reactions (≥ 10%) were: infections, neutropenia, peripheral sensory neuropathy, nausea, constipation, vomiting, diarrhoea, fatigue, pyrexia, alopecia, anaemia, weight decreased, stomatitis, febrile neutropenia, abdominal pain, decreased appetite, insomnia, bone pain, rash, cough, dyspnoea, arthralgia, myalgia, back pain, peripheral motor neuropathy, upper respiratory tract infection, and dizziness.

In patients receiving ADCETRIS combination therapy, serious adverse reactions occurred in 34% of patients. Serious adverse reactions occurring in ≥ 3% of patients included febrile neutropenia (15%), pyrexia (5%), and neutropenia (3%).

Adverse events led to treatment discontinuation in 10% of patients. Adverse events that led to treatment discontinuation in ≥ 2% of patients included peripheral sensory neuropathy, and peripheral neuropathy.

Tabulated list of adverse reactions

Adverse reactions for ADCETRIS are listed by MedDRA System Organ Class and Preferred Term (see Table 5). Within each System Organ Class, adverse reactions are listed under frequency categories of: Very common (≥ 1/10); Common (≥ 1/100 to < 1/10); Uncommon (≥ 1/1,000 to < 1/100); Rare (≥ 1/10,000 to < 1/1,000); Very rare (< 1/10,000); not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

Table 5: Adverse reactions to ADCETRIS

System organ class	**Adverse reactions (monotherapy)**	**Adverse reactions (combination therapy)**
Infections and infestations		
Very common:	Infection[a], upper respiratory tract infection	Infection[a], upper respiratory tract infection
Common:	Herpes zoster, pneumonia, herpes simplex, oral candidiasis	Pneumonia, oral candidiasis, sepsis/septic shock, herpes zoster
Uncommon:	Pneumocystis jiroveci pneumonia, staphylococcal bacteraemia, cytomegalovirus infection or reactivation, sepsis/septic shock	Herpes simplex, Pneumocystis jiroveci pneumonia
Frequency not known:	Progressive multifocal leukoencephalopathy	
Blood and lymphatic system disorders		
Very common:	Neutropenia	Neutropenia[a], anaemia, febrile neutropenia
Common:	Anaemia, thrombocytopenia	Thrombocytopenia
Uncommon:	Febrile neutropenia	
Immune system disorders		
Uncommon:	Anaphylactic reaction	Anaphylactic transfusion reaction
Metabolism and nutrition disorders		
Very common:		Decreased appetite
Common:	Hyperglycaemia	Hyperglycaemia
Uncommon:	Tumour lysis syndrome	Tumour lysis syndrome
Psychiatric disorders		
Very common:		Insomnia

Nervous system disorders		
Very common:	Peripheral sensory neuropathy, peripheral motor neuropathy	Peripheral sensory neuropathy[a], peripheral motor neuropathy[a], dizziness
Common:	Dizziness	
Uncommon:	Demyelinating polyneuropathy	
Respiratory, thoracic and mediastinal disorders		
Very common:	Cough, dyspnoea	Cough, dyspnoea
Gastrointestinal disorders		
Very common:	Nausea, diarrhoea, vomiting, constipation, abdominal pain	Nausea, constipation, vomiting, diarrhoea, abdominal pain, stomatitis
Uncommon:	Pancreatitis acute	Pancreatitis acute
Hepatobiliary disorders		
Common:	Alanine aminotransferase/aspartate aminotransferase (ALT/AST) increased	Alanine aminotransferase/aspartate aminotransferase (ALT/AST) increased
Skin and subcutaneous tissue disorders		
Very common:	Rash[a], pruritus	Alopecia, rash[a]
Common:	Alopecia	Pruritus
Uncommon:	Stevens-Johnson syndrome/toxic epidermal necrolysis	Stevens-Johnson syndrome[b]
Musculoskeletal and connective tissue disorders		
Very common:	Arthralgia, myalgia	Bone pain, arthralgia, myalgia, back pain
Common:	Back pain	
General disorders and administration site conditions		
Very common:	Fatigue, pyrexia, infusion-related reactions[a]	Fatigue, pyrexia
Common:	Chills	Infusion-related reactions[a], chills
Not known:	Infusion site extravasation[c]	
Investigations		
Very common:	Weight decreased	Weight decreased

a. Represents pooling of preferred terms.

b. Toxic epidermal necrolysis was not reported in the combination therapy setting.

c. Extravasation-related reactions include skin redness, pain, swelling, blistering or sloughing at the infusion site.

Description of selected adverse reactions

Neutropenia and febrile neutropenia

Monotherapy

In clinical trials, neutropenia led to dose delays in 14% of patients. Grade 3 neutropenia was reported in 13% and Grade 4 neutropenia was reported in 5% of patients. No patients required dose reduction or discontinued treatment for neutropenia.

Severe and prolonged (≥ 1 week) neutropenia can occur with this treatment which may increase the risk of patients developing serious infections. Febrile neutropenia reported in < 1% of the patients (see section DOSAGE AND ADMINISTRATION).

In the pivotal phase 2 population (SG035-0003 and SG035-0004), the median duration of Grade 3 or Grade 4 neutropenia was limited (1 week); 2% of patients had Grade 4 neutropenia that lasted ≥ 7 days. Less than half of the patients in the pivotal phase 2 population with Grade 3 or Grade 4 neutropenia had temporally associated infections, and the majority of temporally associated infections were Grade 1 or Grade 2.

Combination therapy

In the clinical trials of ADCETRIS as combination therapy, neutropenia led to dose delays in 19% of patients. Grade 3 neutropenia was reported in 17% and Grade 4 neutropenia was reported in 41% of patients. Two percent of patients required dose reduction and < 1% discontinued one of more of the study drugs due to neutropenia.

Febrile neutropenia was reported in 20% of the patients who did not receive primary prophylaxis with G-CSF (see section DOSAGE AND ADMINISTRATION). The frequency of febrile neutropenia was 13% in patients who received primary prophylaxis with G-CSF.

Serious infections and opportunistic infections

Monotherapy

In clinical trials, serious infections and opportunistic infections occurred in 10% of patients, sepsis or septic shock occurred in < 1% of the patients. The most commonly reported opportunistic infections were herpes zoster and herpes simplex.

Combination therapy

In the clinical trials of ADCETRIS as combination therapy, serious infections including opportunistic infections occurred in 15% of patients; sepsis, neutropenic sepsis, septic shock or bacteraemia occurred in 4% of the patients. The most commonly reported opportunistic infections were herpes viral infections.

Peripheral neuropathy

Monotherapy

In clinical trials treatment emergent neuropathy occurred in 59% of the population, peripheral motor neuropathy occurred in 14% of patients. Peripheral neuropathy led to treatment discontinuation in 15%, dose reductions in 15%, and dose delays in 17% of patients. For patients who experienced peripheral neuropathy the median time of onset of peripheral neuropathy was 12 weeks. The median duration of treatment for patients who discontinued due to peripheral neuropathy was 12 cycles.

Among patients who experienced peripheral neuropathy in the pivotal phase 2 studies (SG035-0003 and SG035-0004) and randomised phase 3 monotherapy studies (SGN35-005 and C25001), the median follow up time from end of treatment until last evaluation ranged from 48.9 to 98 weeks. At the time of last evaluation, most of the patients (82-85%) who experienced peripheral neuropathy had resolution or improvement of their peripheral neuropathy symptoms. The median time from onset to resolution or improvement for all events ranged from 16 to 23.4 weeks.

In patients with relapsed or refractory HL or sALCL who were retreated with ADCETRIS (SGN35-006), the majority of patients (80%) also had improvement or resolution of their peripheral neuropathy symptoms at the time of last evaluation.

Combination therapy

In the clinical trial of ADCETRIS as combination therapy with AVD, treatment emergent neuropathy occurred in 67% of the population; peripheral motor neuropathy occurred in 11% of patients. Peripheral neuropathy led to treatment discontinuation in 7%, dose reductions in 21%, and dose delays in 1% of patients. For patients who experienced peripheral neuropathy the median time of onset of peripheral neuropathy was 8 weeks. Patients who discontinued due to peripheral neuropathy received a median of 8 doses of ADCETRIS+AVD (A+AVD) before discontinuation of one or more agents.

Among patients who experienced peripheral neuropathy, the median follow up time from end of treatment until last evaluation was approximately 91 weeks. At the time of last evaluation, most of the patients (76%) who experienced peripheral neuropathy had resolution or improvement of their peripheral neuropathy symptoms. The median time from onset to resolution or improvement of peripheral neuropathy events was 10 weeks (ranged from 0 weeks to 139 weeks).

In the clinical trial of ADCETRIS as combination therapy with CHP, treatment emergent neuropathy occurred in 52% of the population; peripheral motor neuropathy occurred in 9% of patients. Peripheral neuropathy led to treatment discontinuation in 1%, dose reductions in 7% and dose delays in <1% of patients. For patients who experienced peripheral neuropathy the median time of onset was 9.1 weeks. Patients who discontinued due to peripheral neuropathy received a median of 5 doses of ADCETRIS+CHP (A+CHP) before discontinuation of one or more agents.

Among patients who experienced peripheral neuropathy, the median follow up time from end of treatment until last evaluation was approximately 177 weeks. At the time of last evaluation, 64% who experienced peripheral neuropathy had resolution or improvement of their peripheral neuropathy symptoms. The median time from onset to resolution or improvement of peripheral neuropathy events was 19.0 weeks (ranged from 0 weeks to 205 weeks).

Infusion-related reactions

Monotherapy

IRRs, such as headache, rash, back pain, vomiting, chills, nausea, dyspnoea, pruritus and cough were reported in 13% of patients. Anaphylactic reactions have been reported (see section Warnings and Precautions). Symptoms of an anaphylactic reaction may include, but are not limited to, urticaria, angioedema, hypotension and bronchospasm.

Combination therapy

IRRs, such as headache, rash, back pain, vomiting, chills, nausea, dyspnoea, pruritus, cough, infusion site pain and pyrexia were reported in 8% of patients. Anaphylactic reactions have been reported (see section Warnings and Precautions). Symptoms of an anaphylactic reaction may include, but are not limited to, urticaria, angioedema, hypotension and bronchospasm.

Immunogenicity

In clinical trials, patients were periodically tested for antibodies to brentuximab vedotin using a sensitive electrochemiluminescent immunoassay. There was a higher incidence of infusion-related reactions observed in patients with antibodies to brentuximab vedotin relative to patients who tested transiently positive or negative.

The presence of antibodies to brentuximab vedotin did not correlate with a clinically meaningful reduction in serum brentuximab vedotin levels and did not result in a decrease in the efficacy of brentuximab vedotin. While the presence of antibodies to brentuximab vedotin does not necessarily predict the development of an IRR, there was a higher incidence of IRRs observed in patients with persistently positive anti-drug antibodies (ADA) relative to patients with transiently positive ADA and never positive ADA.

There was a trend of increased clearance of brentuximab vedotin in paediatric patients confirmed positive for ADAs. No patients aged < 12 years (0 of 11) and 2 patients aged ≥ 12 years (2 of 23) became persistently ADA positive.

Paediatric population

Safety was evaluated in a phase 1/2 study in paediatric patients aged 7 17 years of age (n = 36) with relapsed or refractory (r/r) HL and sALCL (see section 5.1). In this study in 36 patients, no new safety concerns were reported.

Elderly

Monotherapy

The safety profile in elderly patients is generally in line with that of adult patients. However, elderly patients may be more susceptible to events such as pneumonia, neutropenia and febrile neutropenia.

Combination therapy

In older patients (≥ 60 years of age; n = 186 [21%]), the incidence of adverse events was similar across treatment arms. More serious adverse events and dose modifications (including dose delays, reductions, and discontinuations) were reported in the older patients compared with the overall study population. Advanced age was a risk factor for febrile neutropenia in patients in both arms. Older patients who received G-CSF primary prophylaxis had lower incidence of neutropenia and febrile neutropenia than those who did not receive G-CSF primary prophylaxis.

OVERDOSE AND TREATMENT

There is no known antidote for overdosage of Adcetris. In case of overdosage, the patient should be closely monitored for adverse reactions, particularly neutropenia, and supportive treatment should be administered (See section Warnings and Precautions – Neutropenia).

INCOMPATIBILITIES

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

STORAGE CONDITIONS

Store at 2 - 8°C. Keep the container in the original carton.

Shelf life

Unopened vial:

4 years.

Reconstituted Adcetris Vial:

Chemical and physical in-use stability has been demonstrated for 24 hours at 2 – 8˚C. From a microbiological point of view, the product must be used within 24 hours after vial reconstitution.

Infusion Bag with Diluted Adcetris:

The chemical and physical in-use stability of the diluted solution has been demonstrated for 24 hours at 2 –8˚C when the dilution occurs immediately after reconstitution. From a microbiological point of view, the product must be used within 24 hours after vial reconstitution.

INSTRUCTIONS FOR USE AND HANDLING AND DISPOSAL

Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published.

PACKAGING AVAILABLE

Pack of 1 vial containing 50mg of brentuximab vedotin powder.

NAME AND ADDRESS OF MANUFACTURER/MARKETING AUTHORIZATION HOLDER

Manufacturer

BSP Pharmaceuticals S.p.A
Via Appia Km 65,561
Latina Scalo (LT) 04013, Italy for
Takeda Pharmaceutical Company Ltd.

Product Registration Holder

Takeda Malaysia Sdn Bhd
Unit TB-L13-1, Level 13, Tower B, Plaza 33
No.1, Jalan Kemajuan, Seksyen 13
46200 Petaling Jaya, Selangor, Malaysia

REVISION OF TEXT

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