PRESCRIBING INFORMATION

1. NAME OF THE MEDICINAL PRODUCT

ADCETRIS 50mg 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

4.1.1 Previously untreated Stage III or IV classical Hodgkin lymphoma (cHL), in combination with chemotherapy.
ADCETRIS is indicated for the frontline treatment of adult patients with previously untreated CD30+ advanced cHL in combination with doxorubicin, vinblastine and dacarbazine (AVD)(see section 5.1).

4.1.2 Hodgkin lymphoma (HL) consolidation.
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).

4.1.3 Relapsed or refractory Hodgkin lymphoma (HL).
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.

4.1.4 Frontline systemic anaplastic large cell lymphoma (sALCL) or other CD30-expressing peripheral T-cell lymphomas (PTCL), in combination with chemotherapy
ADCETRIS is indicated for the treatment of patients with CD30-expressing previously untreated peripheral T-cell lymphoma (PTCL) in combination with chemotherapy

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

4.1.6 CD30+ cutaneous T-cell lymphoma (CTCL)
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
ADCETRIS 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) is recommended for all patients beginning with the first dose (see section 4.4).

Refer to the product insert of chemotherapy agents given in combination with ADCETRIS for frontline treatment of patients with HL.

HL at increased risk of relapse or progression following ASCT
The recommended dose is 1.8 mg/kg administered as an intravenous infusion over 30 minutes every 3 weeks.

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 with relapsed or refractory HL 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).

Frontline PTCL

The recommended dose in combination with chemotherapy (cyclophosphamide [C], doxorubicin [H], and prednisone [P]; [CHP]) is 1.8 mg/kg administered as an intravenous infusion over 30 minutes every 3 weeks for 6 to 8 cycles (See section 5.1).

Primary prophylaxis with growth factor support (G-CSF) is recommended for all patients beginning with the first dose (See section 4.4.)

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

Relapsed or refractory sALCL

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

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

General
Do not administer as an IV push or bolus.

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 below 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 (Monotherapy)**
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 GMCSF in subsequent cycles for patients who develop Grade 3 or 4 neutropenia.

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

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

b Patients who develop Grade 3 or 4 lymphopenia may continue study 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 is recommended for all patients receiving combination therapy beginning with the first dose. Continue with the same dose and schedule. Administer G-CSF prophylaxis for subsequent cycles for patients not receiving primary G-CSF prophylaxis.

G-CSF= granulocyte colony-stimulating factor, GM-CSF= granulocyte macrophage colony-stimulating factor, LLN= lower limit of normal; NCI CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events

a Abbreviated description of CTCAE; grading based on NCI CTCAE v4.03

Peripheral Neuropathy
If peripheral sensory or motor neuropathy emerges or worsens during treatment see Table 3 and Table 4 below 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 for Monotherapy

Severity of Peripheral Sensory or Motor Neuropathy (Signs and Symptoms [abbreviated description of CTCAE*])	**Modification of Dose and Schedule (Monotherapy)**
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 1or baseline, then restart treatment at a reduced dose of 1.2 mg/kg up to a maximum of 120mg every 3 weeks
Grade 3 (interfering with activities of daily living)	Withhold dose until toxicity returns to ⩽ Grade 1 or baseline, then restart treatment at a reduced dose of 1.2 mg/kg up to a maximum of 120mg every 3 weeks
Grade 4 (sensory neuropathy which is disabling or motor neuropathy that is life threatening or leads to paralysis)	Discontinue treatment

*Grading based on 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

Severity of Peripheral Sensory	**Modification of Dose and Schedule (Combination Therapy with AVD)**	**Modification of Dose and Schedule (Combination Therapy with CHP)**

or Motor Neuropathy (Signs and Symptoms [abbreviated description of CTCAE*])		
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 0.9mg/kg up to a maximum of 90mg every 2 weeks	Sensory neuropathy: Continue treatment at same dose level Motor neuropathy: Reduce dose to 1.2 mg/kg up to a maximum of 120 mg every 3 weeks
Grade 3 (interfering with activities of daily living)	Withhold treatment with ADCETRIS until toxicity is $\leqslant$ Grade 2, then restart treatment at a reduced dose of 0.9mg/kg up to a maximum of 90mg every 2 weeks. Consider modifying the dose of other neurotoxic agents as per their product information	Sensory neuropathy: Reduce dose to 1.2 mg/kg up to a maximum of 120 mg every 3 weeks Motor neuropathy: Discontinue treatment
Grade 4 (sensory neuropathy that is disabling or motor neuropathy that is life threatening or leads to paralysis)	Discontinue treatment	Discontinue treatment

*Grading based on NCI Common Terminology Criteria for Adverse Events (CTCAE) v3.0; 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 $\geqslant$ 2.0 mg/dL and/or creatinine clearance or calculated creatinine clearance is $\leqslant$ 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 (up to a maximum of 90 mg) administered as an intravenous

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

- Monotherapy

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

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 children less than 18 years have not yet been established. Currently available data are described in Pharmacokinetics (see section number 5.2).
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.

ADCETRIS must not be administered as an intravenous push or bolus. ADCETRIS 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 ADCETRIS causes pulmonary toxicity.

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 ADCETRIS-treated patients. PML has been reported in patients who received this treatment after receiving multiple prior chemotherapy regimens. PML is a rare

demyelinating disease of the central nervous system that results from reactivation of latent JCV and is often fatal.

Patients should be closely monitored for new or worsening neurological, cognitive, or behavioural signs or symptoms, which may be suggestive of PML. ADCETRIS dosing should be held for any suspected case of PML. Suggested evaluation of PML includes neurology consultation, gadolinium-enhanced magnetic resonance imaging of the brain and cerebrospinal fluid analysis for
JCV DNA by polymerase chain reaction 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. ADCETRIS dosing should be permanently discontinued if a diagnosis of PML is confirmed.

The physician should be particularly alert to symptoms suggestive of PML that the patient may not notice (e.g., cognitive, neurological, or psychiatric symptoms).

Pancreatitis
Acute pancreatitis has been observed in patients treated with ADCETRIS. Fatal outcomes have been reported.
Patients should be closely monitored for new or worsening abdominal pain, which may be suggestive of acute pancreatitis. Patient evaluation may include physical examination, laboratory evaluation for serum amylase and serum lipase, and abdominal imaging, such as ultrasound and other appropriate diagnostic measures. ADCETRIS should be held for any suspected case of acute pancreatitis.
ADCETRIS should be discontinued if a diagnosis of acute pancreatitis is confirmed.

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

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

Infusion-related reactions
Immediate and delayed infusion-related reactions (IRR), as well as anaphylaxis, have been reported. Patients should be carefully monitored during and after infusion. If anaphylaxis occurs, administration of ADCETRIS 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 (acetaminophen), an antihistamine and a corticosteroid.

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

Tumour lysis syndrome

Tumour lysis syndrome (TLS) has been reported with ADCETRIS. 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

ADCETRIS treatment may cause a peripheral neuropathy, both sensory and motor. ADCETRIS-induced peripheral neuropathy is typically an effect of cumulative exposure to this medicinal product and is reversible in most cases. 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 change in dose of ADCETRIS or ADCETRIS discontinuation (see section 4.2). Neuropathy appeared to be mitigated by dose delay or subsequent reduction or ADCETRIS discontinuation.

Haematological toxicities

Grade 3 or Grade 4 anaemia, thrombocytopenia, and prolonged (≥1 week) Grade 3 or Grade 4 neutropenia can occur with ADCETRIS. Complete blood counts should be monitored prior to administration of each dose. If Grade 3 or Grade 4 neutropenia develops, manage as needed by dose modifications or discontinuation (see section 4.2). When ADCETRIS is administered in combination with AVD, primary prophylaxis with G-CSF is recommended for all patients beginning with the first dose. In the treatment of patients with previously untreated PTCL, primary prophylaxis with G-CSF is recommended for all patients beginning with the first dose.

Febrile neutropenia

Febrile neutropenia (fever of unknown origin without clinically or microbiologically documented infection with an absolute neutrophil count $<1.0 \times 10^9$/L, fever ≥38.5°C; ref CTCAE v3) has been reported with treatment with ADCETRIS. 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.

Stevens-Johnson syndrome and Toxic Epidermal Necrolysis

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported with ADCETRIS. Fatal outcomes have been reported. If SJS or TEN occurs, treatment with ADCETRIS 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 ADCETRIS. Some cases of GI perforations were reported in patients with GI

involvement of underlying lymphoma. In the event of new or worsening GI symptoms, perform a prompt diagnostic evaluation and treat appropriately.

Hepatic function

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

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.

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).

Sodium content in excipients

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

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).

4.5 Interaction with other medicinal products and other forms of interaction

CYP3A4 Inhibitors, Inducers and Substrates

Co-administration of ADCETRIS 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 ADCETRIS. Therefore, co-administration of ADCETRIS with strong CYP3A4 and P-gp inhibitors may increase the incidence of neutropenia. If neutropenia develops, refer to Table 1 or Table 2 on dosing recommendations for neutropenia (see section 4.2). Patients who are receiving strong CYP3A4 inhibitors and P-gp inhibitors concomitantly with ADCETRIS should be closely monitored for adverse events.

Co-administration of ADCETRIS with rifampicin, a strong CYP3A4 inducer, did not alter the plasma exposure to ADCETRIS; however it reduced exposure to MMAE by approximately 31%.

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

Doxorubicin, Vinblastine and Dacarbazine

The serum and plasma pharmacokinetic characteristics of ADC and MMAE respectively following administration of ADCETRIS in combination with doxorubicin, vinblastine and dacarbazine were similar to that in monotherapy.

Co-administration of ADCETRIS did not affect the plasma exposure of doxorubicin, vinblastine and dacarbazine.

Cyclophosphamide, Doxorubicin, and Prednisone

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

Bleomycin

There were no formal drug-drug interaction studies with brentuximab vedotin and bleomycin. 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 ADCETRIS and until 6 months after treatment.

Pregnancy

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

ADCETRIS may cause fetal harm when administered to pregnant women; therefore women who are pregnant should not begin treatment with ADCETRIS unless the benefit to the mother outweighs the potential risks to the foetus. If the patient becomes pregnant while taking ADCETRIS, the patient should be clearly advised on the potential risks to the foetus.

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

Breastfeeding

There are no data as to whether ADCETRIS 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, ADCETRIS 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 Adcetris, 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
ADCETRIS may have a minor influence on the ability to drive and use machines.

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 in 482 patients across HL, sALCL and CTCL studies (SG035-0003, SG035-0004, SGN35-005, SGN35-006, C25001 and C25007, see section 5.1) the most frequent adverse reactions (≥10%) were infections, peripheral sensory neuropathy, nausea, fatigue, diarrhoea, pyrexia, upper respiratory tract infection, neutropenia, rash, cough, vomiting, arthralgia, peripheral motor neuropathy, infusion-related reactions, pruritus, constipation, dyspnoea, weight decreased, myalgia and abdominal pain.

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

Adverse reactions 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 the 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 the safety information of chemotherapy agents given in combination with ADCETRIS (doxorubicin, vinblastine and dacarbazine [AVD] or cyclophosphamide, doxorubicin, and prednisone [CHP]), refer to their product information.

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

In patients receiving ADCETRIS combination therapy, serious adverse reactions occurred in 34% of patients. Serious adverse reactions occurring in ≥2% of patients included febrile neutropenia (15%), pyrexia (5%), neutropenia (3%), pneumonia (2%) and sepsis (2%).

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. Additionally, there were more serious adverse events and dose modifications (including dose delays, reductions, and discontinuations) reported in the elderly patient population (⩾65 years of age) in both arms. 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.

Tabulated list of adverse reactions

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

Table 5: Adverse reactions to ADCETRIS

System organ class	**Adverse reactions (monotherapy)**	**Adverse reactions (combination therapy)**

Infections and infestations		
Very common:	Infection[a], upper respiratory tract infection	Infection[a], upper respiratory tract infection
Common:	Herpes zoster, pneumonia, herpes simplex, oral candidiasis	Pneumonia, oral candidiasis, sepsis/septic shock, herpeszoster
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 of lymphatic system disorders		
Very common:	Neutropenia	Neutropenia[a], anemia, febrile neutropenia
Common:	Anaemia, thrombocytopenia	Thrombocytopenia
Uncommon:	Febrile neutropenia	
Immune system disorders		
Uncommon:	Anaphylactic reaction	Anaphylactic transfusion reaction
Metabolism and nutrition disorders		
Very common		Decreased appetite
Common:	Hyperglycaemia	Hyperglycaemia
Uncommon:	Tumour lysis syndrome	Tumour lysis syndrome
Nervous system disorders		
Very common:	Peripheral sensory neuropathy, peripheral motor neuropathy	Peripheral sensory neuropathy, peripheral motor neuropathy[a], dizziness
Common:	Dizziness	
Uncommon:	Demyelinating polyneuropathy	
Respiratory, thoracic and mediastinal disorders		
Very common:	Cough, dyspnoea	Cough, dyspnoea
Gastro-intestinal disorders		
Very common:	Nausea, diarrhoea, vomiting, constipation, abdominal pain	Nausea, constipation, vomiting, diarrhoea, abdominal pain, stomatitis
Uncommon:	Pancreatitis acute	Pancreatitis acute
Hepatobiliary disorders		

Common:	Alanine aminotransferase/aspartate aminotransferase (ALT/AST) increased	Alanine aminotransferase (ALT) increased, Aspartate aminotransferase (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	Steven-Johnson syndrome[b]
Musculoskeletal and connective tissue disorders		
Very common:	Arthralgia, myalgia	Bone pain, arthralgia, myalgia, back pain
Common:	Back pain	
General disorders and administration site conditions		
Very common:	Fatigue, pyrexia, infusion-relation reactions[a]	Fatigue, pyrexia
Common:	Chills	Infusion-related reactions[a], chills
Rare:	Extravasation-related reactions [c]	
Investigations		
Very common:	Weight decreased	Weight decreased
Psychiatric Disorders		
Very common:		Insomnia

[a] Represents pooling of preferred terms.

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

[c] Local reactions including skin redness, pain, swelling, blistering or sloughing.

Description of selected adverse reactions

Neutropenia and febrile neutropenia

- Monotherapy

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

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

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

- Combination Therapy

In the clinical trials of ADCETRIS as combination therapy, neutropenia led to dose delays in 19% of patients. Grade 3 neutropenia was reported in 17% and Grade 4 neutropenia was reported in 41% of patients. Two percent of patients required dose reduction and < 1% discontinued one or more of the study drugs due to neutropenia. Febrile neutropenia was reported in 21% of the patients who did not receive primary prophylaxis with G-CSF (see section 4.2). The frequency of febrile neutropenia was 11% in patients who received primary prophylaxis with G-CSF.

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

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

- Combination Therapy

In the clinical trial of ADCETRIS as combination therapy 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 ADCETRIS using a sensitive electro chemiluminescent immunoassay. There was a higher incidence of infusion-related reactions observed in patients with antibodies to ADCETRIS relative to patients who tested transiently positive or negative.

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

4.9 Overdose
There is no known antidote for overdose of ADCETRIS. 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

Pharmacologic class: CD30-directed antibody-drug conjugate

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

Mechanism of action

ADCETRIS is an antibody drug conjugate (ADC) that delivers an antineoplastic agent that results in apoptotic cell death selectively in CD30-expressing tumour cells. Nonclinical data suggest that the biological activity of ADCETRIS results from a multi-step process. Binding of the ADC to CD30 on the cell surface initiates 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 and sALCL 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 ADCETRIS 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 ADCETRIS, the consistent expression of CD30 throughout the classical HL and sALCL disease and therapeutic spectrums and clinical evidence in two CD30-positive malignancies following multiple lines of treatment provide a biologic rationale for its use in patients with relapsed and refractory classical HL and sALCL with or without prior ASCT. 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 hematologic malignancies were evaluable of the 52 patients who received 1.8 mg/kg of ADCETRIS every 3 weeks as part of a phase 1, single-arm, open-label, multicenter cardiac safety study. The primary objective was to evaluate the effect of ADCETRIS on cardiac ventricular 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 ADCETRIS administered at a dose of 1.8 mg/kg every 3 weeks in patients with CD30-expressing malignancies.

Clinical efficacy

Hodgkin lymphoma

Study C25003

The efficacy and safety of ADCETRIS were evaluated in a randomized, open-label, 2-arm, multicentre trial in 1334 patients with previously untreated advanced classical (cHL) in combination with chemotherapy (doxorubicin [A], vinblastine [V] and dacarbazine [D] [AVD]). All patients had CD30-expressing cHL. Sixty-two percent of patients had extranodal site involvement. Of the 1334 patients, 664 patients were randomized to the ADCETRIS + AVD arm and 670 patients were randomized to the ABVD (doxorubicin [A], bleomycin [B], vinblastine [V] and dacarbazine [D]) arm and stratified by the number of International Prognostic Factor Project (IPFP) risk factors and region. Patients were treated with 1.2

mg/kg of ADCETRIS administered as an intravenous infusion over 30 minutes on days 1 and 15 of each 28-day cycle + 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).

In the ADCETRIS + AVD arm: patients had Stage III (36%) or IV disease (64%), and 62% had extranodal involvement at diagnosis. Most patients were male (57%) and white (84%). The median age was 35 years (range, 18-82); 84 patients (13%) were 60 years or older.
These and other demographics/baseline characteristics were well balanced between the 2 treatment arms.

The primary endpoint in Study C25003 was modified PFS (mPFS) per IRF, defined as time from randomization to progression, death, or evidence of non-complete response (non-CR) after completion of frontline therapy per independent review facility (IRF) followed by subsequent anticancer therapy. The median mPFS by IRF assessment was not estimable for either treatment arm. The results showed a statistically significant improvement in modified PFS for ADCETRIS +AVD, with a 2-sided p-value of 0.035 based on a stratified log-rank test. The stratified hazard ratio was 0.770 (95% CI, 0.603; 0.983), indicating a 23% reduction in the risk of modified PFS events for ADCETRIS +AVD versus ABVD. Table 6 provides the efficacy results for modified PFS.

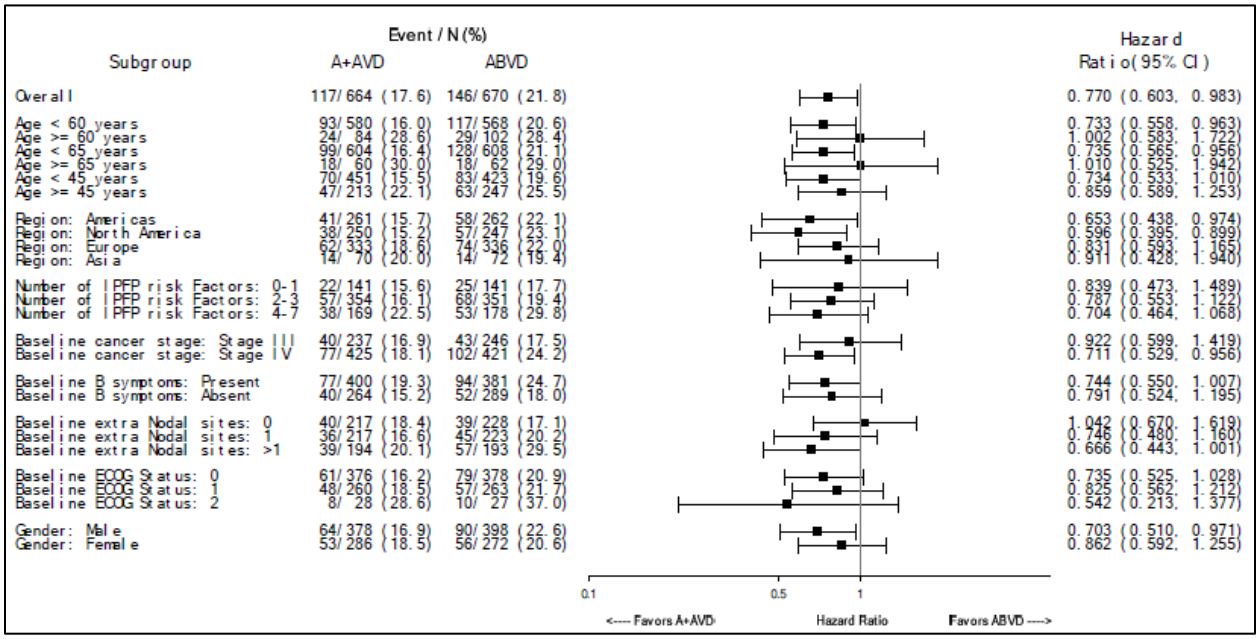
Table 6: Efficacy Results in Previously Untreated Advanced cHL Patients Treated with 1.2mg/kg of ADCETRIS + AVD on Days 1 and 15 of a 28-Day Cycle.

	ADCETRIS + AVD N= 664	ABVD N=670	Stratified Hazard Ratio
	Modified Progression Free Survival (mPFS) Per IRF[a]		
Number of events (%)	117 (18)	146 (22)	0.77 (95% CI [0.60, 098]) Stratified log-rank test p-value= 0.035
Estimated mPFS[a] at 2 Year (5)	82.1 (95% CI [78.8, 85.0])	77.2 (95% CI [73.7, 80.4])	

[a] At the time of analysis, the median follow-up time for both arms was 24.6 months

Pre-specified subgroup analyses of modified PFS per IRF were performed. The analyses showed that efficacy trended consistently in favor of patients who received ADCETRIS + AVD compared with patients who received ABVD for most subgroups, as summarized in Figure 1.

Figure 1: Forest Plot of Hazard Ratio in Modified Progression-Free Survival (mPFS) Per IRF for Subgroup Analyses

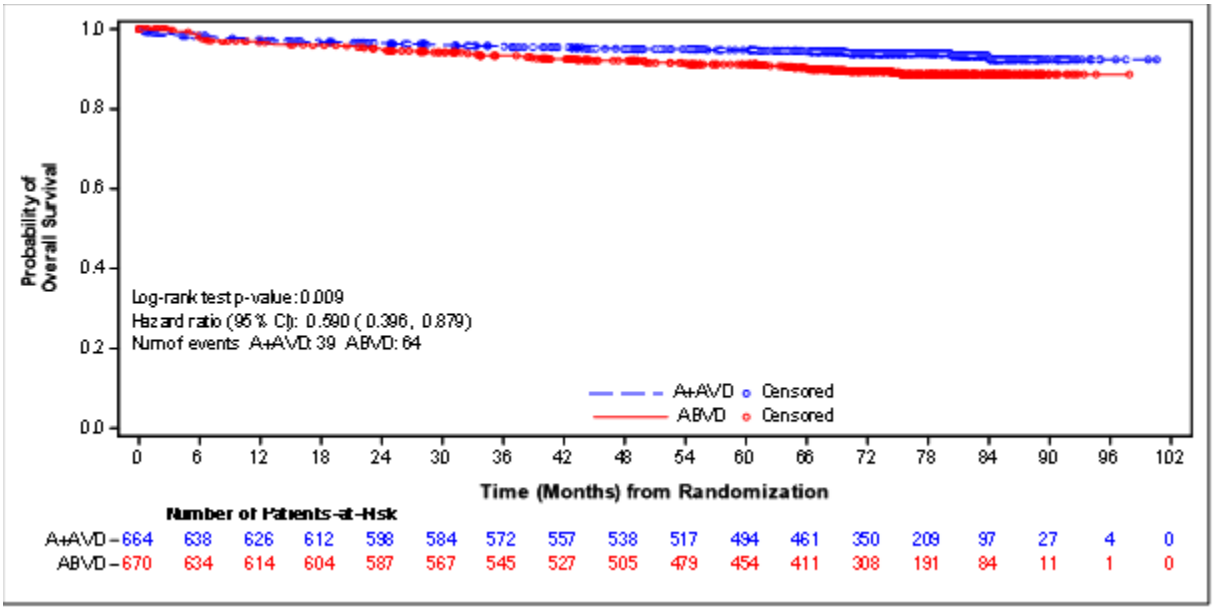


As of a 01 June 2021 cut-off date, approximately 5 years after enrollment of the last patient, the results in the ITT population showed a statistically significant improvement in OS indicating a 41% reduction in the risk of death in the ADCETRIS + AVD arm compared with patients treated with ABVD [HR = 0.59, 95% CI (0.396, 0.879)], see Figure 2.

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

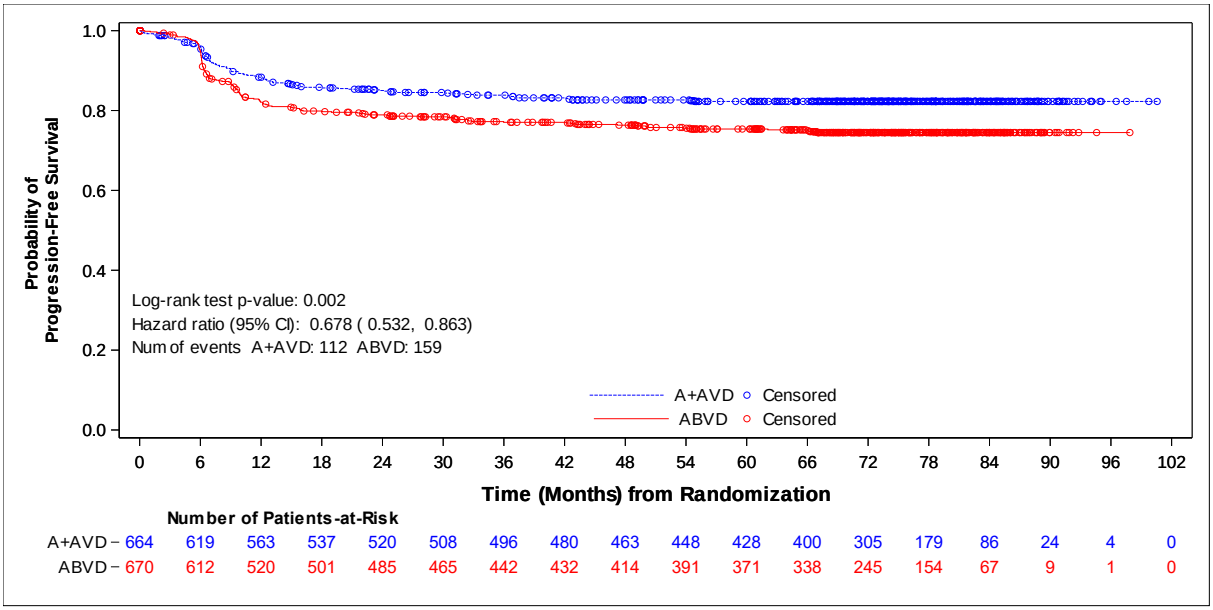


Investigator-determined PFS results showed durable benefit and were consistent with those reported at the time of the primary analysis in both ITT and stage IV populations. PFS was defined as the time from randomization to the sooner of the time of first documentation of PD per investigator or death 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 3. 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 3: 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 ADECETRIS 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 7 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 7: Summary of Baseline Patient and Disease Characteristics in the Phase 3 HL post-ASCT Study

Patient characteristics	**ADCETRIS N = 165**	**Placebo N = 164**
Median age, yrs (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	2 (2-8)	2 (2-7)

regimens (range)		
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.

The efficacy results are shown in Table 8. The primary endpoint of PFS was met and showed a difference in median PFS of 18.8 months in favour of the treatment arm.

Table 8: Efficacy Results in HL Patients at Increased Risk of Relapse or Progression Following ASCT Treated with 1.8 mg/kg of ADCETRIS Every 3 Weeks

	ADCETRIS N = 165	**Placebo N = 164**	**Stratified Hazard Ratio**
Progression Free Survival[a]	**Median per IRF**		
	42.9 months (95% CI [30.4, 42.9])	24.1 months (95% CI [11.5, -])	0.57 (95% CI [0.40, 0.81]) Stratified log-rank test P=0.001
	Median per Investigator		
	Not Reached	15.8 months	0.5

	(95% CI [26.4, -])	(95% CI [8.5, -])	(95% CI [0.36, 0.70])[b]
Overall Survival	**Number of Deaths (%)**		
	28 (17)	25 (15)	1.15 (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 ADCETRIS 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 ADCETRIS 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)]).

Post-hoc Risk Factor Analyses
Post-hoc analyses were performed to evaluate the impact of increased risk (number of risk factors) on clinical benefit (Table 9). 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 9: Summary of PFS per IRF and OS by Number of Risk Factors in the Phase 3 HL post-ASCT Study

Progression Free Survival per IRF

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

[a.] Death without either prior progression or more than one missed assessment visit.

[b.] Indicates results from non-stratified analysis.

[c.] Events are death due to any cause.

At the time of the updated analysis (3 years of follow-up) for patients with 2 or more risk factors, the hazard ratio for PFS per IRF was 0.49 (95% CI [0.34, 0.71]) and the hazard ratio for PFS per investigator was 0.41 (95% CI [0.29, 0.58]) (see Figures 4 and 5).

Figure 4: Kaplan-Meier Plot of PFS per IRF in Patients with ⩾ 2 Risk Factors

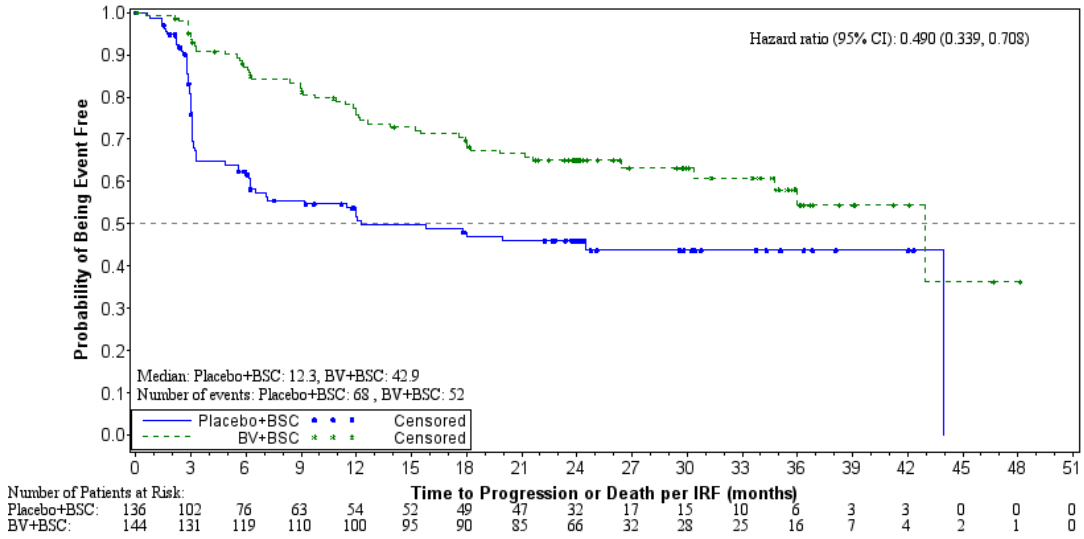
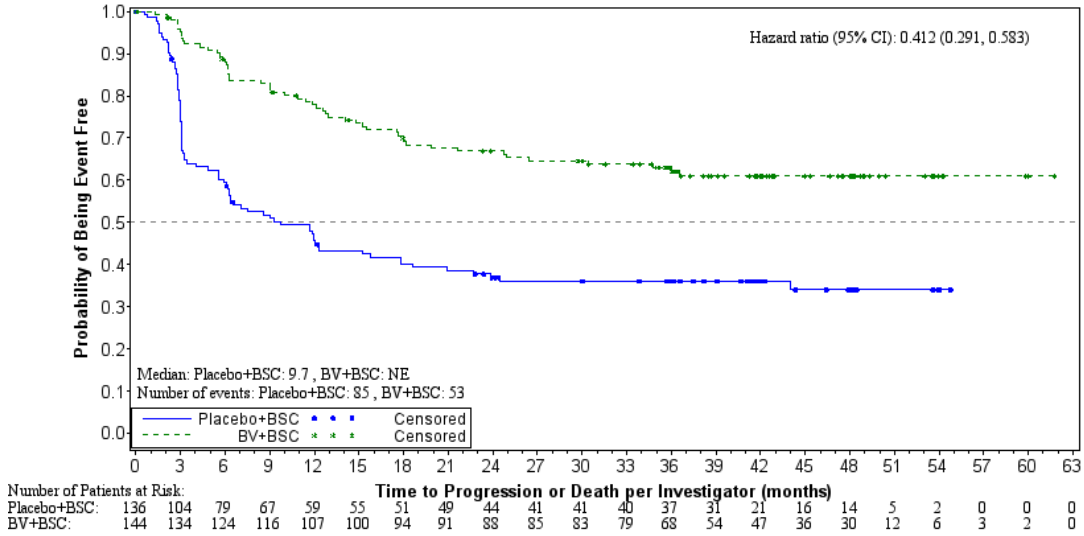


Figure 5: Kaplan-Meier Plot of PFS per Investigator in Patients with ⩾ 2 Risk Factors



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 10 below for a summary of baseline patient and disease characteristics.

Table 10: Summary of baseline patient and disease characteristics in the phase 2 relapsed or refractory
HL study

Patient characteristics	**N = 102**

Median age, yrs (range)	31 years (15-77)
Gender	48M (47%)/54F (53%)
ECOG status 0 1 Prior ASCT Prior chemotherapy Regimens Time from ASCT to first post-transplant relapse Histologically confirmed CD30-expressing disease	 42 (41%) 60 (59%) 102 (100%) 3.5 (1-13) 6.7 mo (0-131) 102 (100%)
Disease characteristics	
Primary Refractory to frontline therapy[a] Refractory to most recent therapy Baseline B symptoms Stage III at initial diagnosis Stage IV at initial diagnosis	72 (71%) 43 (42%) 35 (33%) 27 (26%) 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 11.

Table 11: 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 was1.2+ 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 studies, 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 were collected from patients (n=15) in phase 1 dose escalation and clinical pharmacology studies, and from patients (n=26) in a NPP, with relapsed or refractory HL who had not received an ASCT, and who were treated with 1.8 mg/kg of ADCETRIS every 3 weeks.

Baseline patient characteristics showed failure from multiple prior chemotherapy regimens (median of 3 with a range of 1 to 7) before first administration with ADCETRIS. Fifty nine percent (59%) of patients had advanced stage disease (stage III or IV) at initial diagnosis.

Results from these phase 1 studies and from the NPP experience showed, that in patients with relapsed or refractory HL without prior ASCT, clinically meaningful responses can be achieved as evidenced by an investigator-assessed, objective response rate of 54% and a complete remission rate of 22% after a median of 5 cycles of ADCETRIS.

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. The median number of cycles was 7 (range 1 to 16 cycles). Patients were treated with 1.8 mg/kg of ADECETRIS every 3 weeks. Per IRF, the overall response rate (ORR) in the ITT population was 50% (95% CI, 37; 63%). A best overall response of CR was reported for 7 patients (12%); PR was reported for 23 patients (38%). Twenty eight patients (47%) went on to receive SCT after a median of 7 cycles (range 4 to 16 cycles) of 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). Eleven patients (18%) had received one prior chemotherapeutic regimen. Per IRF, the overall response rate (ORR) in these patients was 45% (95% CI, 17; 77%). A best overall response of CR was reported for 1 patient (9%); PR was reported for 4 patients (36%).

Data were also collected from patients (n=15) in phase 1 dose escalation and clinical pharmacology studies, and from patients (n=26) in a Named Patient Program (NPP), with relapsed or refractory HL who had not received an ASCT, and who were treated with 1.8 mg/kg of ADCETRIS every 3 weeks.

Baseline patient characteristics showed failure from multiple prior chemotherapy regimens (median of 3 with a range of 1 to 7) before first administration with ADCETRIS. Fifty nine percent (59%) of patients had advanced stage disease (stage III or IV) at initial diagnosis.

Results from these phase 1 studies and from the NPP experience showed, that in patients with relapsed or refractory HL without prior ASCT, clinically meaningful responses can be achieved as evidenced by an investigator-assessed, objective response rate of 54% and a complete remission rate of 22% after a median of 5 cycles of ADCETRIS.

Study SGN35-006 (Retreatment Study)

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

Peripheral T-Cell lymphoma

Study SGN35-014

The efficacy and safety of ADCETRIS were evaluated in a randomized, double-blind, double-dummy, active-controlled, multicenter trial of 452 patients with previously untreated PTCL in combination with cyclophosphamide [C], doxorubicin [H], and prednisone [P] (CHP). Of the 452 patients, 226 were randomized to treatment with ADCETRIS + CHP and 226 patients were randomized to treatment with CHOP (cyclophosphamide [C], doxorubicin [H], vincristine [O], and prednisone [P]). Randomization was stratified by ALK-positive sALCL versus all other subtypes and by the International Prognostic Index (IPI) score. Patients were treated with ADCETRIS administered as an intravenous infusion over 30 minutes on Day 1 of each 21-day cycle for 6 to 8 cycles + CHP. The median number of cycles received was 6 (range, 1 to 8 cycles); 70% of patients received 6 cycles of treatment, and 18% received 8 cycles of treatment. Table 12 provides a summary of baseline patient and disease characteristics.

Table 12: Summary of Baseline Patient and Disease Characteristics in the Phase 3 Frontline PTCL Study

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

The primary endpoint in SGN35-014 was PFS per IRF, defined as the time from the date of randomization to the date of first documentation of progressive disease, death due to any cause, or receipt of subsequent anticancer chemotherapy to treat residual or progressive disease, whichever occurs first.

Receipt of post-treatment consolidative radiotherapy, post-treatment chemotherapy for the purpose of mobilizing peripheral blood stem cells, or consolidative autologous or allogeneic stem cell transplant were not considered as disease progression or as having started new anticancer therapy.

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

The primary endpoint and alpha-protected, key secondary endpoints, which were evaluated hierarchically, were met. The median PFS per IRF was 48.2 months on the 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 (Table 13).

Table 13: Efficacy Results in Patients with Previously Untreated PTCL with 1.8 mg/kg of ADCETRIS on Day 1 of a 3-Week Cycle

Primary and Key Secondary Endpoints[a]	**ADCETRIS + CHP N=226**	**CHOP**
PFS per IRF		
Median PFS, months (95% CI)	48.2 (35.2, NE)	20.8 (12.7, 47.6)
Hazard ratio (95% CI)[b]	0.71 (0.54, 0.93)	
P-value[c]	0.0110	
PFS for patients with sALCL		
N	163	151
Number of patients with a PFS event, n (%)	56 (34)	73 (48)
Median PFS, months (95% CI)	55.7 (48.2, NE)	54.2 (13.4, NE)
Hazard ratio (95% CI)[b]	0.59 (0.42, 0.84)	
P-value[c]	0.0031	
OS[d]		
Number of deaths	51 (23)	73 (32)
Median OS, months (95% CI)	NE (NE, NE)	NE (54.2, NE)
Hazard ratio (95% CI)[b]	0.66 (0.46, 0.95)	
P-value[c]	0.0244	
CR Rate[e]		
% (95% CI)	68% (61.2, 73.7)	56% (49.0, 62.3)
P-value[f]	0.0066	
ORR[e]		
% (95% CI)	83% (77.7, 87.8)	72% (65.8, 77.9)
P-value[f]	0.0032	
PFS per investigator[f]		
Median PFS per Investigator, months (95% CI)	*49.8 (41.5, NE)*	*49.8 (41.5, NE)*
Hazard ratio (95% CI)[b]	*0.70 (0.53, 0.92)*	
P-value[c]	*0.0096*	

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

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

b Hazard ratio (A+CHP/CHOP) and 95% confidence intervals are based on a stratified Cox's proportional hazard regression model with stratification factors (ALK-positive sALCL versus all others and International Prognostic Index [IPI] score at baseline). Hazard ratio <1 favors A+CHP arm.

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

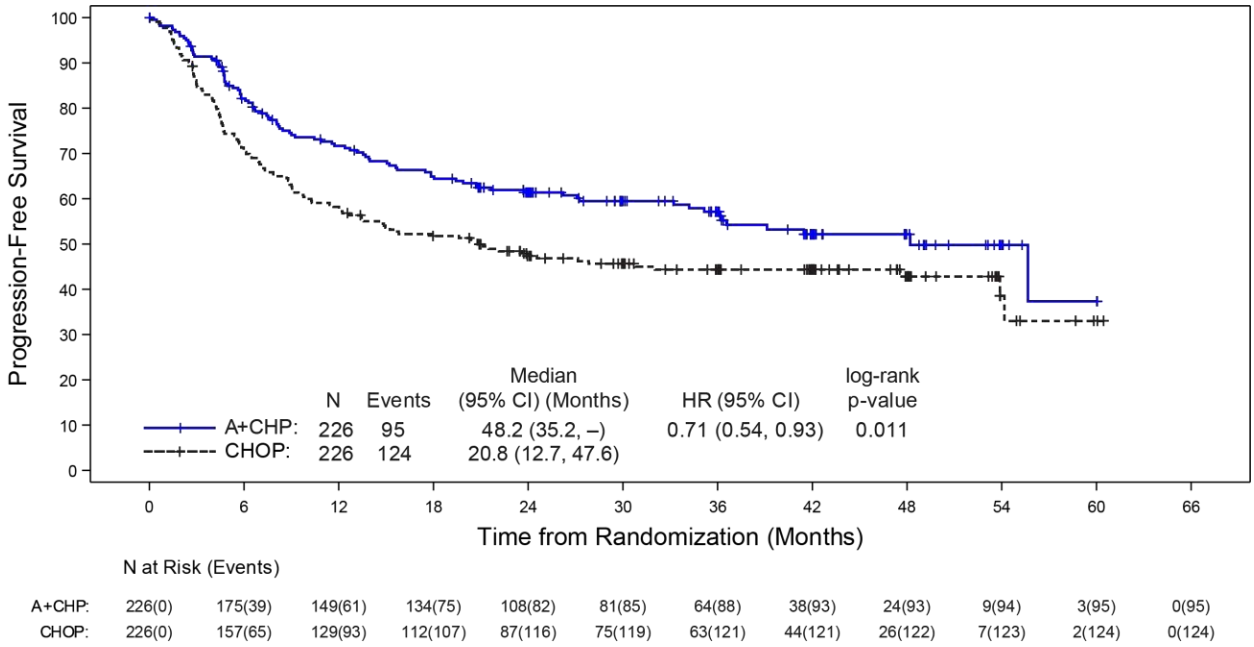
d Median OS follow-up in the ADCETRIS+CHP arm was 41.9 months; in the CHOP arm was 42.2 months

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

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

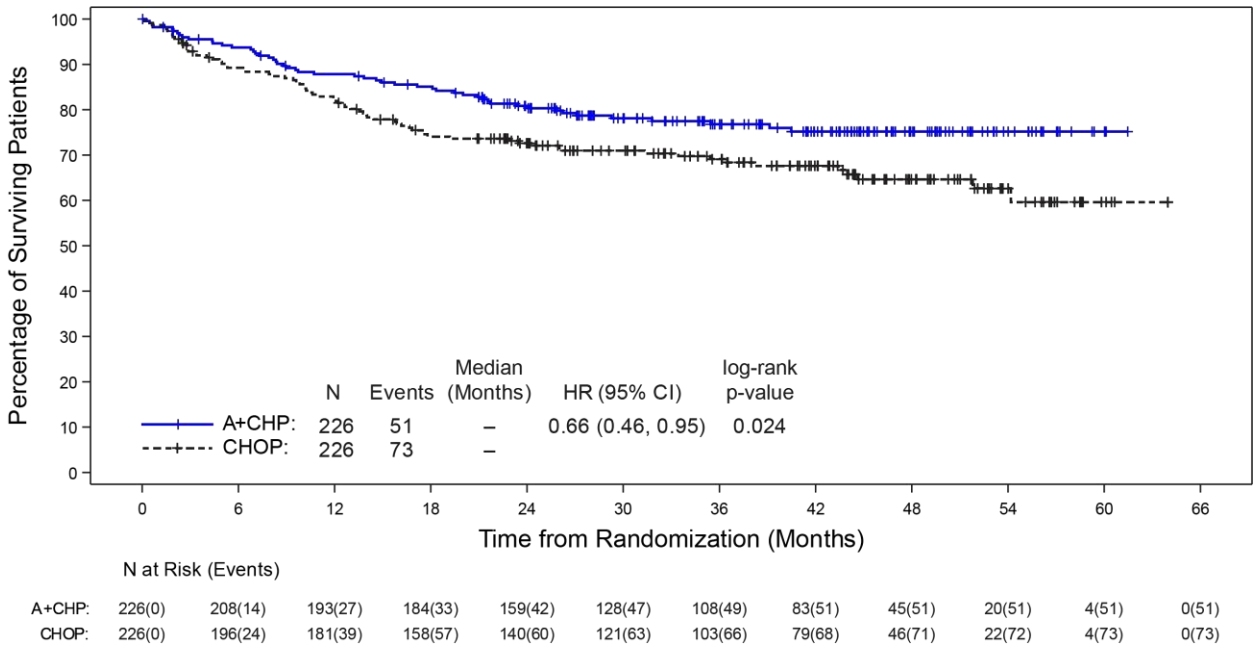
g P-value is for descriptive purpose only.

Figure 6: Kaplan-Meier Plot of PFS per IRF (ECHELON-2, SGN35-014)



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

Figure 7: Overall Survival (ECHELON-2, SGN35-014)



Median overall survival was not reached in either treatment arm

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

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

54 patients had AITL; 30 were randomized to treatment with ADCETRIS + CHP and 24 patients were randomized to treatment with CHOP. The median PFS per IRF was 13.9 months in the ADCETRIS + CHP arm versus 47.57 months in the CHOP arm. The stratified hazard ratio was 1.40 (95% CI: 0.64, 3.07). For overall survival, the stratified hazard ratio was 0.87 (95% CI: 0.29; 2.58). The median OS was not reached in either arm.

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

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

Systemic anaplastic large cell lymphoma

Study SG035-0004

The efficacy and safety of ADCETRIS as a single agent was evaluated in an open-label, single-arm, multicenter study in 58 patients with relapsed or refractory sALCL.
See Table 14 below for a summary of baseline patient and disease characteristics.

Table 14: 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 ADCETRIS was 16.8 months.

Ten (10) patients (17%) received 16 cycles of ADCETRIS; the median number of cycles received was 7 (range, 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 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%. 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 15.

Table 15: Efficacy results in relapsed or refractory sALCL patients treated with 1.8 mg/kg of ADCETRIS 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)	13.2	5.7, 26.3
Complete remission (CR)	26.3	13.2, NE[b]
Progression free survival (PFS)	**Median per IRF**	**95% CI**
	14.6 months	6.9, 20.6
Overall survival		**95% CI**
Median	Not reached	21.3, NE[b]
Estimated 5 year OS rate	60%	47%, 73%

a. The range of DOR was 0.1+months to 21.7+ 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

An exploratory intra-patient analysis showed that approximately 69% of the sALCL patients treated with ADCETRIS as part of the SG035-0004 clinical studies, 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 ADCETRIS of 0.7 months.

Study SGN35-006 (Retreatment study)

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

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, randomized, multicenter 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 16 provides a summary of the baseline patient and disease characteristics.

Table 16: Summary of Baseline Patient and Disease Characteristics in the Phase 3 CTCL Study (ITT) Population

	ADCETRIS N=64	**Physician's Choice (Methotrexate or Bexarotene) N=64**
Patient Characteristics		
Median age (range)	62 years (22-83)	58.5 years (22-83)
Patients ⩾ 65 years old n (%)	28 patients (44%)	24 patients (38%)
Gender n (%)	33M (52%)/31F (48%)	37M (58%)/27F (42%)
ECOG status n (%) 0 1 2	 43 (67) 18 (28) 3 (5)	 46 (72) 16 (25) 2 (3)
Disease Characteristics		
Median number of prior therapies (range)	4(0-13)	3.5(1-15)
Median number of skin-Directed therapy (range)	1(0-6)	1(0-9)
Median number of systemic therapy (range)	2 (0-11)	2 (1-8)

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 $\geqslant$ 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. Table 17 includes the results for ORR4 and other key secondary endpoints.

Table 17: Efficacy Results in CTCL patients treated with 1.8mg/ kg of ADCETRIS Every 3 weeks (ITT Population)

	ADCETRIS N=64	**Physician's Choice (Methotrexate or Bexarotene) N=64**
Objective Response Rate 4 (ORR4) per IRF		
N (%)	36 (56.3)	8 (12.5)
Percent Difference (95% CI)	43.8 (29.1, 58.4)	
p-value	<0.001	
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%.

5.2 Pharmacokinetic properties

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

- Monotherapy

The serum pharmacokinetics of ADC following an intravenous dose of ADCETRIS were similar to other antibody product.

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 Cmax 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 ADCETRIS 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 (C25003). Population pharmacokinetic analysis indicated that the pharmacokinetics of ADCETRIS in combination with AVD were consistent to that in monotherapy.

After multiple-dose, IV infusion of 1.2 mg/kg ADCETRIS every two weeks, maximal serum concentrations of ADC were observed near the end of the infusion and elimination exhibited a 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 ADCETRIS every two weeks, steady-state trough concentrations of ADC and MMAE were achieved by Cycle 3. Once steady-state was achieved, the PK of ADC did not appear to change with time. ADC accumulation (as assessed by AUC14D 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 (VM and VMP) of MMAE were 7.37 l and 36.4 l respectively.

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 ADCETRIS 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 1.457 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 ADCETRIS. Approximately 24% of the total MMAE administered as part of the ADC during a ADCETRIS 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 pharmacokinetics of ADCETRIS and MMAE after the administration of 1.2 mg/kg of ADCETRIS to patients with mild (Child-Pugh A; n=1), moderate (Child-Pugh B; n = 5) and severe (Child-Pugh C; n = 1) hepatic impairment. Compared to patients with normal hepatic function, MMAE exposure increased approximately 2.3-fold (90% CI 1.27 – 4.12 fold) in patients with hepatic impairment.

Renal impairment
A study evaluated the pharmacokinetics of ADCETRIS and MMAE after 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 patients
The population pharmacokinetics of ADCETRIS were examined from several monotherapy studies, including data from 380 patients up to 87 years old (34 patients ⩾ 65 <75 and 17 patients > 75 years of age). Additionally, the population pharmacokinetics of ADCETRIS 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. The safety profile in elderly patients with CTCL was consistent with that of adult patients, therefore dosing recommendations for patients aged 65 and older are the same for adults.

Paediatric population
The pharmacokinetics of ADC and MMAE following an intravenous dose of ADCETRIS were evaluated in a phase 1/2 study in 36 pediatric patients (age 7-17 years) with relapsed or refractory HL or sALCL (See section 5.1). After multiple-dose IV infusion of 1.4 mg/kg or 1.8 mg/kg given every 3 weeks, the pharmacokinetic properties of ADC and MMAE were consistent with that of adults. With body-weight normalized dosing, exposure to ADC and MMAE in adolescents (age 12-17 years) appeared to be comparable with adult exposure, however, there was a trend observed for lower exposures in children (age 7-11 years) at lower body weights. Median ADC and MMAE exposures in adolescents were approximately 3% lower and 13% higher, respectively, whereas median ADC and MMAE exposures in children were approximately 14% and 53% lower, respectively, when compared to adult patients.

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 ADCETRIS on human male and female fertility have not been studied.
However, results of repeat-dose toxicity studies in rats indicate the potential for ADCETRIS to impair male reproductive function and fertility. Testicular atrophy and degeneration were 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 $\geqslant$ 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.

ADCETRIS 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 ADCETRIS.

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
4 years.
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 medicines 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 11mL.

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.

ADCETRIS contains no bacteriostatic preservative.

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.

If not used immediately, the reconstituted solution may be stored at 2 – 8^{o}C (Do not freeze) for no more than 24 hours

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 18: Sample calculations for patients receiving the recommended dose of 1.8 mg/kg of ADCETRIS for weights ranging from 60 kg to 120 kg

Patient weight (kg)	**Total dose = patient weight multiplied by recommended dose [1.8 mg/kg[a]])**	**Total volume to be diluted[b] = 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])**
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[c]	*180 mg [d]*	*36 ml*	*3.6 vials*

a. For a reduced dose, use 1.2 mg/kg for the calculation.
b. To be diluted in 150 ml of diluent and administered by intravenous infusion over 30 minutes every 3 weeks.
c. If patient's weight is more than 100 kg, the dose calculation should use 100 kg.
d. The maximal recommended dose is 180 mg.

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

PRODUCT OWNER
TAKEDA PHARMA A/S, Vallensbaek Strand, Denmark

Date of revision of text
November 2022