# ADCETRIS® (brentuximab vedotin)

# 1 NAME OF THE MEDICINAL PRODUCT & PHARMACEUTICAL FORM

ADCETRIS 50 mg powder for concentrate for solution for infusion.

# 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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).

Each single-use vial contains 50 mg of brentuximab vedotin.

Each mL contains 5 mg of brentuximab vedotin, after reconstitution.

Powder for concentrate for solution for infusion.

White to off-white lyophilized cake or powder.

Excipients (weight per 50 mg vial; concentration after reconstitution):

Citric acid monohydrate
Sodium citrate dihydrate
α,α-Trehalose dihydrate,
Polysorbate 80

# 3 PHARMACEUTICAL PARTICULARS

## *3.1 INCOMPATIBILITIES*

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

## *3.2 SPECIAL PRECAUTIONS FOR STORAGE AND TRANSPORTATION*

Store at 2 – 8˚C.

Keep the container in the original carton.

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.

### *3.3 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.

## 4 CLINICAL PARTICULARS

### *4.1 THERAPEUTIC INDICATIONS*

ADCETRIS is indicated for the treatment of patients with CD30-expressing previously untreated peripheral T - cell lymphoma (PTCL) in combination with cyclophosphamide, doxorubicin and prednisone.

ADCETRIS is indicated for adult patients with previously untreated CD30+ Stage IV Hodgkin lymphoma (HL) in combination with doxorubicin, vinblastine and dacarbazine (AVD).(see sections 4.2 Posology and 8.1 Hodgkin Lymphoma).

ADCETRIS is indicated for the treatment of patients with relapsed or refractory CD30+ Hodgkin lymphoma (HL).

ADCETRIS is indicated for the treatment of patients with relapsed or refractory CD30+ Hodgkin lymphoma (HL) following Autologous Stem Cell Transplant (ASCT) or at least two prior therapies when ASCT or multi-agent chemotherapy is not a treatment option.

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

ADCETRIS is indicated for the treatment of adult patients with histologically confirmed CD30+ mycosis fungoides (MF) or primary cutaneous anaplastic large cell lymphoma (pcALCL) after at least 1 prior systemic therapy.

### *4.2 POSOLOGY AND METHOD OF 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 8.1 Hodgkin Lymphoma ).

Primary prophylaxis with growth factor support (G-CSF) is recommended for all patients with previously intreated HL receiving combination therapy beginning with the first dose (See section 5.2 Special Warnings and Precautions for Use ).

Refer to the product information of chemotherapy agents given in combination with ADCETRIS for patients with previously untreated HL.

The recommended dose is 1.8 mg/kg administered as an intravenous infusion over 30 minutes every 3 weeks.

For patients with HL at risk of relapse or progression following ASCT, ADCETRIS treatment should start following recovery from ASCT based on medical judgment. These patients should receive up to 16 cycles (See section 8. Clinical Studies).

Previously Untreated 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 8.Clinical Studies).

Primary prophylaxis with growth factor support (G-CSF) is recommended for all patients beginning with the first dose (See section 5.2 Special Warnings and Precautions for Use).

Refer to the product information of chemotherapy agents given in combination with ADCETRIS for treatment of patients with previously untreated PTCL.

Relapsed or refractory HL or sALCL
The recommended starting dose for the retreatment of patients with relapsed or refractory HL or sALCLwho 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 8. Clinical Studies)

Patients with histologically confirmed CD30+ mycosis fungoides (MF) or primary cutaneous anaplastic large cell lymphoma (pcALCL) should receive up to 16 cycles.

Continue treatment until disease progression or unacceptable toxicity (See section 5.2 Special Warnings and Precautions for Use).

Patients who achieve stable disease or better should receive a minimum of 8 cycles.

There is clinical experience with treating patients through 16 cycles (approximately 1 year).

The recommended dose is 1.8 mg/kg administered as an intravenous infusion over 30 minutes every 3 weeks.

General
Do not administer as an IV push or bolus.

If patient's weight is more than 100 kg, the dose calculation should use 100 kg (See section 4.2.1 Instruction for reconstitution).

### 4.2.1 Dose Adjustments

Dose Modification and/or Dose Discontinuation

Continue treatment as long as the patient continues to benefit from and tolerates the therapy. See below for recommendations for peripheral neuropathy and neutropenia.

Peripheral Neuropathy

If peripheral sensory or motor neuropathy emerges or worsens during treatment see Table 1 and Table 2 for appropriate recommendations for monotherapy and combination therapy, respectively.

**Table 1: 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 CTCAE*]) | **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) | 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 120 mg 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 2: 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<br>(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<br>(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<br>Motor neuropathy: Reduce dose to 1.2 mg/kg up to a maximum of 120 mg every 3 weeks |
| Grade 3<br>(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<br>Motor neuropathy: Discontinue treatment |
| Grade 4<br>(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

Neutropenia

If neutropenia develops during treatment it should be managed by dose delays (See Section 5.2. Warnings and Precautions). See Table 3 and Table 4 below for appropriate dosing recommendations for monotherapy and combination therapy, respectively.

**Table 3: Dosing Recommendations for New or Worsening Neutropenia with Monotherapy**

<table>
<tr><th></th><th>Monotherapy</th></tr>
<tr><td>Severity Grade of Neutropenia<br>(Signs and Symptoms [abbreviated description of CTCAE[a]])</td><td>Modification of Dosing Schedule</td></tr>
<tr><td>Grade 1 (<LLN - 1500/mm$^3$<br><LLN - 1.5 x 10$^9$/L) or<br>Grade 2 (<1500 - 1000/mm$^3$<br><1.5 – 1.0 x 10$^9$/L)</td><td>Continue with the same dose and schedule</td></tr>
<tr><td>Severity Grade of Neutropenia<br>(Signs and Symptoms [abbreviated description of CTCAE[a]])<br>Grade 1<br>(<LLN - 1500/mm$^3$, <LLN - 1.5 × 10$^9$/L) or<br>Grade 2<br>(<1500 - 1000/mm$^3$, <1.5 - 1.0 × 10$^9$/L)<br>Grade 3<br>(<1000 - 500/mm$^3$, <1.0 - 0.5 × 10$^9$/L) or<br>Grade 4<br>(<500/mm$^3$, <0.5 × 10$^9$/L)<br><br>Grade 3 (<1,000 - 500/mm$^3$<br><1.0 - 0.5 x 10$^9$/L) or<br>Grade 4 (<500/mm$^3$<br><0.5 x 10$^9$/L)</td><td>Withhold dose until<br><br>toxicity returns to ≤ Grade 2 or baseline then resume treatment at the same dose and schedule[b]. Consider G-CSF or GM-CSF in subsequent cycles for patients who develop Grade 3 or 4 neutropenia.</td></tr>
</table>

G-CSF=granulocyte colony-stimulating factor; GM-CSF=granulocyte macrophage colony-stimulating factor; LLN= lower limit of normal

a. Grading based on National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v3.0; see Neutrophils/granulocytes

b. Patients who develop Grade 3 or 4 lymphopenia may continue study treatment without interruption.

**Table 4: 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/mm$^3$, <LLN - 1.5 × 10$^9$/L) or Grade 2 (<1500 - 1000/mm$^3$, <1.5 - 1.0 × 10$^9$/L) Grade 3 (<1000 - 500/mm$^3$, <1.0 - 0.5 × 10$^9$/L) or Grade 4 (<500/mm$^3$, <0.5 × 10$^9$/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

**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 Pharmacokinetics [<6.2>]).

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 Pharmacokinetics [<6.2>]).

Elderly
Based upon population PK analyses and the safety profile in elderly patients, which are consistent with that of adult patients, the dosing recommendations for patients aged 65 and older are the same as for adults. Currently available data are described in sections 5.5, 6.2.6 and 8.

Pediatric population
The safety and efficacy of children less than 18 years have not yet been established.
Currently available data are described in sections 5.6, 6.2.6 and 8.4.

In nonclinical studies, thymus depletion has been observed.

### 4.2.2 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.

Determining Dosage Amount (See Posology and Method of Administration [<4.2>]):

Calculate the dose (mg) and number of vials of ADCETRIS required.

Dose calculation to prepare infusion solution for a normal dose:

a) (1.8 mg/kg) X patient's weight in kg = dose in mg

Note: If patient's weight is more than 100 kg, the dose calculation should use 100 kg.

b) To calculate amount of mLs:

(Dose in mg) divided by (5 mg/mL which is the final concentration in a reconstituted vial) = dose in mL

c) Since 10-mL can be withdrawn from each vial, calculate the number of vials needed to prepare infusion solution:

(Dose in mL) divided by (10-mL/vial) = Number of vials that should be used.

Dose calculation to prepare infusion solution for a reduced dose:

a) (1.2 mg/kg) X pts weight in kg = dose in mg
Note: If patient's weight is more than 100 kg, the dose calculation should use 100 kg.

b) To calculate amount of mLs:
(Dose in mg) divided by (5 mg/mL which is the final concentration a reconstituted vial) = dose in mL

c) Since 10-mL can be withdrawn from each vial, calculate the number of vials needed to prepare infusion solution:
*(Dose in mL) divided by (10-mL/vial) = Number of vials that should be used.*

Instructions for reconstitution

Each 50 mg single-use vial must be reconstituted with 10.5 ml of Water for Injection . 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.

Preparation 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, USP or equivalent, in order to achieve a final concentration of 0.4-1.8 mg/mL brentuximab vedotin. The already reconstituted ADCETRIS can also be diluted into 5% dextrose in water (D5W), USP or equivalent, or Lactated Ringers Solution, USP or equivalent.

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.

*Sterile water for injection (preservative free)

# 5 SAFETY INFORMATION

## 5.2 *CONTRAINDICATIONS*

- Combination use of bleomycin and ADCETRIS due to pulmonary toxicity.
- Hypersensitivity to the active substance or to any of the excipients listed in section 2.

## 5.3 *SPECIAL WARNINGS AND SPECIAL PRECAUTIONS FOR USE*

*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 ADCETRIS 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 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 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).

*Pancreatitis*

Acute pancreatitis has been observed in patients treated with ADCETRIS. 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. ADCETRIS should be discontinued if a diagnosis of acute pancreatitis is confirmed.

*Pulmonary Toxicity*

Cases of pulmonary toxicity, including pneumonitis, interstitial lung disease and acute respiratory distress syndrome (ARDS), some with 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.

*Serious Infections and Opportunistic Infections*

Serious and opportunistic infections such as pneumonia, bacteremia, and sepsis/septic shock (including fatal outcomes) have been reported in patients treated with ADCETRIS. Patients should be carefully monitored during treatment for the emergence of possible bacterial, fungal or viral infections.

*Infusion-Related Reactions*

Infusion-related reactions can occur with ADCETRIS. Carefully monitor patients during infusion. If an infusion-related reaction occurs, the infusion should be interrupted and appropriate medical management instituted. Patients who have experienced a prior infusion-related reaction should be premedicated for subsequent infusions. Premedication may include paracetamol (acetaminophen), an antihistamine and a corticosteroid.

Anaphylaxis has been reported with ADCETRIS. Carefully monitor patients during infusion. If anaphylaxis occurs, immediately discontinue administration of ADCETRIS and administer appropriate medical therapy. There are limited data with retreatment of patients who have experienced an anaphylactic reaction with ADCETRIS.

*Peripheral Neuropathy*

ADCETRIS treatment may cause peripheral neuropathy, both sensory and motor. ADCETRIS-induced peripheral neuropathy is typically cumulative and generally reversible. In clinical trials, the majority of patients had improvement or resolution of some of their symptoms. Patients should be monitored for symptoms of neuropathy, such as hypoesthesia, hyperesthesia, paresthesia, discomfort, a burning sensation, neuropathic pain, or weakness. Patients experiencing new or worsening peripheral neuropathy may require a delay and a change in dose of ADCETRIS or ADCETRIS discontinuation (See section 4.2 Dose adjustments). Neuropathy appeared to be mitigated by dose delay and subsequent reduction or ADCETRIS discontinuation.

*Hematological Toxicities*

Grade 3 or Grade 4 anemia, thrombocytopenia, and prolonged (≥ 1 week) neutropenia can occur with ADCETRIS. Febrile neutropenia has been reported with treatment 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 4 neutropenia develops, manage as needed by dose modifications or discontinuations (See section 4.2.1 Dose Adjustments). In the treatment of patients with previously untreated advanced HL or previously untreated PTCL, primary prophylaxis with G-CSF is recommended for all patients beginning with the first dose.

*Febrile neutropenia*

Febrile neutropenia (fever of unknown origin without clinically or microbiologically documented infection with an absolute neutrophil count < 1.0 x 109/L, fever ≥ 38.5 0C; ref CTCAE v3) has been reported with treatment with ADCETRIS. Complete blood counts should be monitored prior to administration of each dose of treatment. Patients should be monitored closely for fever and managed according to best medical practice if febrile neutropenia develops.

In combination therapy with AVD or CHP, advanced age was a risk factor for febrile neutropenia. When ADCETRIS is administered in combination with AVD or CHP, primary prophylaxis with G-CSF is recommended, beginning with the first dose for all patients regardless of age.

Hyperglycemia

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.

*Tumor Lysis Syndrome*

Tumor lysis syndrome 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 appropriate measures taken.

*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, discontinue ADCETRIS and administer appropriate medical therapy.

*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. Patient experiencing hepatotoxicity may require a delay, change in dose or discontinuation of ADCETRIS.(See Undesirable Effects [<5.5>]).

Renal and Hepatic Impairment

There is limited experience in patients with renal and hepatic impairment. Available data indicate that MMAE clearance might be affected by severe renal impairment, hepatic impairment, and by low serum albumin concentrations. (See Section 6.2 Pharmacokinetic Properties)

Use in Pregnancy

ADCETRIS may cause fetal harm when administered to pregnant women (See Section 5.4 Pregnancy and Lactation).

## 5.4 *INTERACTIONS WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION*

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 section 6.2. Pharmacokinetics ).

Doxorubicin, Vinblastine and Dacarbazine (AVD)

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.

Co administration of brentuximab vedotin is not expected to affect the exposure of CHP.

Bleomycin

There were no formal drug-drug interaction studies with brentuximab vedotin and bleomycin(B). In a phase 1 dose finding and safety study (SGN35-009), unacceptable pulmonary toxicity (including 2 fatal events) was noted in 11 of 25 patients (44%) treated with brentuximab vedotin plus ABVD. No pulmonary toxicity or fatal events were reported with brentuximab vedotin + AVD. Therefore, co-administration of ADCETRIS with bleomycin is contraindicated.

## 5.5 *PREGNANCY AND LACTATION*

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.[65] 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 Special Warnings and Precautions for Use [<5.2>]).

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.

## 5.6 *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 in Table 5-3 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 (SGN35-003, SGN35-004, SGN35-005, SGN35-006, C25001 and C25007, see section 5.1) the most frequent adverse reactions (≥ 10%) were infections, peripheral sensory neuropathy, nausea, fatigue, diarrhoea, pyrexia, upper respiratory tract infection, neutropenia, rash, cough, vomiting, arthralgia, peripheral motor neuropathy, infusion-related reactions, pruritus, constipation, dyspnoea, 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) 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 the phase 1 dose escalation and clinical pharmacology studies (n=15 patients) and in the NPP (n=26 patients) (see section 5.1) were consistent with the safety profile of the pivotal clinical studies.

Combination Therapy

For the safety information of chemotherapy agents given in combination with ADCETRIS (doxorubicin, vinblastine and dacarbazine (AVD) or cyclophosphamide, doxorubicin and prednisone (CHP)), for the treatment of patients with previously untreated HL or previously untreated PTCL, respectively, refer to their product information.

In the studies of ADCETRIS as combination therapy in 662 patients with previously untreated advanced HL (C25003) and 223 patients with previously untreated PTCL (SGN35-014), the most common adverse reactions (≥ 10%) were: infections, neutropenia, nausea, constipation, vomiting, fatigue, peripheral sensory neuropathy, diarrhoea, pyrexia, alopecia, peripheral motor neuropathy, weight decreased, abdominal pain, anaemia, stomatitis, febrile neutropenia, bone pain, insomnia, decreased appetite, rash, cough, arthralgia, back pain, dyspnoea, myalgia, upper respiratory tract infection, alanine aminotransferase increased 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 |
| **Nervous system disorders** | | |
| Very common: | Peripheral sensory neuropathy, peripheral motor neuropathy | Peripheral sensory neuropathy, peripheral motor neuropathy[a], dizziness |
| Common: | Dizziness | |
| Uncommon: | Demyelinating polyneuropathy | |
| **Respiratory, thoracic and mediastinal disorders** | | |
| Very common: | Cough, dyspnoea | Cough, dyspnoea |
| **Gastro-intestinal 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: | StevensJohnson syndrome/toxic epidermal necrolysis | StevensJohnson syndrome[b] |
| **Musculoskeletal and connective tissue disorders** | | |
| Very common: | Arthralgia, myalgia | Bone pain, arthralgia, back pain, myalgia |
| 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 |
| Rare | Extravasation-related reactions[c] | |
| **Investigations** | | |
| Very common: | Weight decreased | Weight decreased |
| **Psychiatric Disorders** | | |
| Very common: | | Insomnia |
| a Represents pooling of preferred terms. | | |
| b Toxic epidermal necrolysis was not reported in the combination therapy setting. | | |
| c. Local reactions including skin redness, pain, swelling, blistering or sloughing | | |

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.

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 4.2). 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 trial 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 randomized phase 3 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 brentuximab vedotin (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 \] , 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 wa’]s 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 r improvement of peripheral neuropathy events was 19.0 weeks (ranged from 0 weeks to 205 weeks).

PML has been reported of the pivotal phase 2 clinical trials.
Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported with brentuximab vedotin in clinical trials and post-marketing use. Fatal outcomes have been reported.

*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 4.4). 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 4.4). 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.

Elderly

Monotherapy
The safety profile in elderly patients was consistent with that of adult patients.

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.

### *5.7 OVERDOSAGE*

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 5.2 Warnings and Precautions for Use - Neutropenia).

## 6 PHARMACOLOGICAL PROPERTIES

### *6.1 PHARMACODYNAMIC PROPERTIES*

#### 6.1.1 Pharmacotherapeutic Group (ATC code) for International Products, and Pharmacologic Class for US product

Pharmacologic class: CD30-directed antibody-drug conjugate ATCcode:
L01XC12
Pharmacotherapeutic group: monoclonal antibodies

#### 6.1.2 Mechanism of Action

ADCETRIS is an Antibody Drug Conjugate (ADC) that delivers an antineoplastic agent that results 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.

#### 6.1.3 Pharmacodynamic 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 brentuximab vedotin 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 brentuximab vedotin administered at a dose of 1.8 mg/kg in patients with CD30-expressing malignancies.

## *6.2 PHARMACOKINETIC PROPERTIES*

### 6.2.1 General Introduction

The pharmacokinetics of ADCETRIS were evaluated in phase 1 studies and in a population pharmacokinetic analysis of data from 314 patients.

### 6.2.2 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 AVD were evaluated in a single phase 3 study in 661 patients. Population pharmacokinetic analysis indicated that the pharmacokinetics of ADCETRIS in combination with AVD were consistent to 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 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.

### 6.2.3 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.

### 6.2.4 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.

### 6.2.5 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 a 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.

### 6.2.6 Other sections may be included such as: drug interactions that were not clinically and or safety significant, linearity/non-linearity, age, gender, interethnic differences, pediatric, smoking, renal impairment, hepatic impairment)

Elderly

The population pharmacokinetics of ADCETRIS were examined from several 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.

# 7 NONCLINICAL TOXICOLOGY

## *7.1 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 brentuximab vedotin to impair male reproductive function and fertility. Testicular atrophy and degeneration were observed in a 4-week rat study when brentuximab vedotin 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.

# 8 CLINICAL STUDIES

## 8.1 Hodgkin Lymphoma

### *8.1.1 Study C25003*

The efficacy and safety of ADCETRIS were evaluated in a randomised, open-label, 2-arm, multicenter trial in 1334 patients with previously untreated advanced HL in combination with chemotherapy (doxorubicin [A], vinblastine [V] and dacarbazine [D] [AVD]). All patients had a histologically confirmed CD30-expressing disease. Sixty-two percent of patients had extranodal site involvement of the 1334 patients, 664 patients were randomised to the ADCETRIS + AVD arm and 670 patients were randomised to the ABVD (doxorubicin [A], bleomycin [B], vinblastine [V] and dacarbazine [D]) arm and stratified by number of International Prognostic Factor Project (IPFP) risk factors and region.

Patients were treated on days 1 and 15 of each 28-day cycle with 1.2 mg/kg of ADCETRIS administered as an intravenous infusion over 30 minutes + doxorubicin 25 mg/m$^2$, vinblastine 6 mg/m$^2$, and dacarbazine 375 mg/m$^2$. The median number of cycles received was 6 (range, 1 to 6 cycles).

**Table 6** provides a summary of the baseline patient and disease characteristics. There were no relevant differences in the patient and disease characteristics between the two arms.

**Table 6: Summary of Baseline Patient and Disease Characteristics in the Phase 3 previously untreated-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)<br>286F (43) | 398M (59)<br>272F (41) |
| ECOG status, n (%) | | |
| 0 | 376 (57) | 378 (57) |
| 1 | 260 (39) | 263 (39) |
| 2 | 28 (4) | 27 (4) |
| Missing | 0 | 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 (%) | | |
| III | 237 (36) | 246 (37) |
| 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 (mPFS) per independent review facility (IRF), defined as time from randomisation to disease progression, death, or evidence of non-complete response (non-CR) after completion of first-line therapy per IRF followed by subsequent anticancer therapy. Timing of the modified event was the date of the first PET scan post completion of first-line therapy demonstrating the absence of complete response (CR), defined as Deauville score of ≥3. The median modified PFS by IRF assessment was not reached in either treatment arm. The results in the intent-to-treat (ITT) population showed a statistically significant improvement in modified PFS for ADCETRIS+ AVD, with a stratified hazard ratio of 0.770 (95% CI, 0.603; 0.983, p = 0.035), indicating a 23% reduction in the risk of modified PFS events for ADCETRIS+ AVD versus ABVD.

A pre-specified subgroup analysis of mPFS by disease stage showed that patients with Stage IV disease had a larger effect compared with the ITT population, with an unstratified hazard ratio of 0.71 (95% CI, 0.53; 0.96), compatible with a 29% reduction in the risk of modified PFS events for ADCETRIS+ AVD versus ABVD. Of the ITT population, 846 patients (64%) had Stage IV disease. **Table 7** provides the efficacy results for modified PFS and overall survival (OS) in the ITT population and patients with Stage IV disease.

**Table 7: Efficacy results for previously untreated HL patients treated with 1.2 mg/kg of ADCETRIS + AVD on days 1 and 15 of a 28-day cycle (ITT and Stage IV)**

| | Intent to Treat (ITT) Population | | | Patients with Stage IV Disease | | |
|---|---|---|---|---|---|---|
| | ADCETRIS + AVD n = 664 | ABVD n = 670 | Stratified Hazard Ratio and p-value | ADCETRIS + AVD n = 425 | ABVD n = 421 | Unstratified Hazard Ratio and p-value |
| Number of events (%) | 117 (18) | 146 (22) | 0.77 (95% CI [0.60, 0.98]) p-value=0.035 | 77 (18) | 102 (24) | 0.71 (95% CI [0.53, 0.96]) p-value=0.023 |
| Estimated mPFS[a] per IRF at 2 Year (%) | 82.1 (95% CI [78.8, 85.0]) | 77.2 (95% CI [73.7, 80.4]) | | 82.0 (95% CI [77.8, 85.5]) | 75.3 (95% CI [70.6, 79.3]) | |
| Overall Survival[b] Number of deaths (%) | 28 (4) | 39 (6) | 0.73 (95% CI [0.45, 1.18]) p-value=0.199 | 14 (3) | 26 (6) | 0.51 (95% CI [0.27, 0.97]) p-value=0.037 |

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

**Figure 1: Modified progression-free survival per IRF in the ITT population (ADCETRIS + AVD vs. ABVD)**

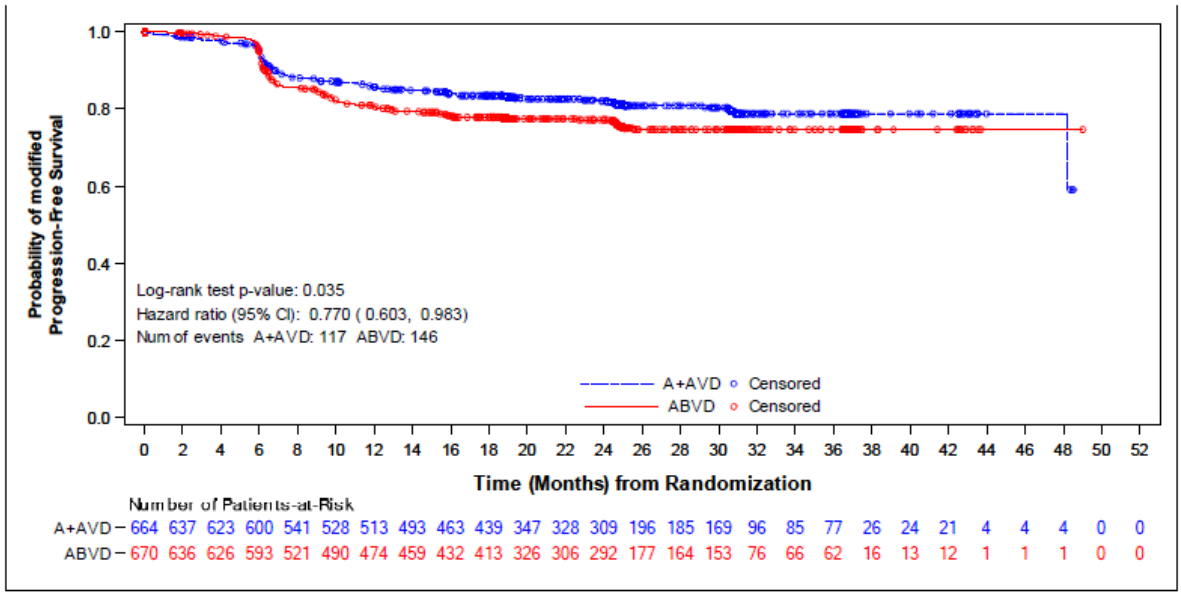
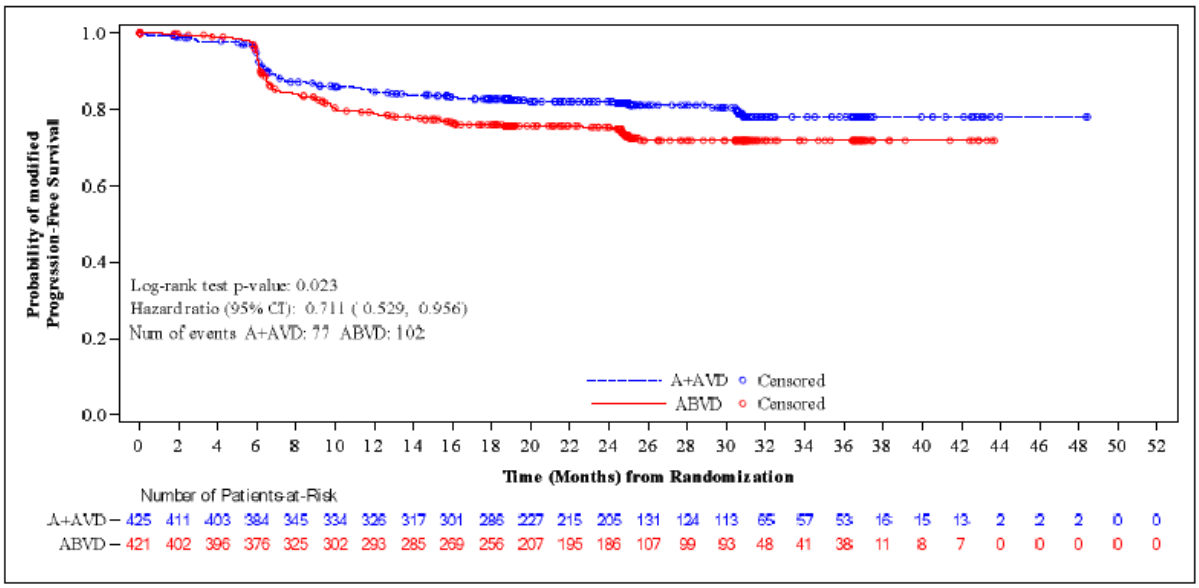


**Figure 2: Modified progression-free survival per IRF in patients with Stage IV disease (ADCETRIS + AVD vs. ABVD)**




Other secondary efficacy endpoints including CR rate and ORR at the end of randomisation regimen, CR rate at the end of first-line 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 favour of ADCETRIS + AVD in both the ITT and Stage IV population.

Pre-specified subgroup analyses of modified PFS per IRF were performed for the ITT population including age, region, cancer stage at baseline, baseline extranodal sites, number of IPFP risk factors, baseline B symptoms, Cycle 2 PET assessment, Cycle 2 PET Deauville score, and receipt of alternative first-line medication (AFM). The analyses showed a consistent trend towards benefit for patients who received ADCETRIS + AVD compared with patients who received ABVD in most subgroups. The efficacy in elderly patient population (patients ≥ 60 years of age [n = 186] [HR = 1.00, 95% CI (0.58, 1.72)] and ≥ 65 years of age [n = 122] [HR = 1.01, 95% CI (0.53, 1.94)]) and patients with no extranodal sites (n = 445) (HR = 1.04, 95% CI [0.67, 1.62]) showed no clinically meaningful difference between the two arms.

Subgroup analyses of modified PFS per IRF for patients with Stage IV disease were performed including age, region, baseline extranodal sites, number of IPFP risk factors, baseline B symptoms, baseline ECOG status and gender. The analyses showed a consistent trend towards benefit for patients who received ADCETRIS + AVD compared with patients who received ABVD in most subgroups. Patients with Stage IV disease for whom extranodal disease was reported ([n = 722] [HR = 0.69, 95% CI (0.50, 0.94)]) showed an mPFS (per IRF) benefit. In patients with Stage IV disease for whom no extranodal disease was reported, no benefit has been shown at time of analysis ([n = 85] [HR = 1.49, 95% CI (0.51, 4.31)]). The significance of this finding in stage IV HL patients with no extranodal disease is not established due to small patient numbers and low event rates (14 events). The efficacy in elderly patients with Stage IV disease in the A + AVD arm (patients ≥ 60 years of age [n = 118] [HR = 0.80, 95% CI (0.42, 1.53)] and ≥ 65 years of age [n = 78] [HR = 0.78, 95% CI (0.36, 1.67)]) showed better benefit compared with elderly patients in ITT population.

In the ITT population, 33% fewer patients treated with ADCETRIS + AVD in the ITT population received subsequent salvage chemotherapy (n = 66) and high-dose chemotherapy and transplant (n = 36) compared with those treated with ABVD (n =

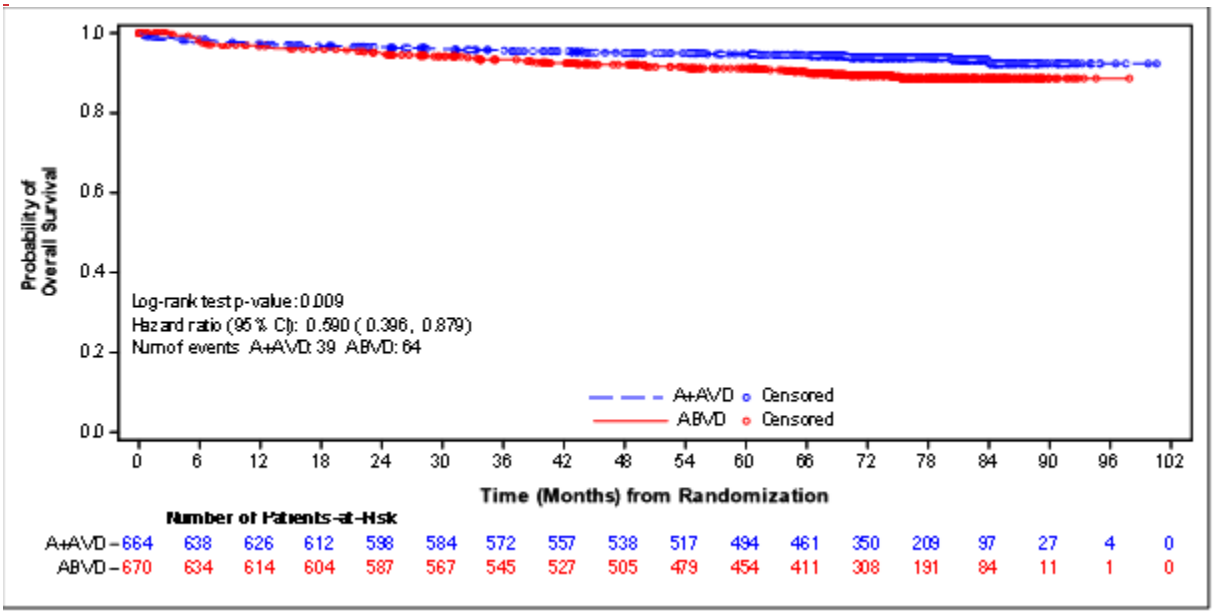
99 and n = 54, respectively). In the Stage IV population, 35% fewer patients treated with ADCETRIS + AVD received subsequent salvage chemotherapy (n = 45) compared with those treated with ABVD (n = 69) and 22% fewer patients treated with ADCETRIS + AVD received high-dose chemotherapy and transplant (n = 29) compared with those treated with ABVD (n = 37). 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 in both the ITT and Stage IV population.

As of a 01 June 2021 cut-off date, approximately 5 years after enrollment of the last patient, the results in the ITT population showed a statistically significant improvement in OS indicating a 41% reduction in the risk of death in the ADCETRIS + AVD arm compared with patients treated with ABVD [HR = 0.59, 95% CI (0.396, 0.879)], see Figure 3.

Overall survival results in the stage IV populations indicated a 14% [HR = 0.86, 95% CI (0.452, 1.648)] and 52% [HR = 0.48, 95% CI (0.286, 0.799)] reduction in the risk of death in the ADCETRIS + AVD arm compared with patients treated with ABVD, respectively.

Median OS was not reached for either A+AVD or ABVD patients (95%◦CI (NE,NE)].

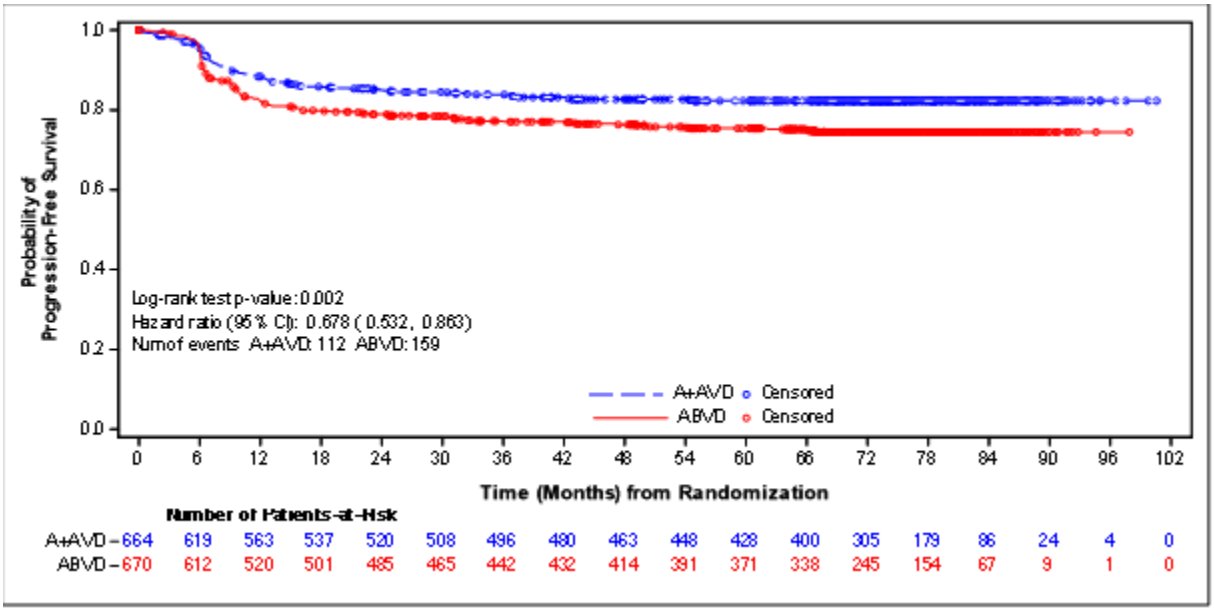
**Figure 3: Overall survival (ADCETRIS + AVD vs. ABVD) (ITT, 6 years median follow up)**




Investigator-determined PFS results showed durable benefit and were consistent with those reported at the time of the primary analysis in both ITT and stage IV populations. PFS was defined as the time from randomization to the sooner of the time of first documentation of PD per investigator or death due to any cause. PFS per investigator results in the ITT population indicated a 32% reduction in the risk of a PFS event in the ADCETRIS + AVD arm compared with patients treated with ABVD [HR = 0.68, 95%◦CI (0.532-0.863)], see Figure 4. PFS per investigator results in the patients with stage IV disease indicated a 28% reduction in the risk of a PFS event in the ADCETRIS + AVD arm compared with patients treated with ABVD [HR = 0.72, 95%◦CI (0.534-0.959)].

By investigator assessment, median PFS was not estimable (NE) 95%◦CI (NE, NE) for either treatment arm.

**Figure 4: Progression-free survival per investigator in the ITT Population (ADCETRIS + AVD vs. ABVD) (6 years median follow up)**




### 8.1.2 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. See **Table 8** for patient characteristics. 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 16 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 8: Summary of baseline patient and disease characteristics in the phase 3 HL post-ASCT Study**

| Patient characteristics | ADCETRIS n = 165 | Placebo n = 164 |
|---|---|---|
| Median age, years (range) | 33 years (18-71) | 32 years (18-76) |
| Gender | 76M (46%)/89F (54%) | 97M (59%)/67F (41%) |
| ECOG status | | |
| 0 | 87 (53%) | 97 (59%) |
| 1 | 77 (47%) | 67 (41%) |
| 2 | 1 (1%) | 0 |
| **Disease characteristics** | | |
| Median number of prior chemotherapy regimens (range) | 2 (2-8) | 2 (2-7) |
| Median time from HL diagnosis to first dose (range) | 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 Disease | 47 (28%) | 46 (28%) |
| HL Status after the end of frontline standard chemotherapy[b] | | |
| Refractory | 99 (60%) | 97 (59%) |
| Relapse occurred <12 months | 53 (32%) | 54 (33%) |
| Relapse occurred > = > 12 months | 13 (8%) | 13 (8%) |

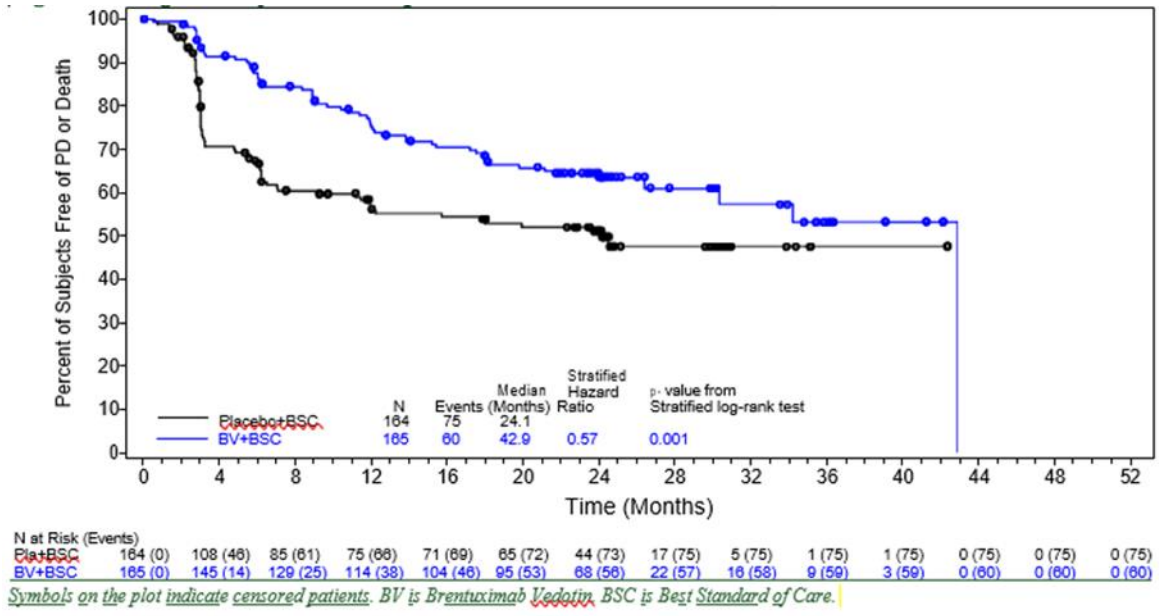
a. For refractory disease, or upon progression or relapse after frontline therapy.
b. Stratification factors at randomisation.

**Table 9: Efficacy results in HL patients at increased risk of relapse or progression following ASCT treated with 1.8 mg/kg of ADCETRIS every 3 weeks**

| | ADCETRIS<br>n = 165 | Placebo<br>n = 164 | Stratified Hazard Ratio |
|---|---|---|---|
| **Progression Free Survival[a]** | **Median per IRF** | | |
| | 42.9 months<br>(95% CI [30.4, 42.9]) | 24.1 months<br>(95% CI [11.5, -]) | 0.57<br>(95% CI [0.40, 0.81])<br>Stratified log-rank test p=0.001 |
| | **Median per Investigator** | | |
| | Not reached<br>(95% CI [26.4, -]) | 15.8 months<br>(95% CI [8.5, -]) | 0.5<br>(95% CI [0.36, 0.70])b |
| **Overall Survival** | **Number of deaths (%)** | | |
| | 28 (17) | 25 (15) | 1.15<br>(95% CI [0.67, 1.97] |

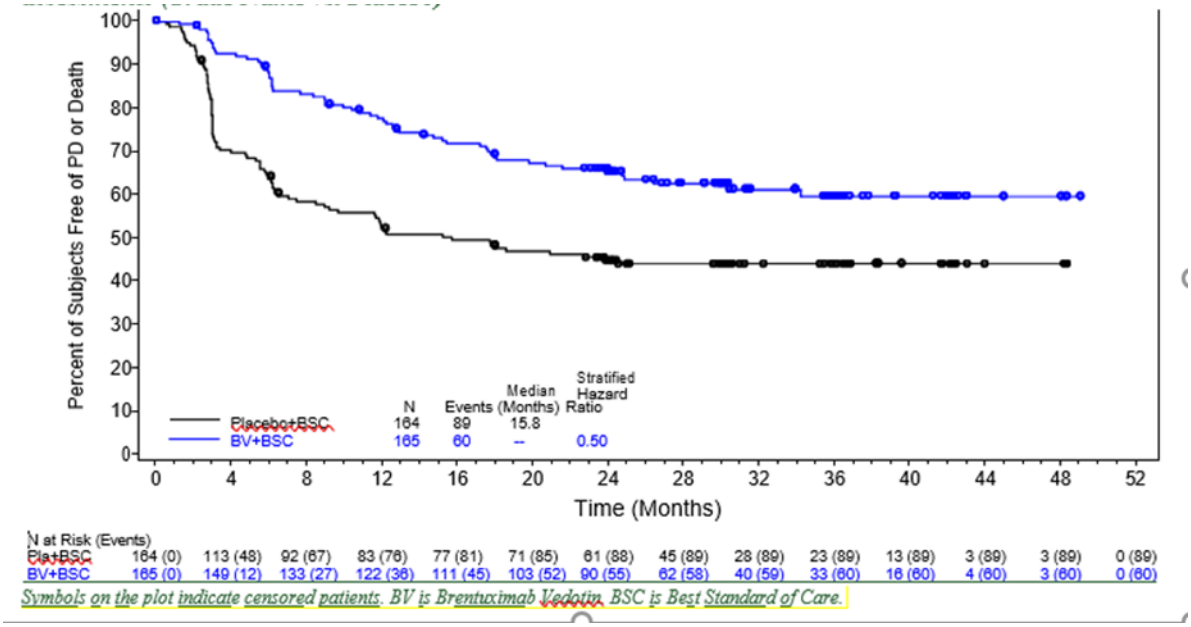
a. At the time of the primary analysis, the median follow-up time for both arms was 30 months (range, 0 to 50).
b. Stratified log-rank test was not performed for PFS per Investigator.

**Figure 5 : 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 6 : Progression-free survival per Investigator using radiographic, biopsy, and clinical lymphoma assessments (ADCETRIS vs. Placebo)**




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 brentuximab vedotin compared with 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.

Post-hoc Risk Factor Analyses

Post-hoc analyses were performed to evaluate the impact of increased risk (number of risk factors) on clinical benefit (**Table 10**). 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.

The results of these post-hoc analyses suggest 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.

**Table 10: Summary of PFS per IRF and OS by number of risk factors in the phase 3 HL post-ASCT Study**

| Progression Free Survival per IRF | | | | | | |
|---|---|---|---|---|---|---|
| | Number of Risk Factors = 1 | | Number of Risk Factors ≥ 2 | | Number of Risk Factors ≥ 3 | |
| | ADCETRISn n = 21 | Placebo n = 28 | ADCETRIS n = 144 | Placebo n = 136 | ADCETRIS n = 82 | Placebo n = 84 |
| Number of patients with disease progression or death[a] (%) | 9 (43) | 7 (25) | 51 (35) | 68 (50) | 32 (39) | 49 (58) |
| Stratified Hazard Ratio | 1.65 (95% CI [0.60, 4.55])[b] | | 0.49 (95% CI [0.34, 0.71]) | | 0.43 (95% CI [0.27, 0.68]) | |
| **Overall Survival** | | | | | | |
| | Number of Risk Factors = 1 | | Number of Risk Factors ≥ 2 | | Number of Risk Factors ≥ 3 | |
| | ADCETRIS n = 21 | Placebo n = 28 | ADCETRIS n = 144 | Placebo n = 136 | ADCETRIS n = 82 | Placebo n = 84 |
| Number of deaths[c] (%) | 5 (24) | 1 (4) | 23 (16) | 24 (18) | 15 (18) | 16 (19) |
| Stratified Hazard Ratio | 7.94 (95% CI [0.93, 68.06])[b] | | 0.94 (95% CI [0.53, 1.67]) | | 0.92 (95% CI [0.45, 1.88]) | |

a. Death without either prior progression or more than one missed assessment visit.
b. Indicates results from non-stratified analysis.
c. Events are death due to any cause.

At the time of the updated analysis (3 years of follow-up) for patients with 2 or more risk factors, the hazard ratio for PFS per IRF was 0.49 (95% CI [0.34, 0.71]) and the hazard ratio for PFS per investigator was 0.41 (95% CI [0.29, 0.58]) (see Figures 7 and 8).

Figure 7: Kaplan-Meier Plot of PFS per IRF in Patients with ≥ 2 Risk Factors

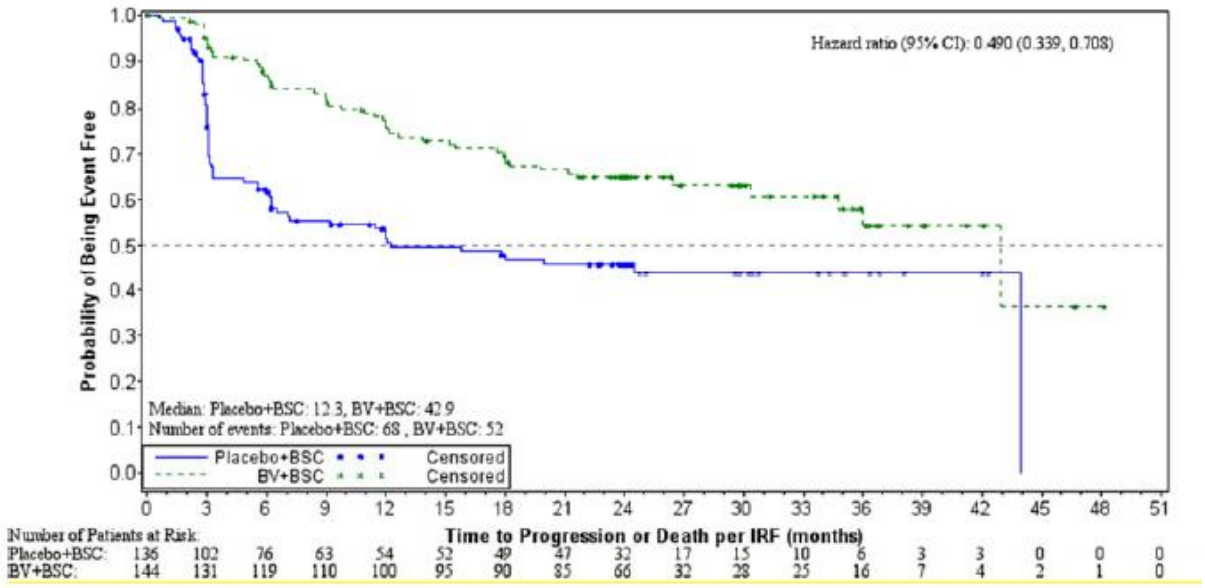
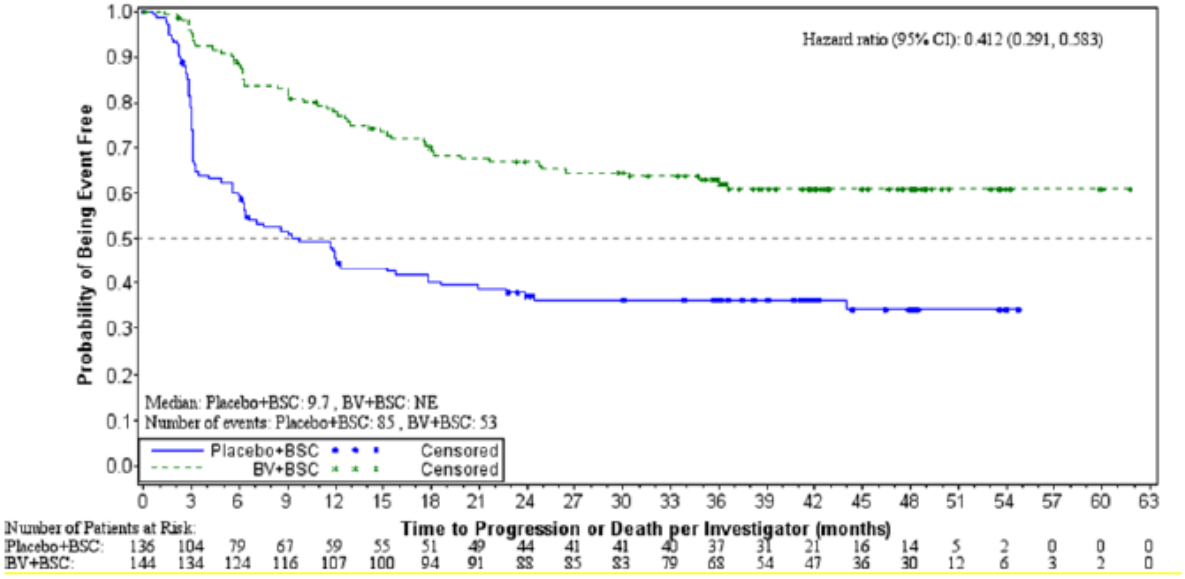



Figure8: Kaplan-Meier Plot of PFS per Investigator in Patients with ≥ 2 Risk Factors



8.1.3 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 HL. See **Table 11** below for a summary of baseline patient and disease characteristics.

**Table 11: Summary of baseline patient and disease characteristics in the phase 2 relapsed or refractory HL study**

| **Patient characteristics** | **n = 102** |
|---|---|
| Median age, years (range) | 31 years (15-77) |
| Gender | 48M (47%)/54F (53%) |
| ECOG status | |
| 0 | 42 (41%) |
| 1 | 60 (59%) |
| Prior ASCT | 102 (100%) |
| Prior chemotherapy Regimens | 3.5 (1-13) |
| Time from ASCT to first post-transplant relapse | 6.7 mo (0-131) |
| Histologically confirmed CD30-expressing disease | 102 (100%) |
| **Disease characteristics** | |
| Primary Refractory to frontline therapy[a] | 72 (71%) |
| Refractory to most recent therapy | 43 (42%) |
| Baseline B symptoms | 35 (33%) |
| Stage III at initial diagnosis | 27 (26%) |
| Stage IV at initial diagnosis | 20 (20%) |

a. Primary refractory HL is defined as a failure to achieve a complete remission to, or progressed within 3 months of completing frontline therapy.

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 12** below for other pre-specified endpoints.

**Table 12: 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) | 27.9 months | 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** | | **95%CI** |
|---|---|---|
| Median | 40.5 months | 28.7,61.61.9 |
| Estimated 5-year OS rate | 41 % | 31%, 51% |

[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, 25221, 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

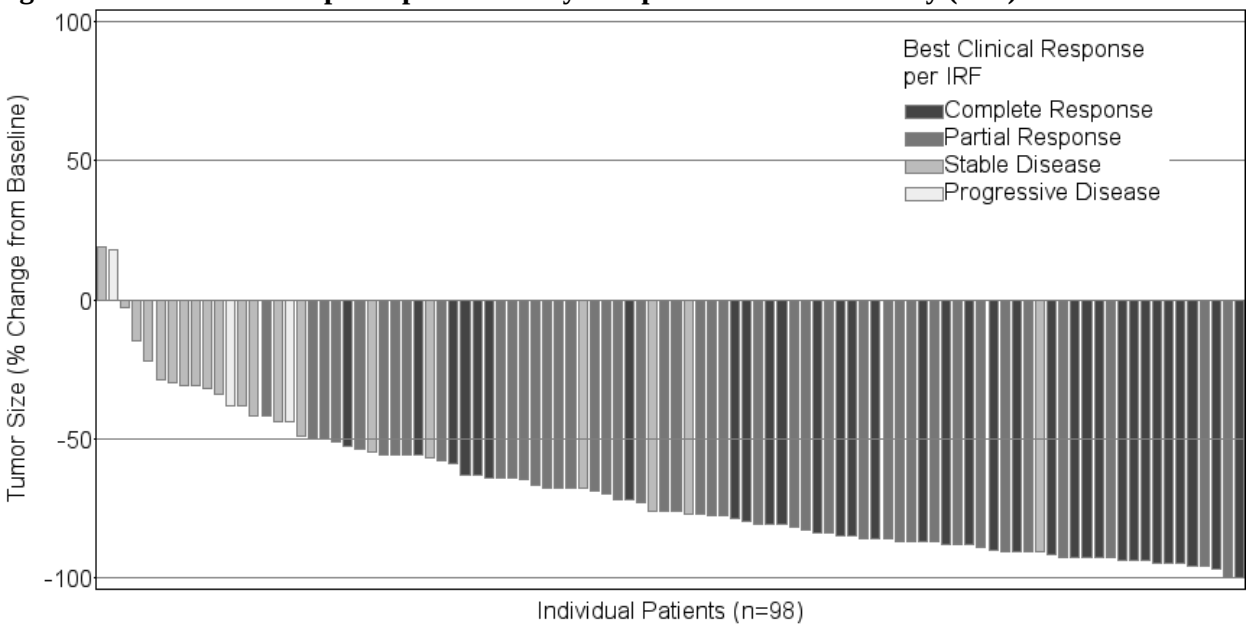
[e] The median follow-up time (time to earliest of progressive disease, death or last contact) from first dose was 5.8 months.

[f] The median observation time (time to death or last contact) from first dose was 35.1 months (range 1.8 to 72.9+ 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 9** for waterfall chart of tumor reduction, ORR and CR.

**Figure 9: Best Clinical Response per Patient by Independent Review Facility (IRF) Determination**



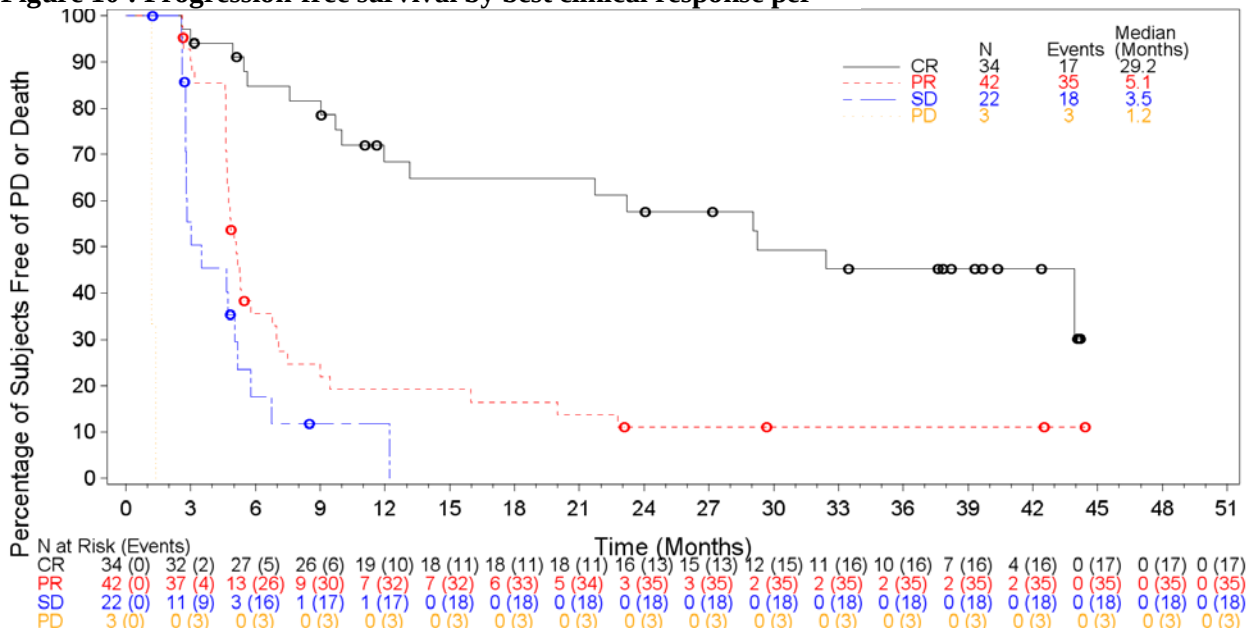

In the designation of CR per Revised Response Criteria for Malignant Lymphoma (Cheson et al., 2007), a post-treatment residual mass of any size is permitted as long as it is PET negative

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 10** for median PFS by best clinical response.

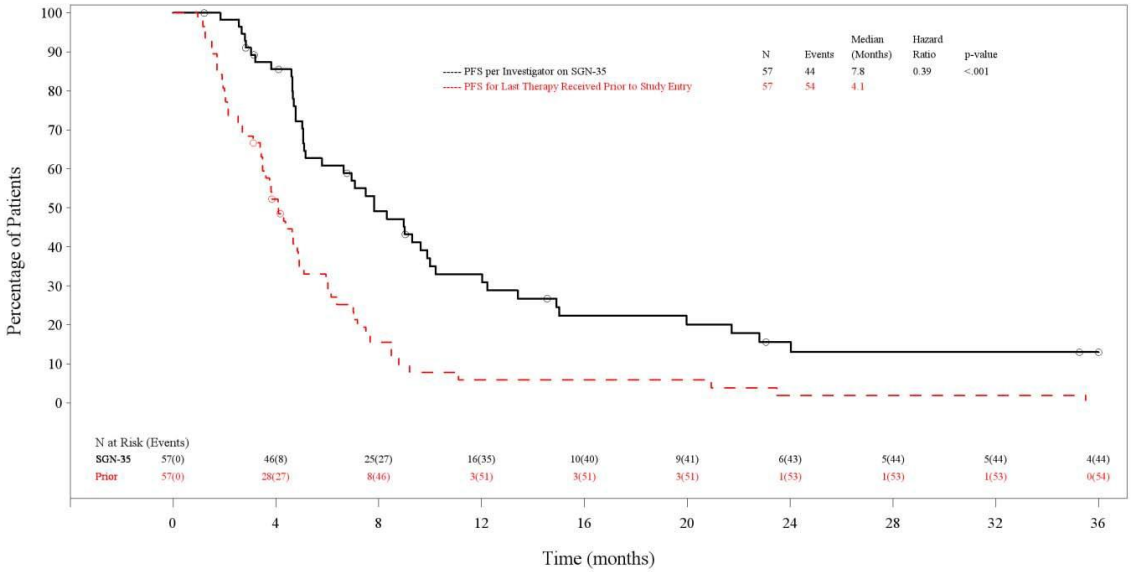
**Figure 10 : Progression-free survival by best clinical response per**



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 11** for a KM plot of PFS with ADCETRIS compared to PFS from the most recent post-ASCT therapy.

**Figure 11: 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. SGN-35 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.

### 8.1.4 Study C25007

**Data in HL Patients Who Are Not Stem Cell Transplant (SCT) Candidates**

A phase 4 single-arm study was conducted in patients with relapsed or refractory HL (n=60) who had received at least one prior chemotherapeutic regimen and at the time of treatment initiation with brentuximab vedotin were not considered candidates for SCT or multiagent chemotherapy. The median number of cycles was 7 (range 1 to 16 cycles). Patients were treated with 1.8 mg/kg of brentuximab vedotin every 3 weeks. Per IRF, the overall response rate (ORR) in the ITT population was 50% (95% CI, 37; 63%). A best overall response of CR was reported for 7 patients (12%); PR was reported for 23 patients (38%). Twenty eight patients (47%) went on to receive SCT after a median of 7 cycles (range 4 to 16 cycles) of brentuximab vedotin treatment. The 32 patients (53%) who did not receive subsequent SCT also received brentuximab vedotin for a median of 7 cycles (range 1 to 16 cycles).

Eleven patients (18%) had received one prior chemotherapeutic regimen. Per IRF, the overall response rate (ORR) CR was reported for 1 patient (9%); PR was reported for 4 patients (36%). in these patients was 45% (95% CI, 17; 77%). A best overall response of CR was reported for 1 patient (9%); PR was reported for 4 patients (36%).

Data were also collected from patients (n = 15) in phase 1 dose escalation and clinical pharmacology studies, and from patients (n = 26) in a 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 ADCETRIS. 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 ADCETRIS.

***8.1.5 Study SGN35-006 (Retreatment Study)***

The efficacy of retreatment in patients who had previously responded (CR or PR) to treatment with ADCETRIS was evaluated in a phase 2, open-label, multicenter trial. Twenty patients with relapsed or refractory HL received a starting dose of 1.8 mg/kg and one patient received a starting dose of 1.2 mg/kg of ADCETRIS administered intravenously over 30 minutes every 3 weeks. The median number of cycles was 7 (range 2 to 37 cycles). Of the 20 evaluable patients with HL, 6 patients (30%) achieved a CR and 6 patients (30%) achieved a PR with ADCETRIS retreatment, for an ORR of 60%. The median duration of response was 9.2 and 9.4 months in patients who achieved OR (CR+PR) and CR, respectively.

## *8.2 Peripheral T- Cell Lymphoma*

### 8.2.1 Study SGN35-014

The efficacy and safety of ADCETRIS were evaluated in a randomized, double-blind, double-dummy, active-controlled, multicenter trial of 452 patients with previously untreated PTCL in combination with cyclophosphamide [C], doxorubicin [H], and prednisone [P] (CHP). Of the 452 patients, 226 were randomized to treatment with ADCETRIS + CHP and 226 patients were randomized to treatment with CHOP (cyclophosphamide [C], doxorubicin [H], vincristine [O], and prednisone [P]). Randomization was stratified by ALK-positive sALCL versus all other subtypes and by the International Prognostic Index (IPI) score. Patients were treated with ADCETRIS administered as an intravenous infusion over 30 minutes on Day 1 of each 21-day cycle for 6 to 8 cycles + CHP. The median number of cycles received was 6 (range, 1 to 8 cycles); 70% of patients received 6 cycles of treatment, and 18% received 8 cycles of treatment. Table 13 provides a summary of baseline patient and disease characteristics.

**Table 13 Summary of baseline patient and disease characteristics in the Phase 3 Frontline PTCL Study**

| Patient Characteristics | ADCETRIS + CHP N=226 | CHOP N=226 |
|---|---|---|
| Median age (range) | 58.0 (18-85) | 58.0 (18-83) |
| Patients ≥ 65 years old (%) | 69 (31) | 70 (31) |
| Male sex, n (%) | 133 (59) | 151 (67) |
| ECOG status, n (%) | | |
| 0 | 84 (37) | 93 (41) |
| 1 | 90 (40) | 86 (38) |
| 2 | 51 (23) | 47 (21) |
| ***Disease Characteristics*** | | |
| *Diagnosis, per local assessment, n (%)* | | |
| *sALCL* | *162 (72)* | *154 (68)* |
| *ALK-positive* | *49 (22)* | *49 (22)* |
| *ALK-negative* | *113 (50)* | *105 (46)* |
| *Peripheral T-cell lymphoma (PTCL-NOS)* | *29 (13)* | *43 (19)* |
| *Angioimmunoblastic T-cell lymphoma (AITL)* | *30 (13)* | *24 (11)* |
| *Adult T-cell leukemia/lymphoma (ATLL)* | *4 (2)* | *3 (1)* |
| *Enteropathy-associated T-cell lymphoma (EATL)* | *1 (0)* | *2 (1)* |
| *Median time from diagnosis to first dose, months (range)* | *0.8 (0, 19)* | *0.9 (0, 10)* |
| *Disease stage at initial diagnosis of PTCL, n (%)* | | |
| *Stage I* | *12 (5)* | *9 (4)* |
| *Stage II* | *30 (13)* | *37 (16)* |
| *Stage III* | *57 (25)* | *67 (30)* |
| *Stage IV* | *127 (56)* | *113 (50)* |
| *IPI score* | | |
| *0* | *8 (4)* | *16 (7)* |
| *1* | *45 (20)* | *32 (14)* |
| *2* | *74 (33)* | *78 (35)* |
| *3* | *66 (29)* | *66 (29)* |
| *4* | *29 (13)* | *25 (11)* |
| *5* | *4 (2)* | *9 (4)* |
| *Extranodal involvement at time of diagnosis, n (%)* | | |
| ≤ 1 site | *142 (63)* | *146 (65)* |
| >1 site | *84 (37)* | *80 (35)* |
| *Baseline bone marrow biopsy-lymphoma involvement, n (%)* | | |
| *Yes* | *30 (13)* | *34 (15)* |
| *No* | *196 (87)* | *192 (85)* |

The primary endpoint in SGN35-014 was PFS per IRF, defined as the time from the date of randomization to the date of first documentation of progressive disease, death due to any cause, or receipt of subsequent anticancer chemotherapy to treat residual or progressive disease, whichever occurs first.
*Receipt of post-treatment consolidative radiotherapy, post-treatment chemotherapy for the purpose of mobilizing peripheral blood stem cells, or consolidative autologous or allogeneic stem cell transplant were not considered as disease progression or as having started new anticancer therapy.*

Upon establishing statistical significance of PFS per IRF, the key secondary endpoints, PFS per IRF for subjects with centrally-confirmed sALCL, CR rate per IRF following the completion of study treatment, OS, and ORR per IRF following the completion of study treatment, were tested by a fixed sequence testing procedure.

The primary endpoint and alpha-protected, key secondary endpoints, which were evaluated hierarchically, were met. The median PFS per IRF was 48.2 months on the Trade Name + CHP arm versus 20.8 months on the CHOP arm. The stratified hazard ratio was 0.71 (95% CI: 0.54, 0.93, P=0.011), indicating a 29% reduction in the risk of PFS events for ADCETRIS + CHP versus CHOP (Table 14).

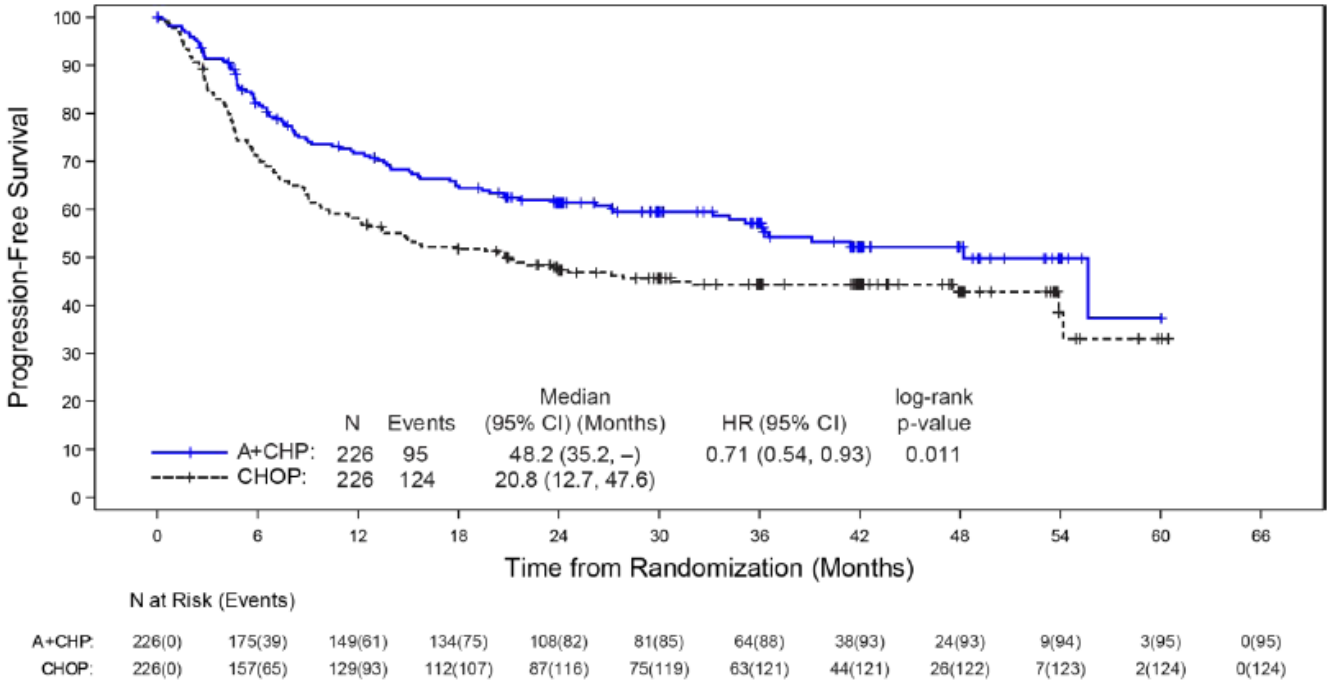
**Table 14: Efficacy Results in Patients with Previously Untreated PTCL with 1.8 mg/kg of ADCETRIS on Day 1 of a 3-Week Cycle**

| **Primary and Key Secondary Endpoints**[a] | **ADCETRIS + CHP N=226** | **CHOP** |
|---|---|---|
| **PFS per IRF** | | |
| 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] | 0.0110 | |
| **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] | 0.0031 | |
| **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] | 0.0244 | |
| **CR Rate**[e] | | |
| % (95% CI) | 68% (61.2, 73.7) | 56% (49.0, 62.3) |
| P-value[f] | 0.0066 | |
| **ORR**[e] | | |
| % (95% CI) | 83% (77.7, 87.8) | 72% (65.8, 77.9) |
| P-value[f] | 0.0032 | |
| *PFS per investigator*[f] | | |
| *Median PFS per Investigator, months (95% CI)* | *49.8 (41.5, NE)* | *23.8 (13.6, NE)* |
| *Hazard ratio (95% CI)*[b] | *0.70 (0.53, 0.92)* | |
| *P-value*[c] | *0.0096* | |

CR=complete remission; IRF=Independent Review Facility; NE: Not estimable; ORR=objective response rate; PFS=progression-free survival.

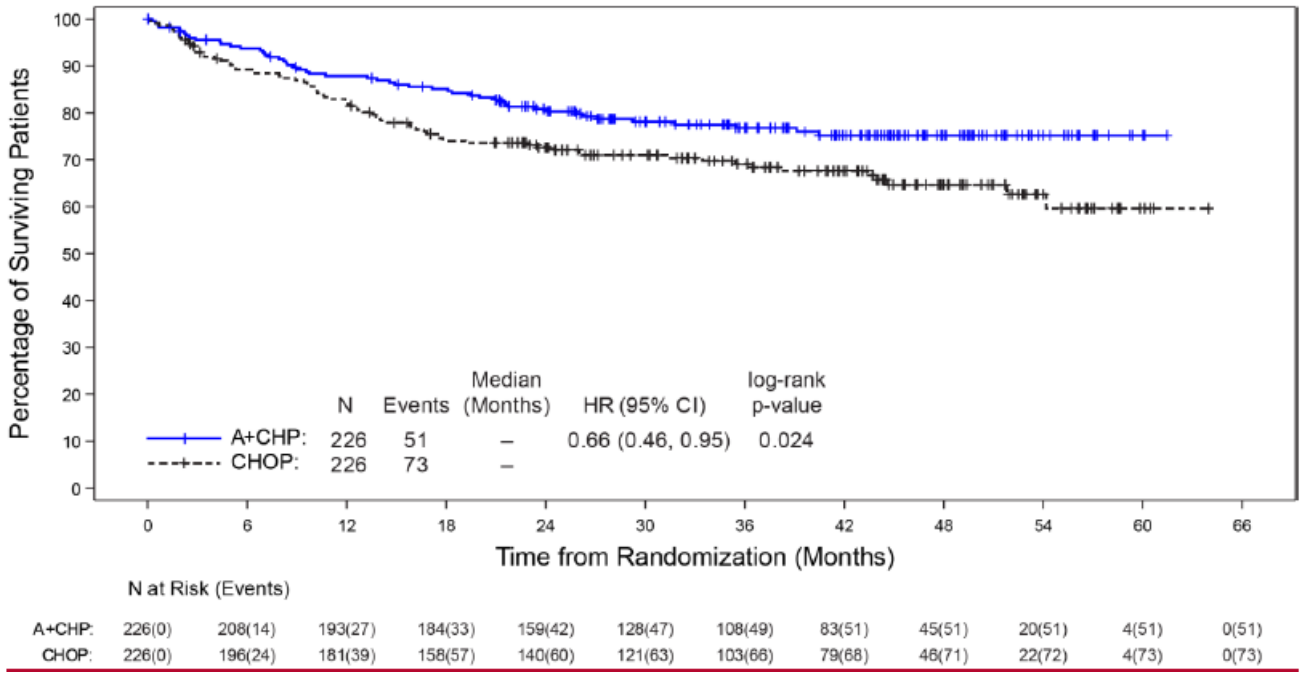
a Efficacy endpoints were tested at a two-sided alpha level 0.05 in the following order: PFS in ITT, PFS in the central sALCL subgroup, complete remission rate, overall survival, and objective response rate in ITT.
b Hazard ratio (A+CHP/CHOP) and 95% confidence intervals are based on a stratified Cox's proportional hazard regression model with stratification factors (ALK-positive sALCL versus all others and International Prognostic Index [IPI] score at baseline). Hazard ratio <1 favors A+CHP arm.
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 Response per 2007 International Working Group Criteria at end of treatment.
f P-value is calculated using a stratified Cochran-Mantel-Haenszel test.
g P-value is for descriptive purpose only.

Figure 12: Kaplan-Meier Plot of PFS per IRF (ECHELON-2, SGN35-014)




A+CHP: ADCETRIS plus CHP (cyclophosphamide, doxorubicin, and prednisone); CHOP: cyclophosphamide, doxorubicin, vincristine, and prednisone; HR: hazard ratio.

Figure 13: Overall Survival (ECHELON-2, SGN35-014)




Median overall survival was not reached in either treatment arm.

A+CHP: ADCETRIS plus CHP (cyclophosphamide, doxorubicin, and prednisone); CHOP: cyclophosphamide, doxorubicin, vincristine, and prednisone; CI: confidence interval; HR: hazard ratio.

Of the 452 patients, 72 patients had PTCL-NOS; 29 were randomized to treatment with ADCETRIS + CHP and 43 patients were randomized to treatment with CHOP. The median PFS per IRF was 21.2 months in the Trade Name + CHP arm versus 11.4 months in the CHOP arm. The stratified hazard ratio was 0.75 (95% CI: 0.41, 1.37).

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 treatment arms.

Medical resource utilization (MRU) was assessed from healthcare data collected from Cycle 1 through long-term follow-up. The hospitalization visit rate was lower in subjects who received A+CHP compared to subjects who received CHOP, but there was no meaningful difference in the median number of hospitalization visits between the arms.

### 8.2.2 Study SG035-0004

The efficacy and safety of brentuximab vedotin as a single agent was evaluated in an open-label, single- arm, multicenter study in 58 patients with relapsed or refractory sALCL. See **Table 15** below for a summary of baseline patient and disease characteristics.

**Table 15: Summary of baseline patient and disease characteristics in the phase 2 relapsed or refractory sALCL study**

| Patient Characteristics | N =58 |
|---|---|
| Age | 52 years (14-76) |
| Gender | 33M (57%)/25F (43%) |
| ECOG status[a] | |
| 0 | 19 (33%) |
| 1 | 38 (66%) |
| Prior ASCT | 15 (26%) |
| Prior chemotherapy regimens | 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 brentuximab vedotin 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 16** below for other prespecified endpoints.

**Table 16: Efficacy Results in Relapsed or Refractory sALCL Patients Treated with 1.8 mg/kg of Brentuximab Vedotin Every 3 Weeks**

| **Best Clinical Response[a] (N = 58[b])** | **IRF** *N (%)* | **95 % CI** | **Investigator** *N (%)* | **95 % CI** |
|---|---|---|---|---|
| Objective response rate (CR + PR) | 50 (86) | 74.6, 93.9 | 50 (86) | 74.6, 93.9 |
| Complete response (CR) | 34(59) | 44.9, 71.4 | 38 (66) | 51.9, 77.5 |
| Partial response (PR) | 16 (28) | N/A | 12 21) | N/A |
| Disease control rate (CR + PR + SD) | 52 (90) | 78.8, 96.1 | 54 (93 | 83.3, 98.1 |

| **Duration of Response[c, d]** | **Median per IRF** | **95 % CI** | **Median per Investigator** | **95 %** |
|---|---|---|---|---|
| Objective response (CR + PR) | 13.2 | 5.7, - 26.3 | 25.6 months | 11.8, NE |
| Complete response (CR) | 26.3 | 13.2, - NE | Not reached | 20, NE |

| **Progression free survival (PFS)[f]** | **Median per IRF** | **95% CI** | **Median per Investigator** | **95 %** |
|---|---|---|---|---|
| | 14.6 months | 6.9 – 20.6 | 20.0 months | 9.4 NE |

| **Overall Survival** | | **95 % CI** |
|---|---|---|
| Median | Not reached | 21.3, NE |

a Independent review facility 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 15.5 months.*

d. At a median duration of treatment of 5.4 months and a current range of 0.7 to 17.3 months, 32 of 50 patients who had an objective response have had disease progression or have died and 18 of 34 patients who had a CR have had disease progression or have died.

e. Not estimable

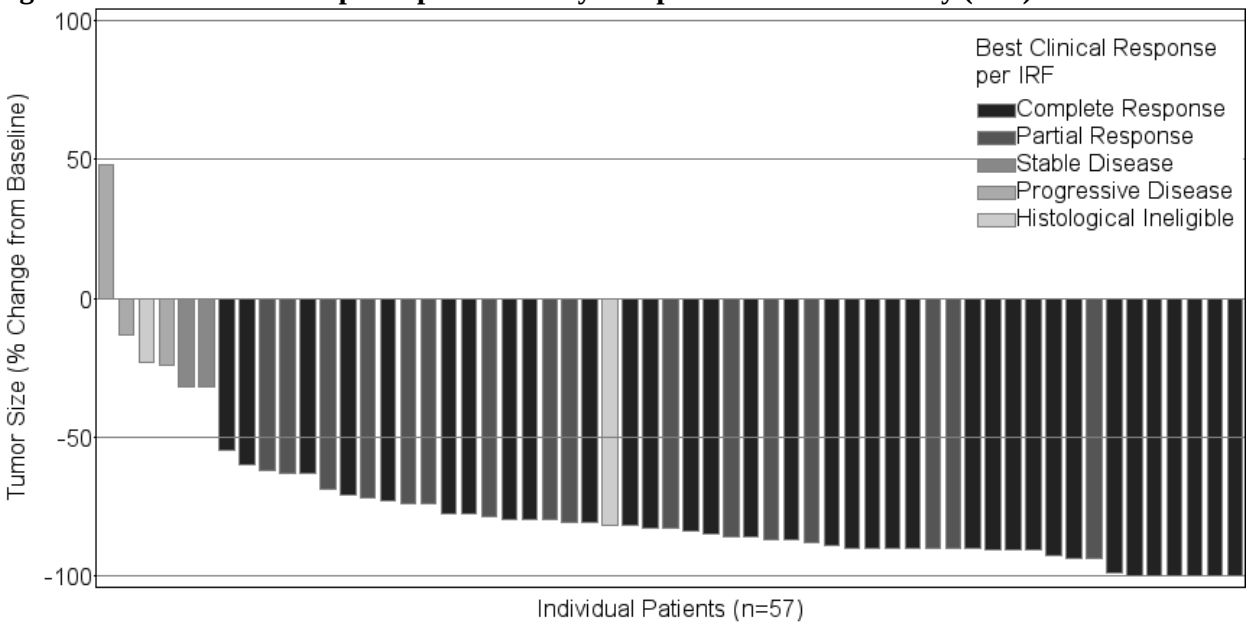
f. *The median follow-up time (time to earliest of progressive disease, death or last contact) from first dose was 14.2 months.*

g. *The median observation time (time to death or last contact) from first dose was 71.4 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 14** for waterfall chart of tumor reduction, ORR and CR.

**Figure 14: Best Clinical Response per Patient by Independent Review Facility (IRF) Determination**



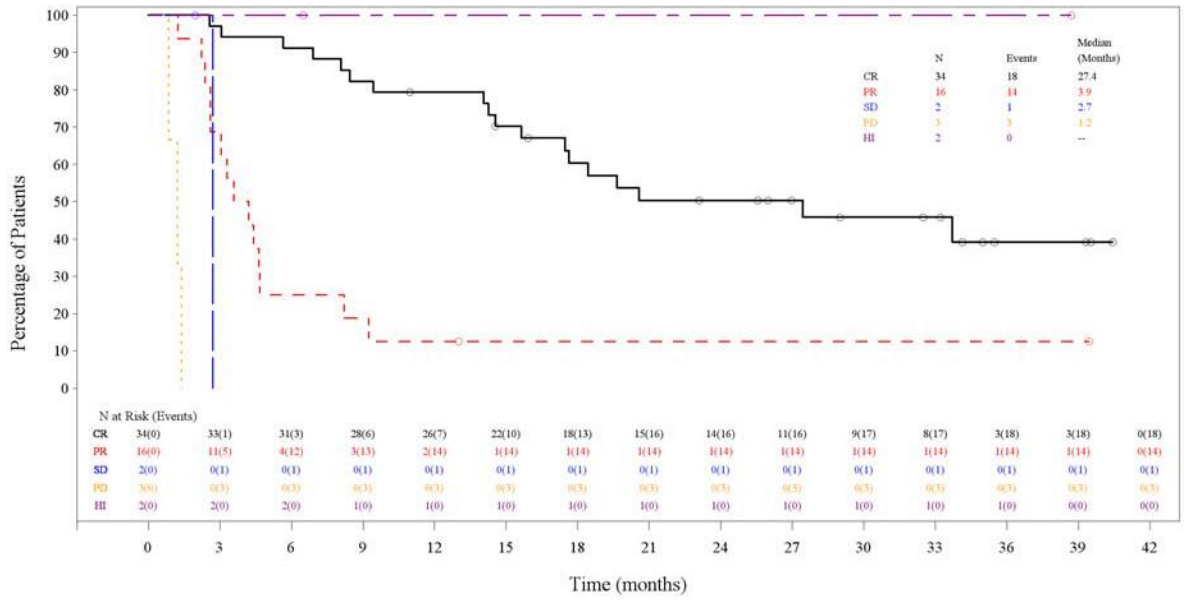

In the designation of CR per Revised Response Criteria for Malignant Lymphoma (Cheson et al., 2007), a post-treatment residual mass of any size is permitted as long as it is PET negative

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 15** for median PFS by best clinical response.

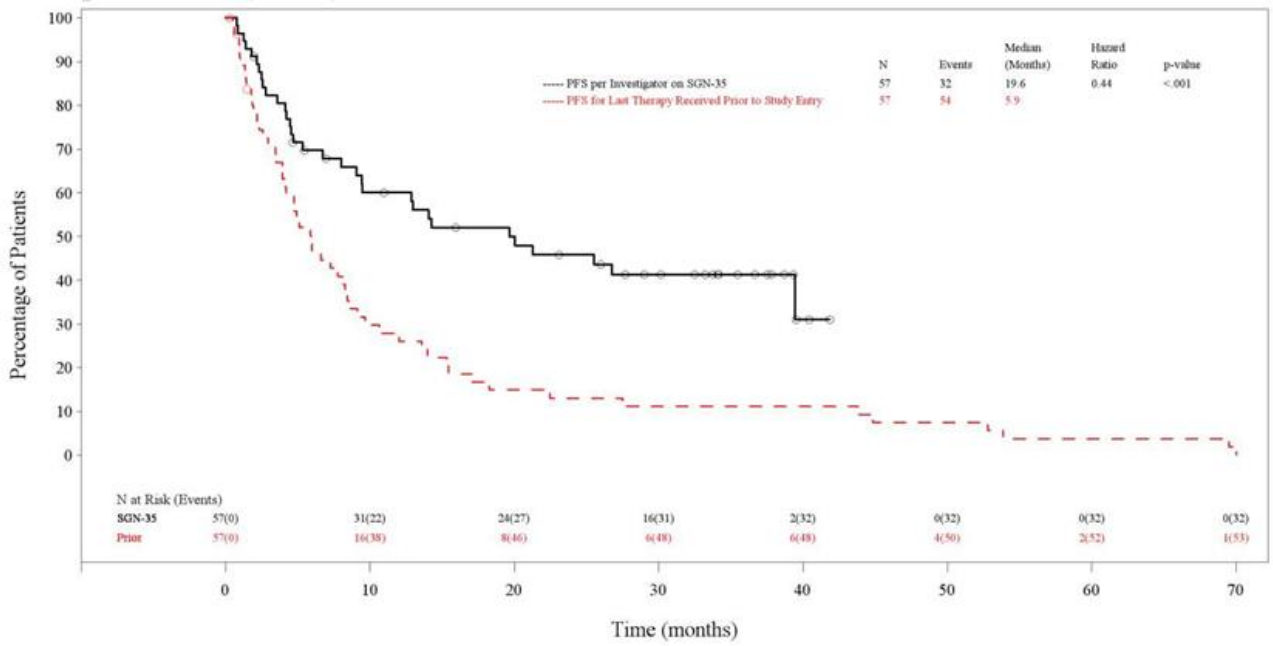
Figure 15: Progression-free survival by best clinical response per IRF




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 16** for a KM plot of PFS with ADCETRIS compared to PFS from last therapy received prior to study.

**Figure 16: Comparison of current PFS per investigator and PFS achieved with the last therapy received prior to study entry**



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 month 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.

### *8.2.3 Study SGN35-006*

***Retreatment study***

The efficacy of retreatment in patients who had previously responded (CR or PR) to treatment with ADCETRIS was evaluated in a phase 2, open-label, multicenter trial. Seven patients with relapsed sALCL received a starting dose of 1.8 mg/kg and one patient received a starting dose of 1.2 mg/kg of ADCETRIS administered intravenously over 30 minutes every 3 weeks. The median number of cycles was 8.5 (range, 2 to 30 cycles). Of the 8 sALCL patients, 3 were retreated twice for a total of 11 retreatment experiences. Retreatment with ADCETRIS resulted in 6 CRs (55%) and 4 PRs (36%), for an ORR of 91%. The median duration of response was 8.8 and 12.3 months in patients who achieved OR (CR+PR) and CR, respectively.

## 8.3 Cutaneous T-Cell Lymphoma

### 8.3.1 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 17** provides a summary of the baseline patient and disease characteristics.

**Table 17: Summary of Baseline Patient and Disease Characteristics in the Phase 3 CTCL Study (ITT Population)**

| Patient characteristics | Brentuximab vedotin N = 64 | Physician's Choice (Methotrexate or Bexarotene) N= 64 |
|---|---|---|
| Median age (range) | 62 years (22-83) | 58.5 years (22-83) |
| Patients ≥ 65 years old n (%) | 28 (44%) | 24 (38%) |
| Gender n (%) | 33M (52%)/31F (48%) | 37M (58%)/27F (42%) |
| ECOG status n (%) | | |
| 0 | 43 (67) | 46 (72) |
| 1 | 18 (28) | 16 (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 therapies (range) | 1 (0-6) | 1 (0-9) |
| Median number of systemic therapies (range) | 2 (0-11) | 2 (1-8) |
| MF, n(%) | 48 (75) | 49 (77) |
| Early (IA-IIA) | 15 (31) | 18 (37) |
| Advanced (IIB-IVB[a]) | 32 (67) | 30 (61) |
| pcALCL, n(%) | 16 (25) | 15 (23) |
| Skin only | 9 (56) | 11 (73) |
| Extracutaneous disease | 7 (44) | 4 (27) |

[a] One patient in each arm had incomplete staging data and are not included in the table

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