# ADCETRIS

## 1. NAME OF THE MEDICINAL PRODUCT

ADCETRIS 50 mg powder for concentrate for solution for infusion.

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 50 mg of brentuximab vedotin.

After reconstitution (see section 6.6), each ml contains 5 mg of brentuximab vedotin.

ADCETRIS 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).

Excipients with known effect

Each vial contains approximately 13.2 mg of sodium.

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Powder for concentrate for solution for infusion.

White to off-white cake or powder.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Hodgkin lymphoma

ADCETRIS is indicated for adult patients with previously untreated CD30+ Stage III or IV Hodgkin lymphoma (HL) in combination with doxorubicin, vinblastine and dacarbazine (AVD)(see sections 4.2 and 5.1).

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

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

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

Systemic anaplastic large cell lymphoma
ADCETRIS in combination with cyclophosphamide, doxorubicin and prednisone (CHP) is indicated for adult patients with previously untreated systemic anaplastic large cell lymphoma (sALCL) (see section 5.1)

ADCETRIS is indicated for the treatment of adult patients with relapsed or refractory sALCL.

Cutaneous T-cell lymphoma
ADCETRIS is indicated for the treatment of adult patients with CD30+ cutaneous T-cell lymphoma (CTCL) after at least 1 prior systemic therapy (see section 5.1).

## 4.2 Posology and method of administration

Brentuximab vedotin should be administered under the supervision of a physician experienced in the use of anti-cancer agents.

Posology

*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 5.1).

Primary prophylaxis with growth factor support (G-CSF), beginning with the first dose, is recommended for all patients with previously untreated HL receiving combination therapy (see section 4.4).

Refer to the summary of product characteristics (SmPC) of chemotherapy agents given in combination with ADCETRIS for patients with previously untreated HL.

*HL at increased risk of relapse or progression*

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

ADCETRIS treatment should start following recovery from ASCT based on clinical judgment. These patients should receive up to 16 cycles (see section 5.1).

*Relapsed or refractory HL*

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

The recommended starting dose for the retreatment of patients who have previously responded to treatment with ADCETRIS is 1.8 mg/kg administered as an intravenous infusion over 30 minutes every 3 weeks. Alternatively, treatment may be started at the last tolerated dose (see section 5.1).

Treatment should be continued until disease progression or unacceptable toxicity (see section 4.4).

Patients who achieve stable disease or better should receive a minimum of 8 cycles and up to a maximum of 16 cycles (approximately 1 year) (see section 5.1).
*Previously untreated sALCL*

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 5.1).

Primary prophylaxis with G-CSF, beginning with the first dose, is recommended for all patients with previously untreated sALCL receiving combination therapy (see section 4.4).

Refer to the SmPCs of chemotherapy agents given in combination with ADCETRIS for patients with previously untreated sALCL.

*Relapsed or refractory sALCL*

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

The recommended starting dose for the retreatment of patients who have previously responded to treatment with ADCETRIS is 1.8 mg/kg administered as an intravenous infusion over 30 minutes every 3 weeks. Alternatively, treatment may be started at the last tolerated dose (see section 5.1).

Treatment should be continued until disease progression or unacceptable toxicity (see section 4.4).

Patients who achieve stable disease or better should receive a minimum of 8 cycles and up to a maximum of 16 cycles (approximately 1 year) (see section 5.1).

*CTCL*

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

Patients with CTCL should receive up to 16 cycles (see section 5.1).
*General*

If the patient's weight is more than 100 kg, the dose calculation should use 100 kg (see section 6.6).

Complete blood counts should be monitored prior to administration of each dose of this treatment (see section 4.4).

Patients should be monitored during and after infusion (see section 4.4).

Dose adjustments

*Neutropenia*

If neutropenia develops during treatment it should be managed by dose delays. See Table 1 and Table 2 for appropriate dosing recommendations for monotherapy and combination therapy, respectively (see also section 4.4).

**Table 1: Dosing recommendations for neutropenia with monotherapy**

| **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 x $10^9$/L) or Grade 2 (< 1500-1000/$mm^3$ < 1.5-1.0 x $10^9$/L) | Continue with the same dose and schedule |
| Grade 3 (< 1,000-500/$mm^3$ < 1.0-0.5 x $10^9$/L) or Grade 4 (< 500/$mm^3$ < 0.5 x $10^9$/L) | Withhold dose until toxicity returns to ≤ Grade 2 or baseline then resume treatment at the same dose and schedule[b]. Consider G-CSF or GM-CSF in subsequent cycles for patients who develop Grade 3 or Grade 4 neutropenia. |

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

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

**Table 2: Dosing recommendations for 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 x $10^9$/L) or Grade 2 (< 1500-1000/$mm^3$ < 1.5-1.0 x $10^9$/L) Grade 3 (< 1,000-500/$mm^3$ < 1.0-0.5 x $10^9$/L) or Grade 4 (< 500/$mm^3$ < 0.5 x $10^9$/L) | Primary prophylaxis with G-CSF, beginning with the first dose, is recommended for all patients receiving combination therapy. Continue with the same dose and schedule. |

a. Grading based on National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v4.03; see Neutrophils/granulocytes; LLN = lower limit of normal.

*Peripheral neuropathy*

If peripheral sensory or motor neuropathy emerges or worsens during treatment see Table 3 and 4 for appropriate dosing recommendations for monotherapy and combination therapy, respectively (see section 4.4).

**Table 3: Dosing recommendations for new or worsening peripheral sensory or motor neuropathy with monotherapy**

| **Severity of peripheral sensory or motor neuropathy (signs and symptoms** [abbreviated description of CTCAE[a]]) | **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 |

[a.] 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 4: 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[a]]) | **Modification of dose and schedule** | **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. | Continue with the same dose and schedule. |
| Grade 2 (interfering with function but not with activities of daily living) | Reduce dose to 0.9 mg/kg up to a maximum of 90 mg every 2 weeks. | Sensory neuropathy: Continue treatment at same dose level.<br>Motor neuropathy: Reduce dose to 1.2 mg/kg, up to a maximum of 120 mg every 3 weeks. |
| Grade 3 (interfering with activities of daily living) | Withhold treatment with ADCETRIS until toxicity is ≤ Grade 2, then restart treatment at a reduced dose to 0.9 mg/kg up to a maximum of 90 mg every 2 weeks. | 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 (sensory neuropathy which is disabling or motor neuropathy that is life threatening or leads to paralysis) | Discontinue treatment. | Discontinue treatment. |

[a.] Grading based on National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v4.03; see neuropathy: motor; neuropathy: sensory; and neuropathic pain.

Special patient populations

*Renal and hepatic impairment*

Combination therapy

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

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

Monotherapy

The recommended starting dose in patients with severe renal impairment is 1.2 mg/kg administered as an intravenous infusion over 30 minutes every 3 weeks. Patients with renal impairment should be closely monitored for adverse events (see section 5.2).

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 section 5.2).

Table 5: Recommended ADCETRIS dose for patients with renal or hepatic impairment

| Severity of renal or hepatic impairment | Monotherapy recommended dose* | Combination therapy with AVD recommended dose* | Combination therapy with CHP recommended dose* |
|---|---|---|---|
| | **Renal impairment** | | |
| Mild (CrCL greater than 50-80 mL/min)<br>Moderate (CrCL 30-50 mL/min) | 1.8 mg/kg up to a maximum of 180 mg every 3 weeks | 1.2 mg/kg up to a maximum of 120 mg every 2 weeks in combination with AVD | 1.8 mg/kg up to a maximum of 180 mg every 3 weeks in combination with CHP |
| Severe (CrCL less than 30 mL/min) | 1.2 mg/kg up to a maximum of 120 mg every 3 weeks | Avoid use | Avoid use |
| | **Hepatic impairment** | | |

| | | | |
|---|---|---|---|
| Mild (Child-Pugh A) | 1.2 mg/kg up to a maximum of 120 mg every 3 weeks | 0.9 mg/kg up to a maximum of 90 mg every 2 weeks in combination with AVD | 1.2 mg/kg up to a maximum of 120 mg every 3 weeks in combination with CHP |
| Moderate (Child-Pugh B)<br>Severe (Child-Pugh C) | 1.2 mg/kg up to a maximum of 120 mg every 3 weeks | Avoid use | Avoid use |

*The dose for patients weighing greater than 100 kg should be calculated based on a weight of 100 kg

*Elderly patients*

The dosing recommendations for patients aged 65 and older are the same as for adults. Currently available data are described in sections 4.8, 5.1 and 5.2.

*Paediatric population*

The safety and efficacy of ADCETRIS in children less than 18 years have not yet been established. Currently available data are described in sections 4.8, 5.1 and 5.2 but no recommendation on a posology can be made.

In nonclinical studies, thymus depletion has been observed (see section 5.3).

Method of administration

The recommended dose of ADCETRIS is infused over 30 minutes.

For instructions on reconstitution and dilution of the medicinal product before administration, see section 6.6.

Brentuximab vedotin must not be administered as an intravenous push or bolus. Brentuximab vedotin should be administered through a dedicated intravenous line and it must not be mixed with other medicinal products (see section 6.2).

## 4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Combined use of bleomycin and brentuximab vedotin causes pulmonary toxicity (see section 4.5).

## 4.4 Special warnings and precautions for use

Progressive multifocal leukoencephalopathy

John Cunningham virus (JCV) reactivation resulting in progressive multifocal leukoencephalopathy (PML) and death can occur in brentuximab vedotin-treated patients. PML has been reported in patients who received this treatment after receiving multiple prior chemotherapy regimens. PML is a rare demyelinating disease of the central nervous system that results from reactivation of latent JCV and is often fatal.

Patients should be closely monitored for new or worsening neurological, cognitive, or behavioural signs or symptoms, which may be suggestive of PML. Brentuximab vedotin 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 with 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. Brentuximab vedotin 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 brentuximab vedotin. Fatal outcomes have been reported.

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

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 brentuximab vedotin. Although a causal association with brentuximab vedotin 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, dyspnoea), a prompt diagnostic evaluation should be performed and patients should be treated appropriately. Consider holding brentuximab vedotin dosing during evaluation and until symptomatic improvement.

Serious infections and opportunistic infections

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

Infusion-related reactions

Immediate and delayed infusion-related reactions (IRR), as well as anaphylactic reactions, have been reported.

Patients should be carefully monitored during and after infusion. If an anaphylactic reaction occurs, administration of brentuximab vedotin should be immediately and permanently discontinued and appropriate medical therapy should be administered.

If an IRR occurs, the infusion should be interrupted and appropriate medical management instituted. The infusion may be restarted at a slower rate after symptom resolution. Patients who have experienced a prior IRR should be premedicated for subsequent infusions. Premedication may include paracetamol, an antihistamine and a corticosteroid.

IRRs are more frequent and more severe in patients with antibodies to brentuximab vedotin (see section 4.8).

Tumour lysis syndrome

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

Peripheral neuropathy

Brentuximab vedotin treatment may cause a peripheral neuropathy, both sensory and motor. Brentuximab vedotin-induced peripheral neuropathy is typically an effect of cumulative exposure to this medicinal product and is reversible in most cases. In clinical trials, the majority of patients had resolution or improvement of their symptoms (see section 4.8). Patients should be monitored for symptoms of neuropathy, such as hypoesthesia, hyperesthesia, paraesthesia, discomfort, a burning sensation, neuropathic pain or weakness. Patients experiencing new or worsening peripheral neuropathy may require a delay and a dose reduction of ADCETRIS or discontinuation of treatment (see section 4.2).

Haematological toxicities

Grade 3 or Grade 4 anaemia, thrombocytopenia, and prolonged (≥1 week) Grade 3 or Grade 4 neutropenia can occur with brentuximab vedotin. Complete blood counts should be monitored prior to administration of each dose. If Grade 3 or Grade 4 neutropenia develops, refer to section 4.2.

Febrile neutropenia

Febrile neutropenia (fever of unknown origin without clinically or microbiologically documented infection with an absolute neutrophil count $<1.0 \times 10^9$/L, fever ≥38.5°C; ref CTCAE v3) has been reported with treatment with brentuximab vedotin. Complete blood counts should be monitored prior to administration of each dose of this 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, beginning with the first dose, is recommended for all patients regardless of age.

Severe cutaneous adverse reactions (SCARs)
Cases of SCARs, including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and drug reaction with eosinophilia and systemic symptoms (DRESS) have been reported with brentuximab vedotin. Fatal outcomes have been reported for SJS and TEN. If SJS, TEN or DRESS occur, brentuximab vedotin should be discontinued and appropriate medical therapy should be administered.

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 brentuximab vedotin. 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 brentuximab vedotin. 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 tested before initiating

the treatment and routinely monitored in patients receiving brentuximab vedotin. Patients experiencing hepatotoxicity may require a delay, change in dose or discontinuation of brentuximab vedotin.

Hyperglycaemia

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

Infusion site extravasation
Extravasation during intravenous infusion has occurred. Given the possibility of extravasation, it is recommended to closely monitor the infusion site for possible infiltration during drug administration.

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 5.2).

CD30+ CTCL

The size of the treatment effect in CD30 + CTCL subtypes other than mycosis fungoides (MF) and primary cutaneous anaplastic large cell lymphoma (pcALCL) is not clear due to lack of high level evidence. In two single arm phase II studies of ADCETRIS, disease activity has been shown in the subtypes Sézary syndrome (SS), lymphomatoid papulosis (LyP) and mixed CTCL histology. These data suggest that efficacy and safety can be extrapolated to other CTCL CD30+ subtypes. Nevertheless, ADCETRIS should be used with caution in other CD30+ CTCL patients after careful consideration of the potential benefit-risk on an individual basis (see section 5.1).

Sodium content in excipients

This medicinal product contains 13.2 mg sodium per vial, equivalent to 0.7% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

## 4.5 Interaction with other medicinal products and other forms of interaction

Interaction with medicinal products metabolized through CYP3A4 route (CYP3A4 inhibitors/inducers)

Co-administration of brentuximab vedotin with ketoconazole, a strong CYP3A4 and P-gp inhibitor, increased the exposure to the antimicrotubule agent MMAE by approximately 73%, and did not alter the

plasma exposure to brentuximab vedotin. Therefore, co-administration of brentuximab vedotin with strong CYP3A4 and P-gp inhibitors may increase the incidence of neutropenia. If neutropenia develops, refer to Tables 1 and 2 for dosing recommendations for neutropenia (see section 4.2).

Co-administration of brentuximab vedotin with rifampicin, a strong CYP3A4 inducer, did not alter the plasma exposure to brentuximab vedotin. Though PK data are limited, co administration of rifampicin appeared to reduce plasma concentrations of MMAE metabolites that could be assayed.

Co-administration of midazolam, a CYP3A4 substrate, with brentuximab vedotin did not alter the metabolism of midazolam; therefore brentuximab vedotin is not expected to alter the exposure to medicines that are metabolised by CYP3A4 enzymes.

Doxorubicin, vinblastine and dacarbazine (AVD)

The serum and plasma pharmacokinetic characteristics of antibody drug conjugate (ADC) and MMAE respectively following administration of brentuximab vedotin in combination with AVD were similar to that in monotherapy.

Co-administration of brentuximab vedotin did not affect the plasma exposure of AVD.

Cyclophosphamide, Doxorubicin and Prednisone (CHP)

The serum and plasma pharmacokinetic characteristics of ADC and MMAE, respectively, following administration of brentuximab vedotin in combination with CHP 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 (see section 4.2).

## 4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential should be using two methods of effective contraception during treatment with brentuximab vedotin and until 6 months after treatment.

Pregnancy

There are no data from the use of brentuximab vedotin in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3).

Brentuximab vedotin should not be used during pregnancy unless the benefit to the mother outweighs the potential risks to the foetus. If a pregnant woman needs to be treated she should be clearly advised on the potential risk to the foetus.

See the fertility section below pertaining to advice for women whose male partners are being treated with brentuximab vedotin.

Breastfeeding

There are no data as to whether brentuximab vedotin or its metabolites are excreted in human milk.

A risk to the newborn/infant cannot be excluded.

A decision should be made whether to discontinue breast-feeding or to discontinue/abstain from this therapy, taking into account a potential risk of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

In non-clinical studies, brentuximab vedotin treatment has resulted in testicular toxicity, and may alter male fertility. MMAE has been shown to have aneugenic properties (see section 5.3). Therefore, men being treated with this medicine are advised to have sperm samples frozen and stored before treatment. Men being treated with this medicine are advised not to father a child during treatment and for up to 6 months following the last dose.

In non-clinical studies, treatment with MMAE containing ADCs other than brentuximab vedotin, have resulted in ovarian toxicity (see section 5.3). See the Women of childbearing potential section above pertaining to advice for women on the use of methods of effective contraception

## 4.7 Effects on ability to drive and use machines

Brentuximab vedotin may have a moderate influence on the ability to drive and use machines (e.g. dizziness), see section 4.8.

## 4.8 Undesirable effects

Summary of the safety profile

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

*Monotherapy*

In the pooled dataset of ADCETRIS as monotherapy across HL, sALCL and CTCL studies (SG0350003, SG0350004, SGN35005, SGN35006, 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, see section 5.1) were consistent with those observed in the combined pivotal phase 2 studies, with the exception of peripheral motor neuropathy, which had a higher incidence (28% vs. 9% in the pivotal phase 2 studies) and was primarily Grade 2. Patients also had a higher incidence of arthralgia, Grade 3 anaemia, and back pain compared to patients observed in the combined pivotal phase 2 studies.

The safety data in patients with relapsed or refractory HL who had not received an autologous stem cell transplant and were treated with the recommended dose of 1.8 mg/kg every three weeks in a single-arm phase 4 study (n = 60), the phase 1 dose escalation and clinical pharmacology studies (n = 15 patients) and in the NPP (n = 26 patients) (see section 5.1) were consistent with the safety profile of the pivotal clinical studies.

*Combination therapy*

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

In the studies of ADCETRIS as combination therapy in 662 patients with previously untreated stage III or IV HL (C25003) and 223 patients with previously untreated CD30+ peripheral T-cell lymphoma (PTCL) (SGN35014), the most common adverse reactions (≥ 10%) were: infections, neutropenia, peripheral sensory neuropathy, nausea, constipation, vomiting, diarrhea, fatigue, pyrexia, alopecia, anaemia, weight decreased, stomatitis, febrile neutropenia, abdominal pain, decreased appetite, insomnia, bone pain, rash, cough, dyspnoea, arthralgia, myalgia, back pain, peripheral motor neuropathy, upper respiratory tract infection, and dizziness.

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

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

Tabulated list of adverse reactions

Adverse reactions for ADCETRIS are listed by MedDRA System Organ Class and Preferred Term (see Table 6). 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 6: 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 reaction |
| **Metabolism and nutrition disorders** | | |
| Very common: | | Decreased appetite |
| Common: | Hyperglycaemia | Hyperglycaemia |
| Uncommon: | Tumour lysis syndrome | Tumour lysis syndrome |
| Psychiatric disorders | | |
| Very common: | | Insomnia |
| **Nervous system disorders** | | |
| Very common: | Peripheral sensory neuropathy, peripheral motor neuropathy | Peripheral sensory neuropathy, peripheral motor neuropathy[a], dizziness |
| Common: | Dizziness | |
| Uncommon: | Demyelinating polyneuropathy | |
| **Respiratory, thoracic and mediastinal disorders** | | |
| Very common: | Cough, dyspnoea | Cough, dyspnoea |
| **Gastrointestinal disorders** | | |
| Very common: | Nausea, diarrhoea vomiting, constipation, abdominal pain | Nausea, constipation, vomiting, diarrhoea, abdominal pain, stomatitis |
| Uncommon: | Pancreatitis acute | Pancreatitis acute |
| **Hepatobiliary disorders** | | |
| | | |
| Common: | Alanine aminotransferase/aspartate aminotransferase (ALT/AST) increased | Alanine aminotransferase/aspartate aminotransferase (ALT/AST) increased |
| **Skin and subcutaneous tissue disorders** | | |
| Very common: | Rash[a], pruritus | Alopecia, rash[a] |
| Common: | Alopecia | Pruritus |
| Uncommon: | Stevens-Johnson syndrome/toxic epidermal necrolysis | Stevens-Johnson syndrome[b] |
| Not known | Drug reaction with eosinophilia and systemic symptoms (DRESS) | |
| **Musculoskeletal and connective tissue disorders** | | |

| | | |
|---|---|---|
| Very common: | Arthralgia, myalgia | Bone pain, arthralgia, myalgia, back pain |
| Common: | Back pain | |
| **General disorders and administration site conditions** | | |
| Very common: | Fatigue, pyrexia, infusion-related reactions[a] | Fatigue, pyrexia |
| Common: | Chills | Infusion-related reactions[a], chills |
| Not known: | Infusion site extravasation[c] | |
| **Investigations** | | |
| Very common: | Weight decreased | Weight decreased |

a. Represents pooling of preferred terms.

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

c. Extravasation may result inrelated reaction include skin redness, pain, swelling, blistering, exfoliation or cellulitis at or surrounding the infusion site.

Description of selected adverse reactions

*Neutropenia and febrile neutropenia*

Monotherapy

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

Severe and prolonged (≥1 week) neutropenia can occur with this treatment which may increase the risk of patients developing serious infections. Febrile neutropenia reported in < 1% of the patients (see section 4.2).

In the pivotal phase 2 population (SG0350003 and SG0350004), 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 trials of ADCETRIS as combination therapy, serious infections including opportunistic infections occurred in 15% of patients; sepsis, neutropenic sepsis, septic shock or bacteraemia occurred in 4% of the patients. The most commonly reported opportunistic infections were herpes viral infections.

*Peripheral neuropathy*

Monotherapy

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

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

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

Combination therapy

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

Among patients who experienced peripheral neuropathy, the median follow up time from end of treatment until last evaluation was approximately 286 weeks. At the time of last evaluation, most of the patients (86%) who experienced peripheral neuropathy had resolution or improvement of their peripheral neuropathy symptoms. The median time from onset to resolution or improvement of peripheral neuropathy events was 17 weeks (ranged from 0 weeks to 283 weeks).

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

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

*Infusion-related reactions*

Monotherapy

IRRs, such as headache, rash, back pain, vomiting, chills, nausea, dyspnoea, pruritus and cough were reported in 13% of patients. Anaphylactic reactions have been reported (see section 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.

Monotherapy Study C25002

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

Combination Use Study C25004
The rate of ADA positivity was low in Study C25004; 4 patients (aged ≥ 12 years) of 59 patients became transiently ADA positive, and no patients became persistently ADA positive. Due to the small number of transiently ADA positive patients, the impact of ADA on efficacy is inconclusive

Paediatric population

Monotherapy Study C25002

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

Combination Use Study C25004
Safety was evaluated in an open-label, multicenter trial in 59 paediatric patients aged 6-17 years of age with previously untreated stage III or IV classical CD30+ HL in combination with chemotherapy (see

section 5.1). In this study, no new safety concerns were reported. The most common serious adverse reaction reported in this study was febrile neutropenia (17%). G-CSF prophylaxis was considered at the physician's discretion. Peripheral neuropathy events (per Standardized MedDRA Query) were reported in 24% of paediatric patients in this study.

Elderly

*Monotherapy*

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

*Combination therapy*

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

### 4.9 Overdose

There is no known antidote for overdose of brentuximab vedotin. In case of overdose, the patient should be closely monitored for adverse reactions, particularly neutropenia, and supportive treatment should be administered (see section 4.4).

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents; other antineoplastic agents; monoclonal antibodies, ATC code: L01XC12

Mechanism of action

Brentuximab vedotin is an ADC that delivers an antineoplastic agent that results in apoptotic cell death selectively in CD30-expressing tumour cells. Nonclinical data suggest that the biological activity of brentuximab vedotin results from a multi-step process. Binding of the ADC to CD30 on the cell surface initiates internalisation of the ADC-CD30 complex, which then traffics 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 tumour cell.

Classical HL , sALCL and subtypes of CTCL (including MF and pcALCL) express CD30 as an antigen on the surface of their malignant cells. This expression is independent of disease stage, line of therapy or transplant status. These features make CD30 a target for therapeutic intervention. Because of the

CD30-targeted mechanism of action brentuximab vedotin is able to overcome chemo-resistance as CD30 is consistently expressed in patients who are refractory to multi-agent chemotherapy, irrespective of prior transplant status. The CD30-targeted mechanism of action of brentuximab vedotin, the consistent expression of CD30 throughout the classical HL, sALCL and CD30+ CTCL disease and therapeutic spectrums and clinical evidence in CD30-positive malignancies following multiple lines of treatment provide a biologic rationale for its use in patients with relapsed and refractory classical HL, sALCL with or without prior ASCT and CD30+ CTCL after at least 1 prior systemic therapy.

Contributions to the mechanism of action by other antibody associated functions have not been excluded.

Pharmacodynamic effects

*Cardiac electrophysiology*

Forty-six (46) patients with CD30-expressing haematologic malignancies were evaluable of the 52 patients who received 1.8 mg/kg of brentuximab vedotin 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 re-polarization 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) around the mean effect on QTc was <10 msec at each of the Cycle 1 and Cycle 3 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 every 3 weeks in patients with CD30-expressing malignancies.

Clinical efficacy and safety

*Hodgkin lymphoma*

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 stage III or IV 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 7 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 7: 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 8 provides the efficacy results for modified PFS and overall survival (OS) in the ITT population and patients with Stage IV disease.

**Table 8: 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

[c]p-value for Stage IV disease is not adjusted for multiplicity.

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

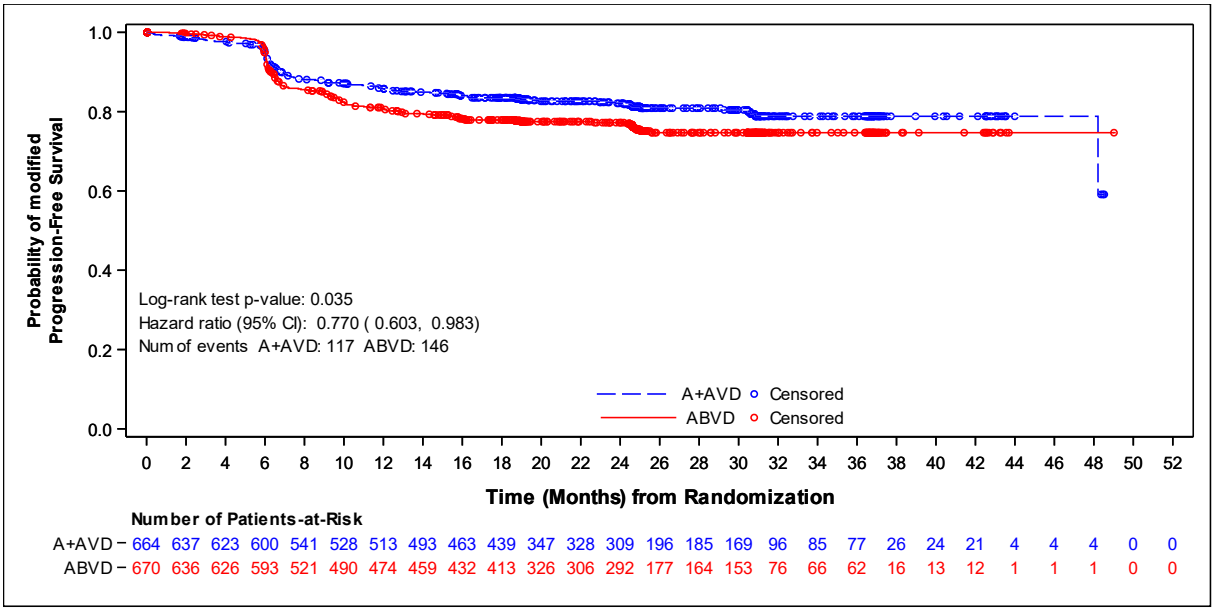
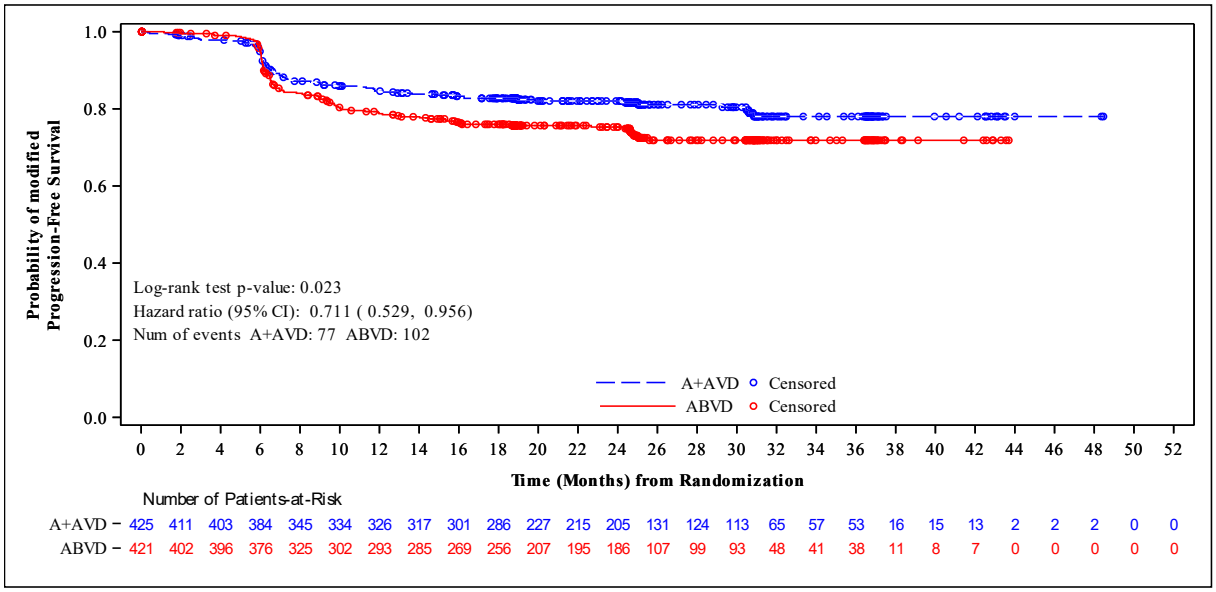


**Figure 2: Modified progression-free survival per IRF in patients with Stage IV disease (ADCETRIS + AVD vs. ABVD)**




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.

Post-hoc 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).

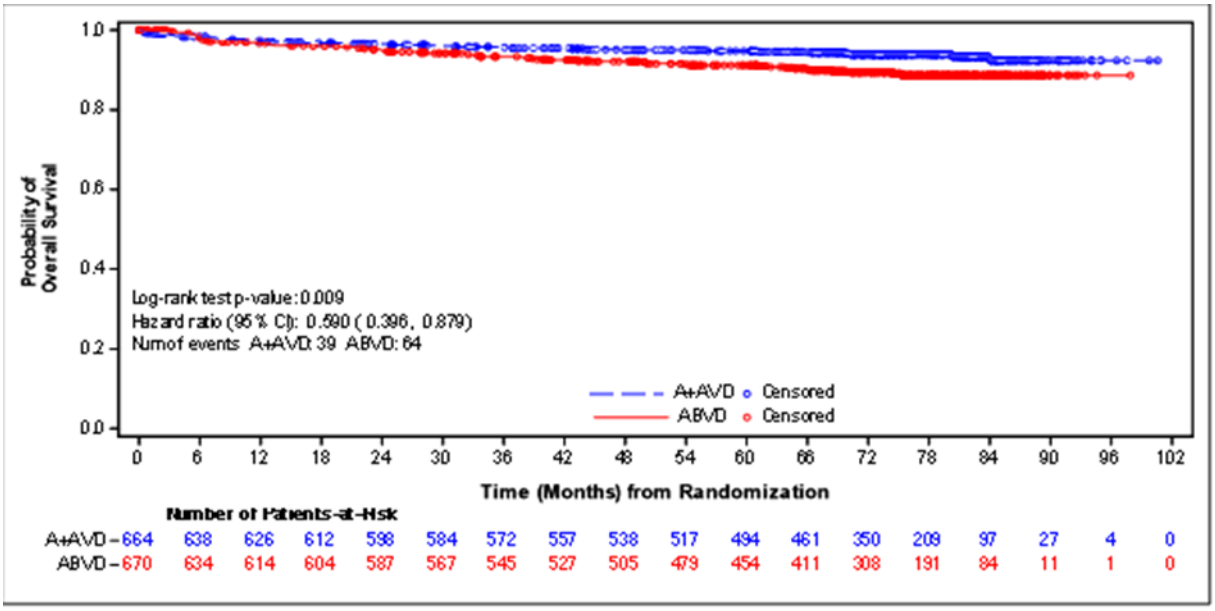
The European Organization for Research and Treatment of Cancer Quality of Life 30-Item Questionnaire (EORTC-QLQ-C30) showed no clinically meaningful difference between the two arms in both the ITT and Stage IV population

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 III and 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)**

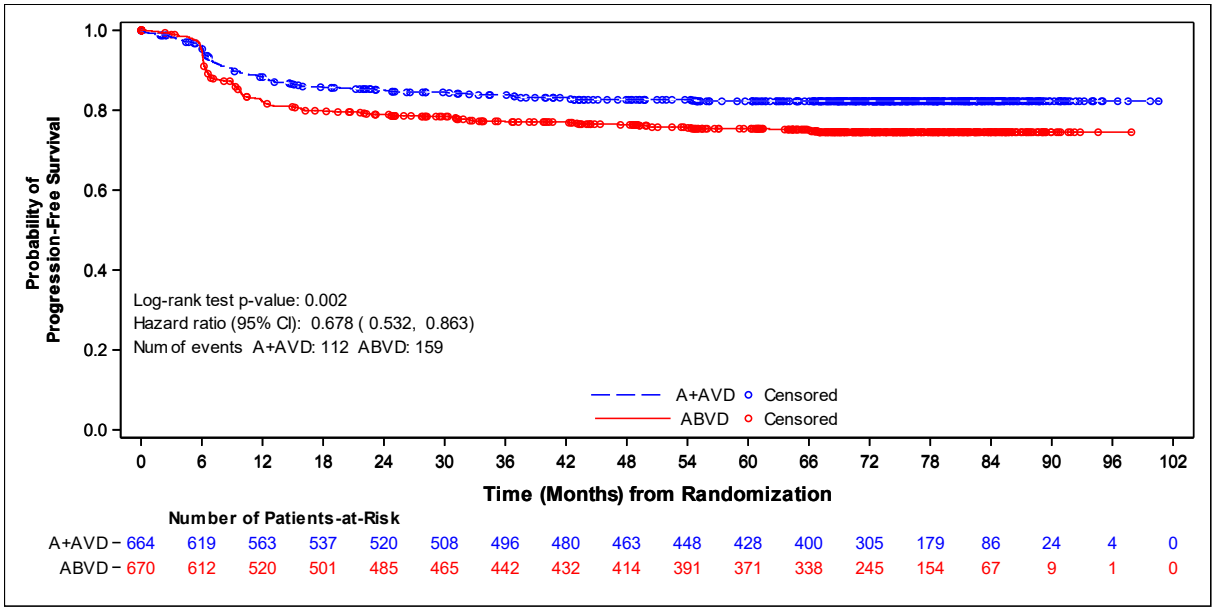



Investigator-determined PFS results showed durable benefit and were consistent with those reported at the time of the primary analysis in both ITT and stage IV populations. PFS was defined as the time from randomization to the sooner of the time of first documentation of PD per investigator or death 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)],

Additionally, with this long term follow-up, PFS per investigator results show a clear benefit in patients with stage III disease, indicating a 40% reduction in the risk of a PFS event per investigator in the ADCETRIS + AVD arm compared with patients treated with ABVD [HR=0.60, 95% CI (0.391-0.93)].

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)**




Study SGN35-005

The efficacy and safety of brentuximab vedotin were evaluated in a randomized, double-blind, placebo-controlled, 2-arm multicenter trial in 329 patients with HL at risk of relapse or progression following ASCT. Patients with known cerebral/meningeal disease, including history of PML were excluded from the study. See Table 9 for patient characteristics. Of the 329 patients, 165 patients were randomized to the treatment arm and 164 patients were randomized to the placebo 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.

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 9: Summary of baseline patient and disease characteristics in the phase3 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 Response | 47 (28%) | 46 (28%) |
| HL Status after the end of frontline standard chemotherapy[b] | | |
| Refractory | 99 (60%) | 97 (59%) |
| Refractory 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 randomization.

Efficacy as of the primary analysis of the primary endpoint results are shown in Table 10. The primary endpoint of PFS per IRF was met and showed a difference in median PFS of 18.8 months in favour of the treatment arm.

**Table 10: Efficacy Results in HL Patients at Increased Risk of Relapse or Progression Following ASCT Treated with 1.8 mg/kg of Brentuximab Vedotin Every 3 Weeks (ITT, primary analysis)**

| | **Brentuximab Vedotin N = 165** | **Placebo 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.

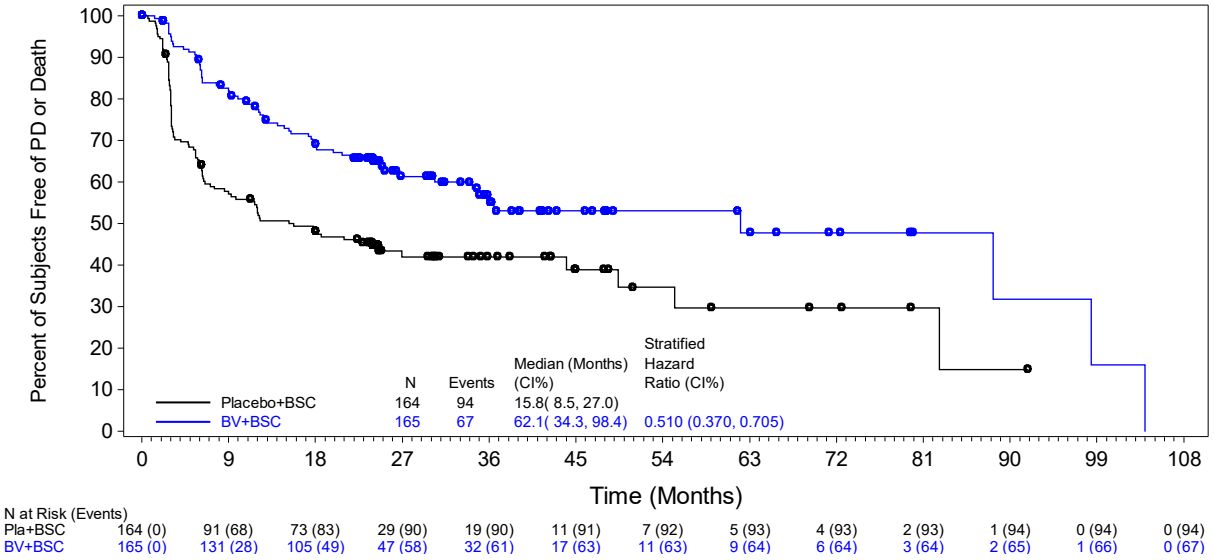
Pre-specified subgroup analyses of PFS per IRF were performed by patients' best response to pre-ASCT salvage therapy, HL status after frontline therapy, age, gender, baseline weight, baseline ECOG performance status, number of treatments pre-ASCT, geographic region, pre-ASCT PET status, B symptom status 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).

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

An updated analysis conducted after 3 years of follow-up showed a sustained PFS improvement per IRF (HR = 0.58 [95% CI (0.41, 0.81)]).

As of study closure, approximately 10 years after enrollment of the first patient, PFS per investigator continued to show a benefit (HR = 0.51 [95% CI (0.37, 0.71)]). Overall survival results were consistent with those reported at the time of primary analysis (HR = 1.11 [95% CI (0.72, 1.70)]).
Figure 5 shows PFS per investigator in the ITT population as of study closure.

**Figure 5: Kaplan-Meier Plot of PFS per investigator (ITT, study closure)**




*Post-hoc Risk Factor Analyses*

Post-hoc analyses were performed for the primary analysis of the primary endpoint to evaluate the impact of increased risk (number of risk factors) on
clinical benefit (Table 11). 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 11: Summary of PFS per IRF and OS by Number of Risk Factors in the Phase 3 HL post-ASCT Study (primary analysis)**

| **Progression Free Survival per IRF** | | | | | | |
|---|---|---|---|---|---|---|
| | **Number of Risk Factors = 1** | | **Number of Risk Factors ≥ 2** | | **Number of Risk Factors ≥ 3** | |
| | **Brentuximab Vedotin N = 21** | **Placebo N = 28** | **Brentuximab Vedotin N = 144** | **Placebo N = 136** | **Brentuximab Vedotin 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 | 1.65 | | 0.49 | | 0.43 | |

| | | | |
|---|---|---|---|
| Hazard Ratio | (95% CI [0.60, 4.55])[b] | (95% CI [0.34, 0.71]) | (95% CI [0.27, 0.68]) |

**Overall Survival**

| | **Number of Risk Factors = 1** | | **Number of Risk Factors ≥ 2** | | **Number of Risk Factors ≥ 3** | |
|---|---|---|---|---|---|---|
| | **Brentuximab Vedotin N = 21** | **Placebo N = 28** | **Brentuximab Vedotin N = 144** | **Placebo N = 136** | **Brentuximab Vedotin 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 6 and 7).

**Figure 6: Kaplan-Meier Plot of PFS per IRF in Patients with ≥ 2 Risk Factors (3-year follow-up)**

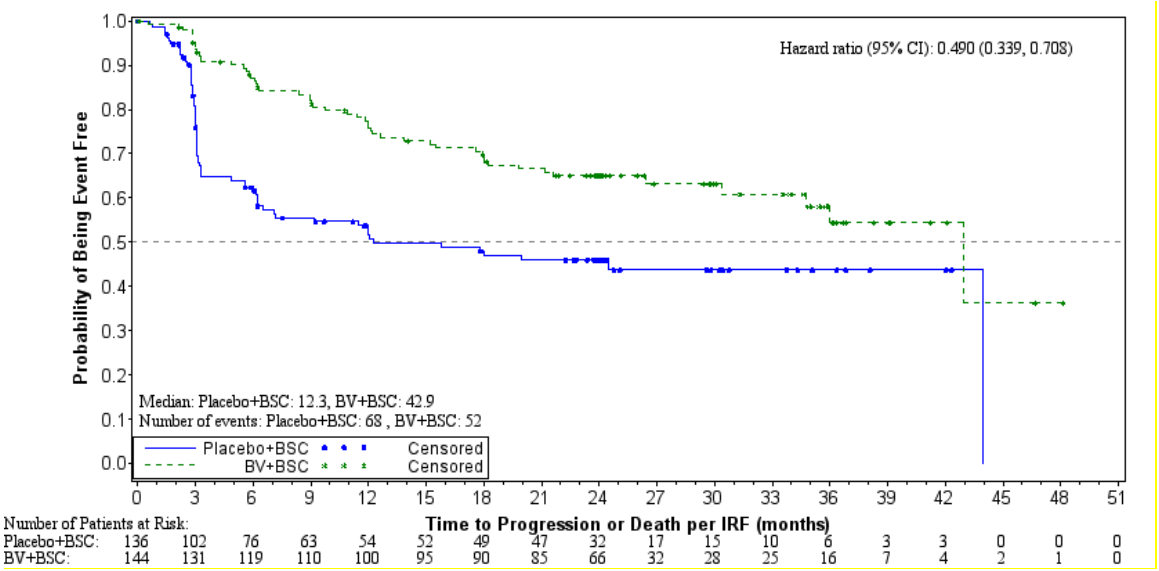
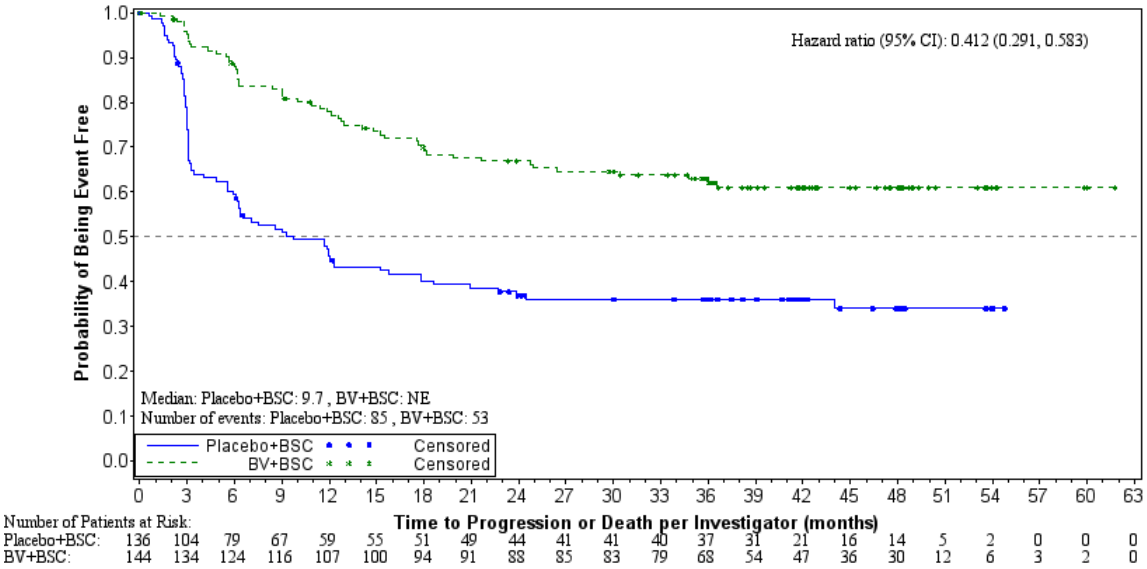


**Figure 7: Kaplan-Meier Plot of PFS per Investigator in Patients with ≥ 2 Risk Factors (3-year follow-up)**




As of study closure, approximately 10 years after enrollment of the first patient, the hazard ratio for PFS per investigator for patients with 2 or more risk factors was 0.41 (95% CI [0.29, 0.58]). The hazard ratio for PFS per investigator for patients with 3 or more risk factors was 0.38 (95% CI [0.25, 0.59]). Overall survival results remained consistent with those observed as of the primary analysis.

Study SG035-0003

The efficacy and safety of ADCETRIS as a single agent was evaluated in a pivotal open-label, single-arm, multicenter study in 102 patients with relapsed or refractory HL. See Table 12 below for a summary of baseline patient and disease characteristics.

**Table 12: 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.

Eighteen (18) patients (18%) received 16 cycles of ADCETRIS; and the median number of cycles received was 9 (ranging from 1 to 16).

Response to treatment with ADCETRIS was assessed by Independent Review Facility (IRF) using the Revised Response Criteria for Malignant Lymphoma (Cheson, 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.
The objective response rate (ORR) per IRF assessment was 75% (76 of 102 patients in the intent-to-treat [ITT] set) and tumour reduction was achieved in 94% of patients. Complete remission (CR) was 33% (34 of 102 patients in the ITT set). The median overall survival (OS) is 40.5 months (the median observation time (time to death or last contact) from first dose was 35.1 months (range 1.8 to 72.9+ months). The estimated overall survival rate at 5 years was 41% (95% CI [31%, 51%]). The investigator assessments were generally consistent with the independent review of the scans. Of the patients treated, 8 responding patients went on to receive an allogeneic SCT. For further efficacy results see Table 13.

**Table 13: Efficacy results in relapsed or refractory Hodgkin lymphoma patients treated with 1.8 mg/kg of ADCETRIS every 3 weeks**

| **Best clinical response (n = 102)** | **IRF n (%)** | **95% CI** |
|---|---|---|
| Objective response rate (CR + PR) | 76 (75) | 64.9, 82.6 |
| Complete remission (CR) | 34 (33) | 24.3, 43.4 |
| Partial remission (PR) | 42 (41) | NA |
| Disease control rate (CR + PR + SD) | 98 (96) | 90.3, 98.9 |
| **Duration of response** | **Median per IRF** | **95% CI** |
| Objective response rate (CR + PR) [a] | 6.7 months | 3.6, 14.8 |
| Complete remission (CR) | 27.9 months | 10.8, NE[b] |
| **Overall survival** | | **95% CI** |
| Median | 40.5 months | 28.7, 61.9 |
| Estimated 5-year OS Rate | 41% | 31%, 51% |

a. The range of DOR was 1.2+ months to 43+ months and the median follow-up time from first dose for patients who achieved objective response (OR) per IRF was 9.0 months.

b. Not estimable.

An exploratory intra-patient analysis showed that approximately 64% of the HL patients treated with ADCETRIS 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.

Of the 35 patients (33%) who had B symptoms at baseline, 27 patients (77%) experienced resolution of all B symptoms at a median time of 0.7 months from initiation of ADCETRIS.

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

Study-C25007

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 ADCETRIS were not considered candidates for SCT or multiagent chemotherapy. Eligible patients were not to have received a prior SCT. The median number of cycles was 7 (range 1 to 16 cycles). Patients were treated with 1.8 mg/kg of ADCETRIS every 3 weeks.
At the time of the primary analysis of the primary endpoint, per IRF, the objective 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%). Among these 30 patients, the median time to

response, defined as the time from first dose to the soonest of PR or CR, was 6 weeks (range, 5 to 39 weeks). The median time to best overall response, defined as the time from first dose to the clinical best response of CR or PR, was 11 weeks (range, 5 to 60 weeks). Twenty-eight patients (47%) went on to receive SCT after a median of 7 cycles (range, 4 to 16 cycles) of ADCETRIS treatment. The 32 patients (53%) who did not receive subsequent SCT also received ADCETRIS for a median of 7 cycles (range, 1 to 16 cycles).

Of the 60 patients in the study, 49 patients (82%) received > 1 prior cancer-related treatment and 11 patients (18%) received 1 prior cancer-related treatment. Per IRF, the ORR was 51% (95% CI [36%, 66%]) for the patients who had received > 1 prior cancer-related treatment and 45% (95% CI [17%, 77%]) for the patients who had received 1 prior cancer-related treatment. For the patients who received > 1 prior cancer-related treatment, a best overall response of CR was reported for 6 patients (12%); PR was reported for 19 patients (39%). For the patients who received 1 prior cancer-related treatment, CR was reported for 1 patient (9%) and PR was reported for 4 patients (36%). Out of the 49 patients receiving > 1 line of prior treatment, 22 patients (45%) received subsequent SCT; of the 11 patients who had received 1 prior treatment, 6 patients (55%) received subsequent SCT.

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 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.

Study SGN35-006 (Retreatment Study)

The efficacy of retreatment in patients who had previously responded (CR or PR) to treatment with brentuximab vedotin 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 brentuximab vedotin 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.

*Systemic anaplastic large cell lymphoma*

Study SGN35-014

The efficacy and safety of ADCETRIS were evaluated in a randomised, double-blind, double-dummy, active-controlled, multicenter trial of 452 patients with previously untreated CD30+ PTCL in combination with cyclophosphamide [C], doxorubicin [H] and prednisone [P] (CHP). For enrollment, the trial required CD30 expression ≥10% per immunohistochemistry. Only patients with CD30+ PTCLs who were eligible for a cyclophosphamide [C], doxorubicin [H], vincristine [O] and prednisone [P] (CHOP)-based regimen were included. The combination of ADCETRIS + CHP has not been studied in all PTCL subtypes. See Table 13 for enrolled PTCL subtypes. Of the 452 patients, 226 were randomised to treatment with ADCETRIS + CHP and 226 patients were randomised to treatment with CHOP.

Randomisation was stratified by ALK-positive sALCL versus all other subtypes and by the International Prognostic Index (IPI) score. Patients were treated with 1.8 mg/kg of ADCETRIS administered as an intravenous infusion over 30 minutes on day 1 of each 21-day cycle + CHP (cyclophosphamide 750 mg/m$^2$ every 3 weeks by IV infusion; doxorubicin 50 mg/m$^2$ every 3 weeks by IV infusion; and prednisone 100 mg on Days 1 to 5 of each 3-week cycle, orally) for 6 to 8 cycles. 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 14 provides a summary of baseline patient and disease characteristics.

**Table 14: Summary of baseline patient and disease characteristics in the phase 3 previously untreated PTCL study (ITT and sALCL)**

| | **ITT Population** | | **sALCL Population[b]** | |
|---|---|---|---|---|
| **Patient characteristics** | **ADCETRIS + CHP n=226** | **CHOP n=226** | **ADCETRIS + CHP n=162** | **CHOP n=154** |
| Median age (range) | 58.0 (18-85) | 58.0 (18-83) | 55.0 (18-85) | 54.0 (18-83) |
| Patients ≥ 65 years old (%) | 69 (31) | 70 (31) | 38 (23) | 36 (23) |
| Male sex, n (%) | 133 (59) | 151 (67) | 95 (59) | 110 (71) |
| ECOG status, n (%) | | | | |
| 0 | 84 (37) | 93 (41) | 58 (36) | 53 (34) |
| 1 | 90 (40) | 86 (38) | 62 (38) | 61 (40) |
| 2 | 51 (23) | 47 (21) | 41 (25) | 40 (26) |
| **Disease characteristics** | | | | |
| Diagnosis, per local assessment, n (%)[a] | | | | |
| sALCL | 162 (72) | 154 (68) | 162 (100) | 154 (100) |
| ALK-positive | 49 (22) | 49 (22) | 49 (30) | 49 (32) |
| ALK-negative | 113 (50) | 105 (46) | 113 (70) | 105 (68) |
| Peripheral T-cell lymphoma (PTCL-NOS) | 29 (13) | 43 (19) | NA | NA |
| Angioimmunoblastic T-cell lymphoma (AITL) | 30 (13) | 24 (11) | NA | NA |
| Adult T-cell leukemia/lymphoma (ATLL) | 4 (2) | 3 (1) | NA | NA |
| Enteropathy-associated T-cell lymphoma (EATL) | 1 (0) | 2 (1) | NA | NA |
| Median time from diagnosis to first dose, months (range) | 0.8 (0, 19) | 0.9 (0, 10) | 0.8 (0, 19) | 0.9 (0, 10) |
| Disease stage at initial diagnosis of PTCL, n (%) | | | | |
| Stage I | 12 (5) | 9 (4) | 12 (7) | 7 (5) |
| Stage II | 30 (13) | 37 (16) | 22 (14) | 27 (18) |
| Stage III | 57 (25) | 67 (30) | 29 (18) | 46 (30) |
| Stage IV | 127 (56) | 113 (50) | 99 (61) | 74 (48) |
| IPI score | | | | |
| 0 | 8 (4) | 16 (7) | 7 (4) | 14 (9) |
| 1 | 45 (20) | 32 (14) | 34 (21) | 18 (12) |
| 2 | 74 (33) | 78 (35) | 58 (36) | 60 (39) |
| 3 | 66 (29) | 66 (29) | 37 (23) | 40 (26) |
| 4 | 29 (13) | 25 (11) | 22 (14) | 16 (10) |
| 5 | 4 (2) | 9 (4) | 4 (2) | 6 (4) |
| Extranodal involvement at time of diagnosis, n (%) | | | | |

| | | | | |
|---|---|---|---|---|
| ≤ 1 site | 142 (63) | 146 (65) | 94 (58) | 95 (62) |
| >1 site | 84 (37) | 80 (35) | 68 (42) | 59 (38) |
| Baseline bone marrow biopsy-lymphoma involvement, n (%) | | | | |
| Yes | 30 (13) | 34 (15) | 15 (9) | 13 (8) |
| No | 196 (87) | 192 (85) | 147 (91) | 141 (92) |

[a.] As per the 2008 WHO classification.
[b.] For patients with locally-diagnosed sALCL.

The primary endpoint in SGN35-014 was PFS per IRF, defined as the time from the date of randomisation 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 mobilising 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.

Key secondary endpoints included PFS per IRF for patients 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 which were tested by a fixed sequence testing procedure following the statistical significance of PFS per IRF.

The primary endpoint and alpha-protected, key secondary endpoints, which were evaluated hierarchically, were met. The median PFS per IRF for the ITT population was 48.2 months on the ADCETRIS + 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. For overall survival, the stratified hazard ratio was 0.66 (95% CI: 0.46; 0.95, p=0.024), a 34% reduction in the risk of OS events for ADCETRIS + CHP versus CHOP.

PFS per IRF for patients with centrally-confirmed sALCL was a pre-specified key secondary endpoint. The median PFS per IRF was 55.7 months on the ADCETRIS + CHP arm versus 54.2 months on the CHOP arm. The stratified hazard ratio was 0.59 (95% CI: 0.42; 0.84), compatible with a statistically significant 41% reduction in the risk of PFS events for ADCETRIS + CHP versus CHOP (p-value=0.003), see Figure 8 and Table 15.

Subgroup analyses were performed for patients with locally-diagnosed sALCL. For overall survival, the stratified hazard ratio was 0.54 (95% CI: 0.34; 0.87), a 46% reduction in the risk of OS events for ADCETRIS + CHP versus CHOP, see Figure 9. At the end of treatment, the CR rate by IRF assessment was 71.0% for patients on the ADCETRIS + CHP arm compared with 53.2% for patients on the CHOP arm with a difference of 17.7% (95% CI: 7.2%; 28.3%). At the end of treatment, the ORR rate by IRF assessment was 87.7% for patients on the ADCETRIS + CHP arm compared with 70.8% for patients on the CHOP arm with a difference of 16.9% (95% CI: 8.1%; 25.7%). In the subgroup of patients with ALK+ sALCL and ALK- sALCL the stratified hazard ratio for PFS per IRF was 0.29 (95% CI: 0.11; 0.79) and 0.65 (95% CI: 0.44; 0.95), respectively.

**Table 15: Efficacy results in patients with previously untreated sALCL with 1.8 mg/kg of ADCETRIS on day 1 of a 3-week cycle**

| | **ADCETRIS + CHP n=162[a]** | **CHOP n=154[a]** |
|---|---|---|
| **PFS per IRF** | | |
| Number of patients with a PFS event, n (%) | 56 (34) | 73 (48) |
| Median PFS, months (95% CI) | 55.66 (48.20, NE) | 54.18 (13.44, NE) |
| Hazard ratio (95% CI)[b] | 0.59 (0.42, 0.84) | |
| p-value[c] | 0.0031 | |
| **Estimated PFS (95% CI)[d] at:** | | |

| | | |
|---|---|---|
| 6 months | 88.0%<br>(81.8%, 92.2%) | 68.4%<br>(60.3%, 75.2%) |
| 12 months | 78.7%<br>(71.4%, 84.4%) | 60.3%<br>(51.9%, 67.6%) |
| 24 months | 68.4%<br>(60.4%, 75.2%) | 53.9%<br>(45.5%, 61.5%) |
| 36 months | 65.5%<br>(57.1%, 72.7%) | 50.2%<br>(41.6%, 58.1%) |
| **OS**[e] | | |
| Number of deaths (%) | 29 (18) | 44 (29) |
| Median OS, months (95% CI) | NE (NE, NE) | NE (NE, NE) |
| Hazard ratio (95% CI)[b] | 0.54 (0.34, 0.87) | |
| p-valuec, [f] | 0.0096 | |
| **CR Rate**[g] | | |
| % (95% CI) | 71% (63.3%, 77.8%) | 53% (45.0%, 61.3%) |
| p-value[f, h] | 0.0004 | |
| **ORR**[g] | | |
| % (95% CI) | 88% (81.6%, 92.3%) | 71% (62.9%, 77.8%) |
| p-value[f, h] | <0.0001 | |

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

[a] PFS per IRF is calculated using patients with centrally-confirmed sALCL, with n=163 patients in A+CHP arm and n=151 in CHOP arm. OS, CR, and ORR are calculated using patients with locally-diagnosed sALCL

[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 favours A+CHP arm.

[c] p-value is calculated using a stratified log-rank test.

[d] PFS rate is estimated using Kaplan-Meier methods and 95% CI is calculated using the complementary log-log transformation method.

[e] Median OS follow-up in the A+CHP arm was 38.5 months; in the CHOP arm was 41.0 months.

[f] p-value is not adjusted for multiplicity.

[g] Response per 2007 International Working Group Criteria at end of treatment.

[h] p-value is calculated using a stratified Cochran-Mantel-Haenszel test.

**Figure 8: Progression-free survival per IRF in the sALCL population (ADCETRIS + CHP vs. CHOP)** (primary analysis)

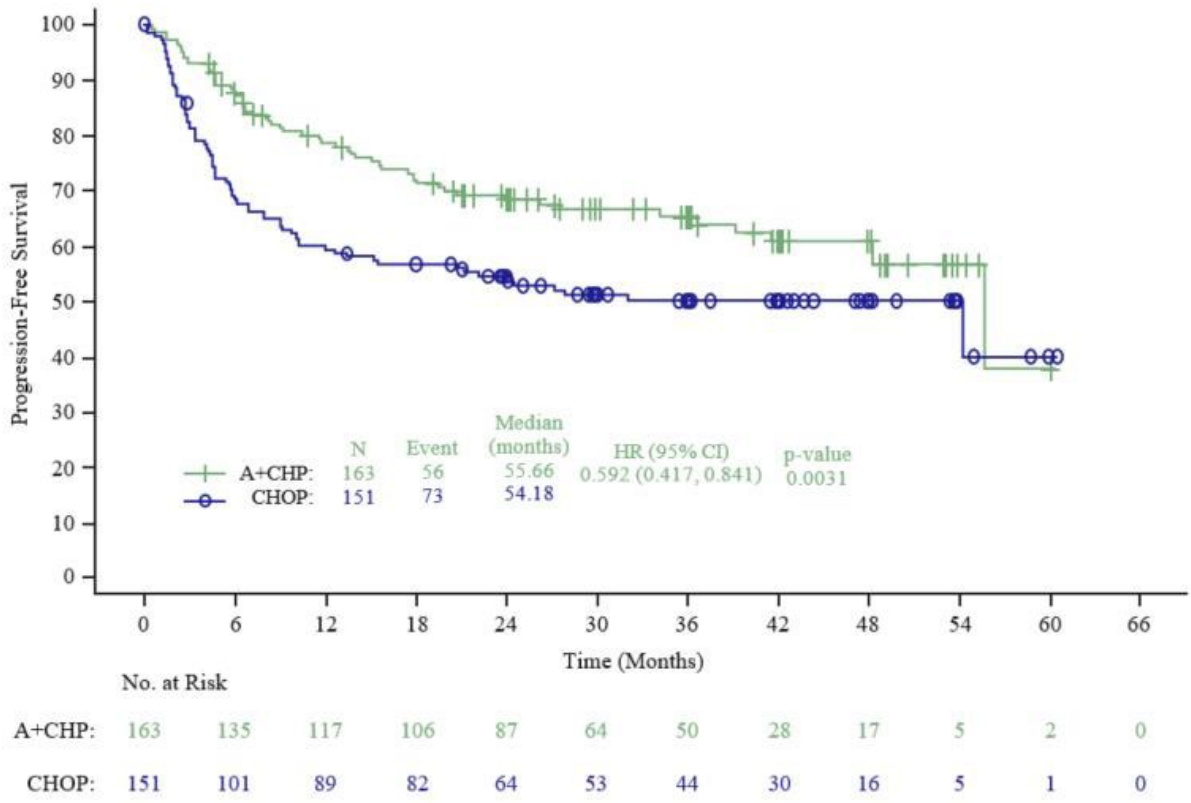


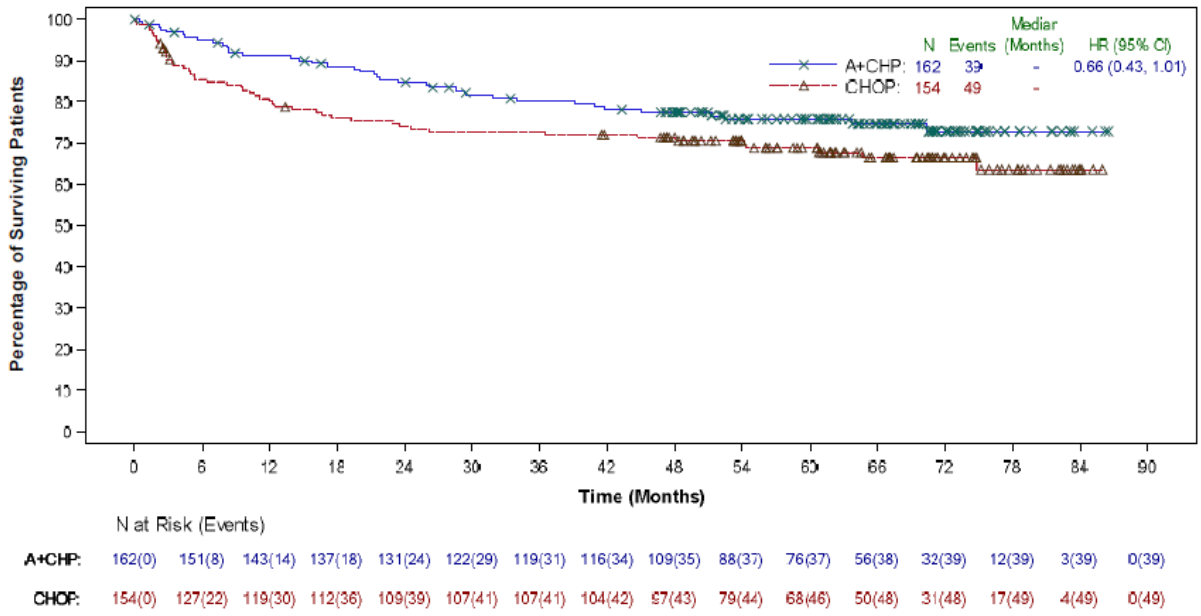

**Figure 9: Overall survival in the sALCL population (ADCETRIS + CHP vs. CHOP)** (primary analysis)

*p-value for overall survival is not adjusted for multiplicity.

As of study closure more than 7 years after enrollment of the first patient, PFS per investigator results in the ITT population indicated a 30% reduction in the risk of a PFS event in the ADCETRIS+CHP arm compared with patients treated with CHOP (HR = 0.70 [95% CI (0.53, 0.91)]). PFS per investigator results in the sALCL population indicated a 45% reduction in the risk of a PFS event in the ADCETRIS+CHP arm compared with patients treated with CHOP (HR = 0.55 [95% CI (0.39, 0.79)]).

As of study closure, overall survival results continued to show a benefit and were consistent with those reported at the time of the primary analysis. Overall survival results in the ITT population indicated a 28% reduction in the risk of death in the ADCETRIS+CHP arm compared with patients treated with CHOP (HR = 0.72 [95% CI (0.53 to 0.99)]). Overall survival results in the sALCL population indicated a 34% reduction in the risk of death in the ADCETRIS+CHP arm compared with patients treated with CHOP (HR = 0.66 [95% CI (0.43, 1.01)]), see Figure 10.

**Figure 10: Overall survival in the sALCL population (ADCETRIS + CHP vs. CHOP) (study closure)**




Study SG035-0004

The efficacy and safety of brentuximab vedotin as a single agent was evaluated in an open-label, single-arm, multicenter study (study SG035-0004) in 58 patients with relapsed or refractory sALCL. See Table 16 below for a summary of baseline patient and disease characteristics.

**Table 16: Summary of baseline patient and disease characteristics in the phase 2 relapsed or refractory sALCL study**

| **Patient characteristics** | **N = 58** |
|---|---|
| Median age, yrs (range) | 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 (range) | 2 (1-6) |
| Histologically confirmed CD30-expressing disease | 57 (98%) |
| Anaplastic lymphoma kinase (ALK)-negative disease | 42 (72%) |
| **Disease characteristics** | |
| Primary Refractory to frontline therapy[b] | 36 (62%) |
| Refractory to most recent therapy | 29 (50%) |
| Relapsed to most recent therapy | 29 (50%) |
| Baseline B symptoms | 17 (29%) |
| Stage III at initial diagnosis | 8 (14%) |
| Stage IV at initial diagnosis | 21 (36%) |

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

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

The median time from initial sALCL diagnosis to first dose with brentuximab vedotin was 16.8 months.

Ten (10) patients (17%) received 16 cycles of brentuximab vedotin; the median number of cycles received was 7 (range, 1 to 16).

Response to treatment with brentuximab vedotin was assessed by Independent Review Facility (IRF) using the Revised Response Criteria for Malignant Lymphoma (Cheson, 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.

The ORR per IRF assessment was 86% (50 of 58 patients in the ITT set). CR was 59% (34 of 58 patients in the ITT set) and tumour reduction was achieved in 97% of patients. The estimated overall survival at 5 years was 60% (95% CI [47%,73%]). The median observation time (time to death or last contact) from first dose was 71.4 months. The investigator assessments were generally consistent with the independent review of the scans. Of the patients treated, 9 responding patients went on to receive an allogeneic stem cell transplant (SCT) and 9 responding patients went on to autologous SCT. For further efficacy results, see Table 17 and Figure 11.

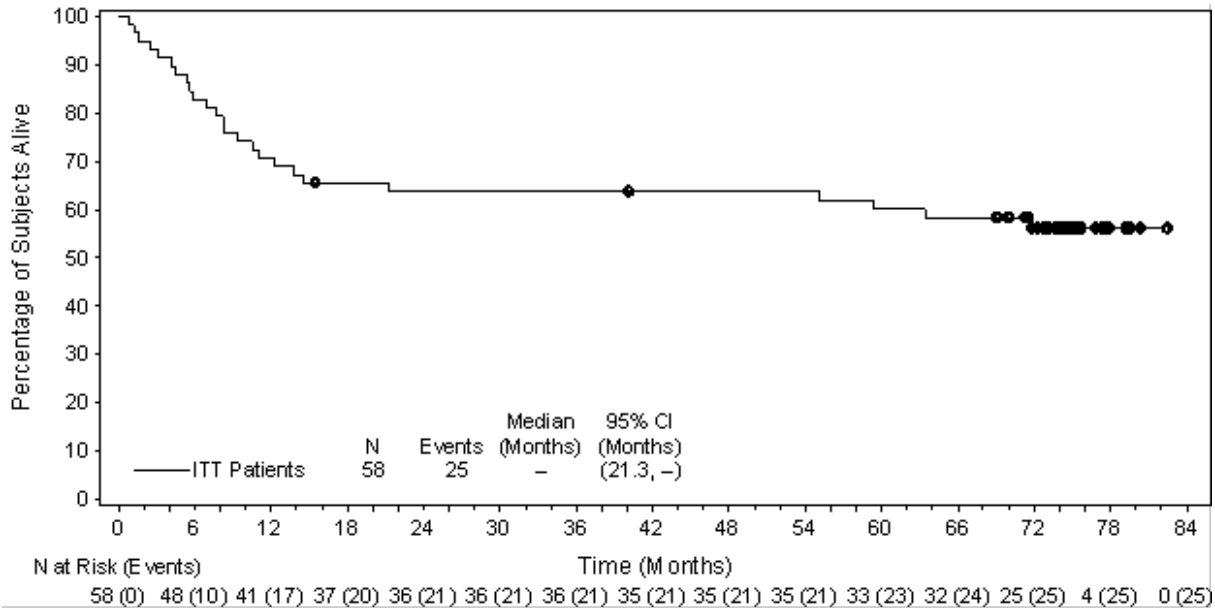
**Table 17: Efficacy results in relapsed or refractory sALCL patients treated with 1.8 mg/kg of brentuximab vedotin every 3 weeks**

| **Best clinical response (n = 58 )** | **IRF n (%)** | **95% CI** |
|---|---|---|
| Objective response rate (CR + PR) | 50 (86) | 74.6, 93.9 |
| Complete remission (CR) | 34 (59) | 44.9, 71.4 |
| Partial remission (PR) | 16 (28) | NA |
| Disease control rate (CR + PR + SD) | 52 (90) | 78.8, 96.1 |
| **Duration of response** | **Median per IRF** | **95% CI** |
| Objective response (CR + PR)[a] | 13.2 | 5.7, 26.3 |
| Complete remission (CR) | 26.3 | 13.2, NE[b] |
| **Progression Free Survival** | **Median per IRF** | **95% CI** |
| Median | 14.6 | 6.9, 20.6 |
| **Overall survival** | **Median** | **95% CI** |
| Median | Not reached | 21.3, NE[b] |

a. The range of DOR was 0.1 months to 39.1+ months and the median follow-up time from first dose for patients who achieved objective response (OR) per IRF was 15.5 months.

b. Not estimable.

**Figure 11: Kaplan-Meier Plot of OS**




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.

Of the 17 patients (29%) who had B symptoms at baseline, 14 patients (82%) experienced resolution of all B symptoms in a median time from initiation of brentuximab vedotin of 0.7 months.

Study C25006

The efficacy and safety of ADCETRIS as a single agent were also evaluated in a phase 4 open-label, single-arm multicenter study in 50 patients with relapsed or refractory sALCL. The ORR per IRF assessment was 64% (32 of 50 patients in the ITT set). The median DOR per IRF was not reached (95% CI 19.71 months, NE). The CR rate was 30% (15 of 50 patients in the ITT set), and tumour reduction (of any degree) was achieved in 93% of evaluable patients. The median DOCR per IRF was not reached (95% CI 10.61 months, NE). Response assessments were generally consistent between IRF and investigator. Of the patients treated, 13 patients went on to receive a haematopoietic stem cell transplant.

Pooled data from studies C25006 and SG035-0004 (N=108) show an ORR per IRF of 76% (82 of 108 patients in the ITT set). The median DOR per IRF was 17.0 months (95% CI 12.62, 32.46). CR was 45% (49 of 108 patients in the ITT set) and tumour reduction (of any degree) was achieved in 96% of evaluable patients. The median DOCR per IRF was 26.3 months (95% CI 16.16, NE). Response assessments per IRF and investigator were generally consistent.

Study SGN35-006 (Retreatment study)

The efficacy of retreatment in patients who had previously responded (CR or PR) to treatment with brentuximab vedotin 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 brentuximab vedotin 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.

*Cutaneous T-cell lymphoma*

Study C25001

The efficacy and safety of ADCETRIS as a single agent was evaluated in a pivotal phase 3, open-label, randomised, multicentre study in 128 patients with histologically confirmed CD30+ CTCL. CD30 positivity was defined as ≥10% target lymphoid cells demonstrating membrane, cytoplasmic, and/or Golgi staining pattern based on an immunohistochemistry assay (Ventana anti-CD30 [Ber-H2]). Patients with a diagnosis of mycosis fungoides [MF] or primary cutaneous anaplastic large cell lymphoma [pcALCL] were considered eligible for the study. Patients were stratified by these disease types and randomised 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 with a concurrent diagnosis of systemic ALCL, Sezary syndrome and other non-Hodgkin lymphoma (except for lymphomatoid papulosis [LyP]) were excluded from this study. 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 18 provides a summary of the baseline patient and disease characteristics.

**Table 18: Summary of baseline patient and disease characteristics in the phase 3 CTCL Study (ITT Population)**

| Patient characteristics | ADCETRIS 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

The most common prior skin directed therapies in the ITT population were radiotherapy (64%), phototherapy (48%) and topical steroids (17%). The most common prior systemic therapies in the ITT population were chemotherapy (71%), immunotherapy (43%) and bexarotene (38%).

The primary endpoint was objective response rate that lasts at least 4 months (ORR4) (duration from first response to last response ≥ 4 months), as determined by an independent review of the Global Response Score (GRS) consisting of skin evaluations (modified severity weighted assessment tool [mSWAT] as assessed per investigator), nodal and visceral radiographic assessment, and detection of circulating Sézary cells (Olsen 2011). Table 19 includes the results for ORR4 and other key secondary endpoints.

**Table 19: Efficacy results in CTCL patients treated with 1.8 mg/kg of ADCETRIS every 3 weeks (ITT population)**

| | ADCETRIS (n = 64) | | Physician's Choice (Methotrexate or Bexarotene) n = 64 |
|---|---|---|---|
| **Objective Response Rate lasting at least 4 months (ORR4) per IRF** | | | |
| n (%) | 36 (56.3) | | 8 (12.5) |
| Percent Difference (95% CI) | | 43.8 (29.1, 58.4) | |
| p-value | | <0.001 | |
| **Complete Response (CR) per IRF** | | | |
| n (%) | 10 (15.6) | | 1 (1.6) |
| Percent Difference (95% CI) | | 14.1 (-4.0, 31.5) | |
| Adjusted p-value[a] | | 0.0046 | |
| **Progression Free Survival (PFS) per IRF** | | | |
| Median (months) | 16.7 | | 3.5 |
| Hazard Ratio | | 0.270 | |
| 95% CI | | (0.17, 0.43) | |
| Adjusted p-value[a] | | <0.001 | |

[a] Calculated from a weighted Holm's procedure

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

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

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

*Paediatric population*

Combination therapy

C25004

The safety and anti-tumour activity of ADCETRIS were evaluated in an open-label, multicenter trial in 59 paediatric patients (6-17 years of age) with previously untreated stage III or IV classical CD30+ HL in combination with chemotherapy (doxorubicin [A], vinblastine [V] and dacarbazine [D] [AVD]). All patients had a histologically confirmed CD30-expressing disease. Fifty-nine percent of patients (n = 35) had extranodal site involvement. All 59 paediatric patients were treated on days 1 and 15 of each 28-day cycle with 48 mg/m2 of ADCETRIS administered as an intravenous infusion over 30 minutes + doxorubicin 25 mg/m2, vinblastine 6 mg/m2, and dacarbazine 375 mg/m2. The BSA-based dose of ADCETRIS was chosen to match the observed PK exposures in adults in Study C25003. The paediatric maximum tolerated dose (MTD) was not reached. The majority of patients (88%) achieved an objective response by IRF assessment at the EOT, with 76% achieving a CR. No patient died. A total of 13 patients (22%) in the safety population were reported to have received irradiation after Cycle 6.

Monotherapy
C25002

The safety, pharmacokinetics and anti-tumour activity of ADCETRIS in 36 paediatric patients (7-17 years of age) with r/r HL and sALCL (children aged 7-11 years, n = 12 and adolescents aged 12 to 17 years, n = 24) were evaluated in a phase 1/2 open-label, single-agent, multicentre dose-escalation study (C25002). Phase 1 of the study assessed the safety profile (see section 4.8), determined the paediatric maximum tolerated dose (MTD) and/or recommended phase 2 dose (RP2D), and assessed the pharmacokinetics of ADCETRIS (see section 5.2). Phase 1 included 3 r/r HL patients treated at 1.4 mg/kg and 9 patients (7 r/r HL and 2 sALCL) treated at 1.8 mg/kg. The MTD was not reached. The RP2D was determined to be 1.8 mg/kg. Across the study, a total of 16 patients with r/r HL and 17 patients with r/r sALCL, of whom 10 were in first relapse, were treated with 1.8 mg/kg of ADCETRIS. The best overall response rate (ORR) per independent review facility (IRF) was analysed across both study phases at the RP2D. Of these 33 patients who received the RP2D, 32 were evaluable for response. The ORR was 47% in response-evaluable patients with r/r HL, 53% in patients with r/r sALCL and 60% in sALCL patients in first relapse. Eight HL patients and 9 sALCL patients went on to receive SCT following treatment with ADCETRIS.

## 5.2 Pharmacokinetic properties

Monotherapy

The pharmacokinetics of brentuximab vedotin were evaluated in phase 1 studies and in a population pharmacokinetic analysis of data from 314 patients. In all clinical trials, brentuximab vedotin was administered as an intravenous infusion.

Maximum concentrations of brentuximab vedotin ADC were typically observed at the end of infusion or the sampling timepoint 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. Minimal to no accumulation of ADC was observed with multiple doses at the every 3-week schedule, consistent with the terminal half-life estimate. Typical $C_{max}$ and AUC of ADC after a single 1.8 mg/kg in a phase 1 study was approximately 31.98 µg/ml and 79.41 µg/ml x day respectively.

MMAE is the major metabolite of brentuximab vedotin. Median $C_{max}$, AUC and $T_{max}$ of MMAE after a single 1.8 mg/kg of the ADC in a phase 1 study was approximately 4.97 ng/ml, 37.03 ng/ml x day and 2.09 days respectively. MMAE exposures decreased after multiple doses of brentuximab vedotin with approximately 50% to 80% of the exposure of the first dose being observed at subsequent doses. MMAE is further metabolized mainly to an equally potent metabolite; however, its exposure is an order of magnitude lower than that of MMAE. Thus, it is not likely to have any substantial contribution to the systemic effects of MMAE.

In the first cycle, higher MMAE exposure was associated with an absolute decrease in neutrophil count.

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 brentuximab vedotin every two weeks, maximal serum concentrations of ADC were observed near the end of the infusion and elimination exhibited a multi-exponential 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 brentuximab vedotin 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.

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 medicines. *In vitro*, MMAE was a substrate of P-gp and was not an inhibitor of P-gp at clinical concentrations.

In humans, the mean steady state volume of distribution was approximately 6-10 L for ADC. Based on population PK estimation the typical apparent volume of distribution of MMAE was 35.5 L.

Metabolism

The ADC is expected to be catabolised as a protein with component amino acids recycled or eliminated.

*In vivo* data in animals and humans suggest that only a small fraction of MMAE released from brentuximab vedotin is metabolized. The levels of MMAE metabolites have not been measured in human plasma. At least one metabolite of MMAE has been shown to be active *in vitro.*

MMAE is a substrate of CYP3A4 and possibly CYP2D6. *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 only CYP3A4/5 at concentrations much higher than was achieved during clinical application. MMAE does not inhibit other isoforms.

MMAE did not induce any major CYP450 enzymes in primary cultures of human hepatocytes.

Elimination

The ADC is eliminated by catabolism with a typical estimated CL and half life of 1.5 L/day and 4-6 days respectively.

The elimination of MMAE was limited by its rate of release from ADC, typical apparent CL and half life of MMAE was 19.99 L/day and 3-4 days respectively.

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

Pharmacokinetics in special populations

Population PK analysis showed that baseline serum albumin concentration was a significant covariate of MMAE clearance. The analysis indicated that MMAE clearance was 2-fold lower in patients with low serum albumin concentrations <3.0 g/dL compared with patients with serum albumin concentrations within the normal range.

*Hepatic impairment*

A study evaluated the PK of brentuximab vedotin 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 (90% CI 1.27-4.12 fold) in patients with hepatic impairment.

*Renal impairment*

A study evaluated the PK of brentuximab vedotin 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 (90% CI 0.85-4.21 fold) in patients with severe renal impairment (creatinine clearance < 30 ml/min). No effect was observed in patients with mild or moderate renal impairment.

*Elderly*

The population pharmacokinetics of brentuximab vedotin 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.

*Paediatric population*
Monotherapy
C25002

The pharmacokinetics of brentuximab vedotin ADC and MMAE following a 30-minute intravenous infusion of BV administered at 1.4 mg/kg or 1.8 mg/kg given every 3 weeks were evaluated in a phase 1/2 clinical trial of 36 paediatric patients (7-17 years of age) with r/r HL and sALCL (children aged 7-11 years, n = 12 and adolescents aged 12 to 17 years, n = 24) (see section 5.1). The $C_{max}$ of ADC was typically observed at the end of infusion or the sampling closest to the end of infusion. A multi-exponential decline in ADC serum concentrations was observed with a terminal half-life of approximately 4 to 5 days. Exposures were approximately dose proportional with a trend observed for lower ADC exposures at lower ages/ body weights in the study population.
Median ADC AUC in children and adolescents from this study was approx. 14% and 3% lower than in adult patients, respectively, while MMAE exposures were 53% lower and 13% higher, respectively, than in adult patients. Median $C_{max}$ and AUC of ADC after a single 1.8 mg/kg dose were 29.8 µg/ mL and 67.9 µg*day/ mL, respectively, in patients < 12 years of age and 34.4 µg/mL and 77.8 µg*day/mL, respectively, in patients ≥ 12 years of age. Median $C_{max}$, AUC, and $T_{max}$ of MMAE after a single 1.8 mg/kg dose were 3.73 ng/mL, 17.3 ng*day/mL, and 1.92 days, respectively, in patients < 12 years of age and 6.33 ng/mL, 42.3 ng*day/mL, and 1.82 days, respectively, in patients ≥ 12 years of age. There was a trend of increased clearance of brentuximab vedotin in paediatric patients confirmed positive for ADAs. No patients aged < 12 years (0 of 11) and 2 patients aged ≥ 12 years (2 of 23) became persistently ADA positive.

Combination therapy
C25004

The pharmacokinetics of brentuximab vedotin ADC and MMAE following a 30-minute intravenous infusion of BV administered at 48 mg/m2 every 2 weeks in combination with doxorubicin, vinblastine, and dacarbazine (AVD) were evaluated in a phase 1/2 clinical trial of 59 paediatric patients (6-17 years of age) with stage III or IV newly diagnosed CD30+ classical Hodgkin lymphoma (children aged 6-11 years, n = 11 and adolescents aged 12 to 17 years, n = 48). The Cmax of ADC occurred in serum approximately at the end of infusion and declined in a multiexponential manner with a terminal half-life of approximately 4 days. The Cmax of MMAE occurred in plasma approximately 2 days following BV administration with a half-life of approximately 2 days. Geometric mean Cmax and AUC of ADC following a single 48 mg/m2 dose were 22.5 µg/mL and 46.7 µg*day/mL, respectively. Geometric mean Cmax and AUC of MMAE following a single 48 mg/m2 dose were 4.9 ng/mL and 27.2 ng*day/mL, respectively. Similar ADC exposures were achieved following body surface area-based dosing of BV at 48 mg/m2 in combination with AVD among paediatric age groups (< 12 years, 12 – 16 years and > 16 years).

## 5.3 Preclinical safety data

MMAE has been shown to have aneugenic properties in an *in vivo* rat bone marrow micronucleus study. These results were consistent with the pharmacological effect of MMAE on the mitotic apparatus (disruption of the microtubule network) in cells.

The effects of brentuximab vedotin 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 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.
Brentuximab vedotin caused embryo-foetal lethality in pregnant female rats.

In nonclinical studies, lymphoid depletion and reduced thymic weight were observed, consistent with the pharmacologic disruption of microtubules caused by MMAE derived from brentuximab vedotin.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

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

### 6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

### 6.3 Shelf life

Please see expiry date on outer carton.

After reconstitution/dilution, from a microbiological point of view, the product should be used immediately. However, chemical and physical in-use stability has been demonstrated for 24 hours at 2°C-8°C.

### 6.4 Special precautions for storage

Store in a refrigerator (2°C-8°C).

Do not freeze.

Keep the vial in the original carton in order to protect from light.

For storage conditions after reconstitution and dilution of the medicinal product, see section 6.3.

### 6.5 Nature and contents of container

Type I glass vial with a butyl rubber stopper and an aluminium/plastic flip-off seal, containing 50 mg powder.

Pack of 1 vial.

### 6.6 Special precautions for disposal and other handling

General precautions

Procedures for proper handling and disposal of anticancer medicinal products should be considered.

Proper aseptic technique throughout the handling of this medicinal product should be followed.

Instructions for reconstitution

Each single use vial must be reconstituted with 10.5 ml of water for injections to a final concentration of 5 mg/ml. Each vial contains a 10% overfill giving 55 mg of ADCETRIS per vial and a total

reconstituted volume of 11 ml.

1. Direct the stream toward the wall of the vial and not directly at the cake or powder.
2. Gently swirl the vial to aid dissolution. DO NOT SHAKE.
3. The reconstituted solution in the vial is a clear to slightly opalescent, colourless solution with a final pH of 6.6.
4. The reconstituted solution should be inspected visually for any foreign particulate matter and/or discoloration. In the event of either being observed, discard the medicinal product.

Preparation of infusion solution

The appropriate amount of reconstituted ADCETRIS must be withdrawn from the vial(s) and added to an infusion bag containing sodium chloride 9 mg/ml (0.9%) solution for injection in order to achieve a final concentration of 0.4-1.2 mg/ml ADCETRIS. The recommended diluent volume is 150 ml. The already reconstituted ADCETRIS can also be diluted into 5% dextrose for injection or Lactated Ringer's for injection.

Gently invert the bag to mix the solution containing ADCETRIS. DO NOT SHAKE.

Any portion left in the vial, after withdrawal of the volume to be diluted, must be disposed of in accordance with local requirements.

Do not add other medicinal products to the prepared ADCETRIS infusion solution or intravenous infusion set. The infusion line should be flushed following administration with sodium chloride 9 mg/ml (0.9%) solution for injection, 5% dextrose for injection, or Lactated Ringer's for injection.

Following dilution, infuse the ADCETRIS solution immediately at the recommended infusion rate.

Total storage time of the solution from reconstitution to infusion should not exceed 24 hours.

Determining dosage amount:

*Calculation to determine the total ADCETRIS dose (ml) to be further diluted (see section 4.2):*

$$\frac{\text{ADCETRIS dose (mg/kg) x patient's body weight (kg)}}{\text{Reconstituted vial concentration (5 mg/ml)}} = \text{Total ADCETRIS dose (ml) to be further diluted}$$

Note: If patient's weight is more than 100 kg, the dose calculation should use 100 kg. The maximal recommended dose is 180 mg.

*Calculation to determine the total number of ADCETRIS vials needed:*

$$\frac{\text{Total ADCETRIS dose (ml) to be administered}}{\text{Total volume per vial (10 ml/vial)}} = \text{Number of ADCETRIS vials needed}$$

**Table 20: Sample calculations for patients receiving the recommended dose of 1.8 mg/kg, 1.2 mg/kg or 0.9 mg/kg of ADCETRIS for weights ranging from 60 kg to 120 kg[a,b]**

| Recommended dose | Patient weight (kg) | Total dose = patient weight multiplied by recommended dose | Total volume to be diluted[c] = total dose divided by reconstituted vial concentration (5 mg/mL) | Number of vials needed = total volume to be diluted divided by total volume per vial (10 mL/vial) |
|---|---|---|---|---|
| 1.8 mg/kg (up to a maximum of 180 mg) | 60 kg | 108 mg | 21.6 mL | 2.16 vials |
| | 80 kg | 144 mg | 28.8 mL | 2.88 vials |
| | 100 kg | 180 mg | 36 mL | 3.6 vials |
| | 120 kg[d] | 180 mg | 36 mL | 3.6 vials |
| 1.2 mg/kg (up to a maximum of 120 mg) | 60 kg | 72 mg | 14.4 mL | 1.44 vials |
| | 80 kg | 96 mg | 19.2 mL | 1.92 vials |
| | 100 kg | 120 mg | 24 mL | 2.4 vials |
| | 120 kg[d] | 120 mg | 24 mL | 2.4 vials |
| 0.9 mg/kg (up to a maximum of 90 mg) | 60 kg | 54 mg | 10.8 mL | 1.08 vials |
| | 80 kg | 72 mg | 14.4 mL | 1.44 vials |
| | 100 kg | 90 mg | 18 mL | 1.8 vials |
| | 120 kg[d] | 90 mg | 18 mL | 1.8 vials |

a. This table provides sample calculations for adult patients.
b. For paediatric patients studied in clinical trials (6-17 years of age), body surface area-based dosing was calculated as 48 mg/m2 every two weeks in combination with AVD in a 28-day cycle or 72 mg/m2 every three weeks as monotherapy. (See sections 5.1 and 5.2 for information on clinical studies conducted in paediatric patients.)
c. To be diluted in 150 mL of diluent and administered by intravenous infusion over 30 minutes.
d. If patient's weight is more than 100 kg, the dose calculation should use 100 kg.

Disposal

ADCETRIS is for single use only.
Any unused product or waste material should be disposed of in accordance with local requirements

## 7. MARKETING AUTHORISATION HOLDER
Takeda (Thailand ) Ltd , Bangkok , Thailand

## 8. MARKETING AUTHORISATION NUMBER(S)
1C 10/60 (NB)

## 9. DATE OF FIRST AUTHORISATION
27 April 2017

## 10. DATE OF REVISION OF THE TEXT
Feb 2024