AUSTRALIAN PRODUCT INFORMATION
ADCETRIS® (BRENTUXIMAB VEDOTIN)

1 NAME OF THE MEDICINE

brentuximab vedotin

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

ADCETRIS contains 50 mg brentuximab vedotin per vial. Following reconstitution with 10.5 mL sterile water for injection, a solution containing 5 mg/mL brentuximab vedotin is produced.

For the full list of excipients, see section 6.1 List of Excipients.

3 PHARMACEUTICAL FORM

Powder for injection. White to off-white lyophilized cake or powder.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Hodgkin lymphoma

Treatment of patients with previously untreated CD30+ Stage III or Stage IV Hodgkin lymphoma (HL) in combination with doxorubicin, vinblastine, and dacarbazine (AVD).

Treatment of adult patients with previously untreated CD30+ Stage IIB with large mediastinal mass and/or extranodal disease, Stage III or Stage IV HL in combination with etoposide, cyclophosphamide, doxorubicin, dacarbazine, dexamethasone (BrECADD).

Treatment of adult patients with CD30+ HL at higher risk of relapse or progression following ASCT.

Treatment of adult patients with relapsed or refractory CD30+ HL:

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

Peripheral T-cell lymphoma

Treatment of adult patients with previously untreated CD30+ peripheral T-cell lymphoma (PTCL) in combination with cyclophosphamide, doxorubicin, and prednisone (CHP).

Treatment of adult patients with relapsed or refractory systemic anaplastic large cell lymphoma (sALCL).

Cutaneous T cell lymphoma

Treatment of adult patients with CD30+ cutaneous T-cell lymphoma (CTCL) after at least 1 prior systemic therapy.

4.2 DOSE 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

ADCETRIS in combination with doxorubicin [A], vinblastine [V] and dacarbazine [D] [A+AVD]:

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 5.1 Pharmacodynamic Properties, Clinical Trials). If the patient's weight is more than 100 kg, the dose calculation should use 100 kg (see Table 8).

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

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

ADCETRIS in combination with etoposide [E], cyclophosphamide [C], doxorubicin [A], dacarbazine [D], dexamethasone [D] [BrECADD]:

The recommended dose in combination with chemotherapy (etoposide [E], cyclophosphamide [C], doxorubicin [A], dacarbazine [D], dexamethasone [D] [BrECADD]) is 1.8 mg/kg administered as an intravenous infusion over 30 minutes every 3 weeks for up to 6 cycles (see 5.1 Pharmacodynamic Properties, Clinical Trials). If the patient's weight is more than 100 kg, the dose calculation should use 100 kg (see Table 8).

Primary prophylaxis with growth factor support (G-CSF) must be given beginning on day 5 of each cycle, for all adult patients receiving BrECADD (see 5.1 Pharmacodynamic Properties, Clinical Trials).

Pretreatment with dexamethasone for 4 days before the first cycle of chemotherapy is recommended for patients > 40 years of age or at physician's discretion.

An antibiotic prophylaxis must be given 3 times a week during the whole duration of chemotherapy.

Refer to Table 5 for dosing recommendations for chemotherapy agents given in combination with ADCETRIS for patients with previously untreated HL.

Relapsed or refractory HL

The recommended dose is 1.8 mg/kg administered as an intravenous infusion over 30 minutes every 3 weeks. If the patient's weight is more than 100 kg, the dose calculation should use 100 kg (see Table 8).

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.

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 5.1 Pharmacodynamic Properties, Clinical Trials).

HL at 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. If the patient's weight is more than 100 kg, the dose calculation should use 100 kg (see Table 8).

ADCETRIS treatment should start following recovery from ASCT based on medical judgment. These patients should receive up to 16 cycles (see 5.1 Pharmacodynamic Properties, Clinical Trials).

Previously untreated PTCL

The recommended dose in combination with chemotherapy (cyclophosphamide [C], doxorubicin [H], and prednisone [P]; [CHP]) is 1.8 mg/kg administered as an intravenous infusion over 30 minutes

every 3 weeks for 6 to 8 cycles. If the patient's weight is more than 100 kg, the dose calculation should use 100 kg (see Table 8).

Primary prophylaxis with G-CSF, beginning with the first dose, is recommended for all patients with previously untreated PTCL receiving combination therapy (see Special Warnings and Precautions for use).

Refer to the product information of chemotherapy agents given in combination with ADCETRIS for 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. If the patient's weight is more than 100 kg, the dose calculation should use 100 kg (see Table 8).

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.

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 5.1 Pharmacodynamic Properties, Clinical Trials).

Relapsed or refractory CTCL after prior systemic treatment

The recommended dose is 1.8 mg/kg administered as an intravenous infusion over 30 minutes every 3 weeks. If the patient's weight is more than 100 kg, the dose calculation should use 100 kg (see Table 8).

Patients with CTCL should receive up to 16 cycles (see 5.1 Pharmacodynamic Properties, Clinical Trials).

General

Complete blood counts and hepatic function tests should be monitored prior to administration of each dose of this treatment (see 4.4 Special Warnings and Precautions for use).

Patients should be monitored during and after infusion (see 4.4 Special Warnings and Precautions for use).

Dose adjustments

Renal and hepatic impairment

Monotherapy

ADCETRIS should be used with caution in patients with severe renal impairment due to the potential for increased exposure of monomethyl auristatin E (MMAE) and increased toxicity (see 5.2 Pharmacokinetic Properties). The following dosage is recommended:

- Mild (creatinine clearance 50–80 mL/min) or moderate (creatinine clearance 30–50 mL/min) renal impairment: 1.8 mg/kg every 3 weeks
- Severe (creatinine clearance less than 30 mL/min) renal impairment: In patients with active disease and no other treatment options, consider use with caution after evaluating benefit-risk at a starting dose of 1.2 mg/kg every 3 weeks
- Dialysis dependent: no information

ADCETRIS should be used with caution in patients with hepatic impairment due to the potential for increased exposure of MMAE and increased toxicity (see 4.4 Special Warnings and Precautions for use and 5.2 Pharmacokinetic Properties).

The following dosage is recommended:

- Mild (Child-Pugh A) hepatic impairment: 1.2 mg/kg every 3 weeks
- Moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment: In patients with active disease and no other treatment options, consider use with caution after evaluating benefit-risk at a starting dose of 1.2 mg/kg every 3 weeks

Patients should be closely monitored for the development of serious hepatotoxicity during ADCETRIS therapy as this risk may be greater with pre-existing 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 ≥ 0.177 mmol/L (2.0 mg/dL) and/or creatinine clearance or calculated creatinine clearance is ≤ 40 mL/minute. Use of ADCETRIS in combination with chemotherapy should be avoided in patients with severe renal impairment.

Patients with hepatic impairment should be closely monitored for adverse events.

See Table 1 for starting dose recommendations for patients with hepatic impairment receiving combination therapy.

Table 1 Recommended starting dose for patients with hepatic impairment receiving combination therapy

	Combination with AVD Recommended starting dose	**Combination with CHP Recommended starting dose**
Mild hepatic impairment	0.9 mg/kg administered as an intravenous infusion over 30 minutes every 2 weeks.	1.2 mg/kg administered as an intravenous infusion over 30 minutes every 3 weeks.
Moderate to severe hepatic impairment	There is no clinical trial experience using ADCETRIS in combination with chemotherapy in patients with moderate or severe 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.	

Neutropenia

If neutropenia develops during treatment it should be managed by dose delays or dose adjustment in subsequent cycles. See Table 2, Table 3, Table 4 and Table 5 below for appropriate dosing recommendations for monotherapy and combination therapy, respectively (see 4.4 Special Warnings and Precautions for use).

Table 2 Dosing recommendations for neutropenia with monotherapy

Severity grade of neutropenia (signs and symptoms [abbreviated description of CTCAE[a]]**)**	**Modification of dose and schedule**
Grade 1 (<LLN - 1500/mm^3 <LLN - 1.5 x 10^9/L) or Grade 2 (<1500 - 1000/mm^3 <1.5 – 1.0 x 10^9/L)	Continue with the same dose and schedule
Grade 3 (<1,000 - 500/mm^3 <1.0 - 0.5 x 10^9/L) or Grade 4 (<500/mm^3 <0.5 x 10^9/L)	Withhold dose until toxicity returns to ≤ Grade 2 or baseline then resume treatment at the same dose and schedule[b]. Consider growth factor support (G-CSF or GM-CSF) in subsequent cycles for patients who develop Grade 3 or Grade 4 neutropenia.

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

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

Table 3 Dosing recommendations for neutropenia during combination therapy (A+AVD, A+CHP)

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) or Grade 3 (< 1,000-500/mm^3 < 1.0-0.5 x 10^9/L) or Grade 4 (< 500/mm^3 < 0.5 x 10^9/L)	Primary prophylaxis with G-CSF, beginning with the first dose, is recommended for all patients receiving combination therapy. Continue with the same dose and schedule.

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

Table 4 Dosing recommendations for brentuximab vedotin for haematological toxicities during BrECADD combination therapy

Severity grade (signs and symptoms [abbreviated description of CTCAE[a]]**)**	**Modification of dose and schedule**
Leukocytes ≥ 2500/mm^3 ≥ 2.5x 10^9/L OR Neutrophils ≥ 1500/mm^3 ≥ 1.5x 10^9/L AND Thrombocytes ≥ 80,000/ mm^3 ≥ 80x10^9/L	Continue with the same dose and schedule.
Leukocytes < 2000-1000/mm^3 < 2.0-1.0 x 10^9/L OR Neutrophils < 1,000-500/mm^3 < 1.0-0.5 x 10^9/L AND Thrombocytes < 50,000- 25,000/mm^3 < 50.0-25.0 x 10^9/L	Withhold treatment until toxicity returns to baseline; if the events do not recover by day 28 of the cycle, a dose reduction of 1.2 mg/kg up to a maximum of 120 mg every 3 weeks can be considered.
Leukocytes < 1000/ mm^3 < 1.0 x 10^9/L OR Neutrophils < 500/mm^3 < 0.5 x 10^9/L AND Thrombocytes < 25,000/mm^3 < 25.0 x 10^9/L)	Withhold treatment until toxicity returns to baseline then resume ADCETRIS treatment with a reduced dose of 1.2 mg/kg up to a maximum of 120 mg every 3 weeks.

a. Grading based on National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v5.0; see Neutrophils/granulocytes; LLN = lower limit of normal.

In patients receiving the BrECADD regimen, toxicities should also be managed using the dose reductions outlined in Table 5. Toxic events requiring dose reduction are leukopaenia (< 1.0 x 10^9 for more than 4 days), thrombocytopaenia (< 25.0 x 10^9 for one or more days), CTCAE grade 4 infection, other CTCAE grade 4 toxicities and any treatment delay of more than 2 weeks due to inadequate recovery of blood values. If one or more events occur in a given cycle, the dose of each drug should be reduced to the level below and continue for the following cycles.

If events occur in two successive cycles, the dose should be reduced to baseline level shown in Table 5.

Table 5 Dose levels for BrECADD treatment regimen

Dose Level	cyclophosphamide [C]	doxorubicin [A]	etoposide [E]	dacarbazine (D)	dexamethasone (D)
4	1250 mg/m^2	40 mg/m^2	150 mg/m^2	250 mg/m^2	40 mg
3	1100 mg/m^2	40 mg/m^2	125 mg/m^2	250 mg/m^2	40 mg
2	950 mg/m^2	40 mg/m^2	100 mg/m^2	250 mg/m^2	40 mg
1	800 mg/m^2	40 mg/m^2	100 mg/m^2	250 mg/m^2	40 mg
Baseline	650 mg/m^2	35 mg/m^2	100 mg/m^2	250 mg/m^2	40 mg

Use in the elderly

The safety and efficacy of ADCETRIS as part of the BrECADD regimen have not been established in patients over the age of 60 years.

Peripheral neuropathy

If peripheral sensory or motor neuropathy emerges or worsens during treatment see Table 6 and Table 7 for appropriate dosing recommendations for monotherapy and combination therapy, respectively (see 4.4 Special Warnings and Precautions for use).

Table 6 Dosing recommendations for new or worsening peripheral sensory or motor neuropathy with monotherapy

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

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

Table 7 Dosing recommendations for new or worsening peripheral sensory or motor neuropathy during combination therapy

	Combination therapy with AVD[a]	**Combination therapy with CHP[a]**	**Combination therapy BrECADD[b]**
Severity of peripheral sensory or motor neuropathy (signs and symptoms [abbreviated description of CTCAE]**)**	**Modification of dose and schedule**		
Grade 1 (paraesthesia and/or loss of reflexes, with no loss of function)	Continue with the same dose and schedule.	Continue with the same dose and schedule.	Continue with the same dose and schedule.
Grade 2 (interfering with function but not with activities of daily living)	Reduce dose to 0.9 mg/kg up to a maximum of 90 mg every 2 weeks.	Sensory neuropathy: Continue treatment at same dose level. Motor neuropathy: Reduce dose to 1.2 mg/kg, up to a	Withhold treatment with ADCETRIS until symptoms have subsided to ≤ grade 1 level or initial state, then restart ADCETRIS treatment at a

		maximum of 120 mg every 3 weeks.	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 treatment with ADCETRIS until toxicity is ≤ Grade 2, then restart treatment at a reduced dose to 0.9 mg/kg up to a maximum of 90 mg every 2 weeks.	Sensory neuropathy: Reduce dose to 1.2 mg/kg up to a maximum of 120 mg every 3 weeks. Motor neuropathy: Discontinue treatment.	
Grade 4 (sensory neuropathy which is disabling or motor neuropathy that is life threatening or leads to paralysis)	Discontinue treatment.	Discontinue treatment.	Discontinue treatment.

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

b. Grading based on NCI CTCAE v4.0

Method of administration

The recommended dose of ADCETRIS is infused over 30 minutes.

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.

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.

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

Preparation of infusion solution:

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

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

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

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

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

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

Determining dosage amount

Calculation to determine the total ADCETRIS dose (mL) to be further diluted:

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

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 8 Sample calculations for patients receiving the recommended dose of 1.8 mg/kg, 1.2 mg/kg or 0.9 mg/kg of ADCETRIS for weights ranging from 60 kg to 120 kg

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

a. To be diluted in 150 mL of diluent and administered by intravenous infusion over 30 minutes.

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

4.3 CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients (see List of Excipients).

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).

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.

Cases of pulmonary toxicity most commonly developed during the first 5 cycles of ADCETRIS and presented with cough, dyspnoea and interstitial lung infiltrates on radiological studies. Severity has been variable, with increased severity more likely with early onset. Some cases in which pneumonitis developed after the first cycle of ADCETRIS have had a fulminant course, requiring mechanical ventilation, treatment with high dose systemic corticosteroids and discontinuation of ADCETRIS. Some of these cases have had fatal outcome despite these measures; in others, the pneumonitis has resolved and treatment with ADCETRIS was resumed without recurrence of pneumonitis. Non-serious cases were more likely to occur after 3-5 cycles. These have been variably managed with ADCETRIS continued or dose delay or discontinuation. Corticosteroids were not administered and in many of these patients the pneumonitis did not resolve.

In the event of new or worsening symptoms that are rapidly progressive or occur in the first one to two cycles, ADCETRIS should be with-held and treatment with systemic corticosteroids commenced. If full resolution occurs, resumption of ADCETRIS treatment may be considered. If the presentation is non-serious with onset after several cycles of ADCETRIS, management may be by dose delay. Systemic corticosteroids may be considered.

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.

Serious infections and opportunistic infections

Serious infections such as pneumonia, staphylococcal bacteraemia, sepsis/septic shock (including fatal outcomes) and herpes zoster, cytomegalovirus (CMV) (reactivation) and opportunistic infections such as Pneumocystis jiroveci pneumonia and oral candidiasis have been reported in patients treated with 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 infusion-related reaction occurs, the infusion should be interrupted and appropriate medical management instituted. The infusion may be restarted at a slower rate after symptom resolution. Patients who have experienced a prior infusion-related reaction should be pre-medicated for subsequent infusions. Premedication may include paracetamol, an antihistamine and a corticosteroid.

Infusion-related reactions are more frequent and more severe in patients with antibodies to ADCETRIS (see 4.8 Adverse Effects).

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 with a 16-week median time from onset to resolution.

In clinical trials, the majority of patients had improvement or resolution of some of their symptoms (see 4.8 Adverse Effects). Patients should be monitored for symptoms of neuropathy, such as hypoesthesia, hyperesthesia, paraesthesia, discomfort, a burning sensation, neuropathic pain or weakness. Patients experiencing new or worsening peripheral neuropathy may require a delay and a dose reduction of ADCETRIS or discontinuation of treatment (see 4.2 Dose and Method of Administration).

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 discontinuations (refer to 4.2 Dose and Method of Administration).

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 Common Terminology Criteria for Adverse Events (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.

In combination therapy with AVD, CHP or as the BrECADD regimen, advanced age was a risk factor for febrile neutropenia. When ADCETRIS is administered in combination with AVD or CHP, primary prophylaxis with G-CSF, beginning with the first dose, is recommended for all patients regardless of age. When ADCETRIS is administered in combination as part of the BrECADD regimen, primary prophylaxis with G-CSF must be given beginning on day 5 of each cycle for all adult patients regardless of age.

Severe cutaneous adverse reactions (SCARs)

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

Gastrointestinal complications

Serious 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 lymphoma patients with pre-existing GI involvement. In the event of new or worsening GI symptoms, consider withholding ADCETRIS, perform a prompt diagnostic evaluation and treat appropriately.

Hepatotoxicity

Cases of hepatoxicity, ranging from asymptomatic elevations in serum transaminase levels to hepatic failure and fulminant hepatitis have been reported in patients receiving ADCETRIS. These have included fatal outcomes. Pre-existing liver disease, comorbidities, and concomitant medications may increase the risk of serious or fatal hepatotoxicity.

Hepatotoxicity most commonly presents as asymptomatic minor elevations in transaminases, although cholestasis has also been reported. In most patients with minor elevations, ADCETRIS was continued and the elevated transaminase levels resolved. Dose delay or reduction or discontinuation

has also been described. The use of immunosuppressive drugs, including corticosteroids in the treatment of hepatitis associated with ADCETRIS has not been described.

Liver function should be tested before initiating the treatment and with every cycle during treatment with ADCETRIS. Depending on the severity of the hepatotoxicity event, consider delaying, reducing the dose or discontinuing ADCETRIS (see 4.2 Dose and Method of Administration).

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.

Long-term safety

There is insufficient evidence to judge the safety of treatment extended past 12 months.

Use in hepatic impairment

An excretion study found that approximately 75% of the clearance of unchanged MMAE is by excretion in the faeces. This is thought to be due to biliary excretion. The liver is a major route of elimination of the unchanged active metabolite MMAE. Limited clinical data from patients who were administered 1.2 mg/kg of ADCETRIS suggest that exposure to MMAE increased approximately 2.3-fold in patients with any degree of hepatic impairment. ADCETRIS should be used with caution in patients with hepatic impairment. Patients should be closely monitored for adverse events. Treatment with ADCETRIS should be discontinued in patients with hepatic impairment who are not demonstrating an adequate response to treatment.

Use in renal impairment

An excretion study found that approximately 25% of the clearance of unchanged MMAE is by excretion in the urine. A study evaluated the PK of brentuximab vedotin and MMAE after the administration of 1.2 mg/kg of ADCETRIS to patients with mild (n=4), moderate (n=3) and severe (n=3) renal impairment. Patients requiring dialysis were excluded from this study. Compared to patients with normal renal function, MMAE exposure increased approximately 1.9-fold in patients with severe renal impairment (creatinine clearance < 30 ml/min). ADCETRIS should be used with caution in patients with renal impairment. Patients should be closely monitored for adverse events (see 4.2 Dose and Method of Administration).

Use in the elderly

Based upon population PK analyses and the similar safety profile in elderly patients with CTCL, no dosage adjustments are required in patients aged 65 and older (see 5.2 Pharmacokinetic Properties, Pharmacokinetics in Special Populations, Elderly Patients).

The safety and efficacy of ADCETRIS as part of the BrECADD regimen has not been established in patients over the age of 60 years.

Paediatric use

The safety and efficacy of ADCETRIS in children less than 18 years have not yet been established. Clinical studies of ADCETRIS did not include sufficient numbers of subjects less than or younger than 18 years of age to determine whether they respond differently from adult subjects aged 18 years or older. Findings from nonclinical studies that may be relevant to the paediatric population were lymphoid depletion and reduced thymic weight. These observations in nonclinical studies were consistent with the pharmacologic disruption of microtubules caused by MMAE derived from ADCETRIS.

Effects on laboratory tests

No data available

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

The combined use of ADCETRIS and bleomycin is associated with pulmonary toxicity and is therefore contraindicated (see 4.3 Contraindications).

There are no drug-drug interactions data available with other chemotherapy regimens.

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

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 see 4.2 Dose and Method of Administration.

Co-administration of ADCETRIS with rifampicin, a strong CYP3A4 inducer, did not alter the plasma exposure to brentuximab vedotin; 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 metabolised by CYP3A4 enzymes.

Doxorubicin, Vinblastine and Dacarbazine

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

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

Cyclophosphamide, Doxorubicin, and Prednisone

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

Etoposide, Cyclophosphamide, Doxorubicin, Dacarbazine, Dexamethasone (BrECADD)

The pharmacokinetics of ADC and MMAE have not been characterised in the setting of BrECADD. Exposures of brentuximab vedotin and concurrent chemotherapy are not expected to be affected in the BrECADD regimen.

Co-administration with other CYP substrates

In vitro studies indicated that clinical drug-drug interactions are unlikely to occur as a result of MMAE-mediated inhibition or induction of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 or CYP2D6.

Co-administration with Drugs that are Substrates of Transporters

In vitro, MMAE was not a substrate for the BCRP, MRP2, OATP1B1, OATP1B3, OAT1 or OCT2 transporters.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

The effects of ADCETRIS on human male and female fertility have not been studied.

However, results from toxicity studies in rats indicate the potential for brentuximab vedotin to impair male reproductive function and fertility. Seminiferous tubule degeneration, sertoli cell vacuolation, reduced spermatogenesis and aspermia were observed in male rats that received weekly IV injections of ≥ 5 mg/kg brentuximab vedotin. The no effect dose (0.5 mg/kg) is below the recommended human dose of 1.8 mg/kg based on body weight. Testicular atrophy and degeneration had not fully reversed following a 16-week treatment-free period. MMAE, the main active metabolite of brentuximab vedotin, 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.

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. Effects on spermatogenesis cannot be excluded after a 6-month treatment-free period.

While not observed with brentuximab vedotin, ovarian effects were observed in repeat dose toxicity studies of other MMAE-containing ADCs. A mild to moderate decrease in, or absence of, secondary and tertiary ovarian follicles was observed in young female cynomolgus monkeys at doses ≥ 3 mg/kg weekly for 4 weeks. These effects showed evidence of recovery 6 weeks after the end of dosing and no changes were observed in primordial follicles.

Use in pregnancy (Category D)

There are no adequate and well-controlled studies with ADCETRIS in pregnant women. However, based on its mechanism of action and findings in animals, ADCETRIS can cause fetal harm when administered to a pregnant woman.

Embryofetal toxicities were seen in a rat embryofetal development study in which pregnant rats received two IV doses of ≥ 3 mg/kg brentuximab vedotin during a period of organogenesis, and included an increased incidence of post-implantation loss, decreased number of foetuses and an increase in the incidence of external malformations (umbilical hernias and malrotated hindlimbs).

ADCETRIS should not be used during pregnancy unless the benefit to the mother outweighs the potential risks to the fetus. If a pregnant woman needs to be treated, she should be clearly advised on the potential risk to the fetus. Women of childbearing potential should be using two methods of effective contraception during treatment with ADCETRIS and until 6 months after treatment.

See the ‘Effects on Fertility’ section above pertaining to advice for women whose male partners are being treated with ADCETRIS.

Use in lactation

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.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Brentuximab vedotin may have a minor influence on the ability to drive and use machines.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Summary of the safety profile

The safety profile of ADCETRIS is based on available clinical trial data, the Named Patient Program (NPP), and post-marketing experience to date. Frequencies of adverse reactions described below and in Table 9 have been determined based on data generated from clinical studies.

Monotherapy

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

Serious adverse drug reactions occurred in 12% of patients. The frequency of unique serious adverse drug reactions was ≤1%. Adverse events led to the discontinuation of study treatment in 24% of patients receiving ADCETRIS.

The safety data in patients retreated with ADCETRIS (SGN35-006) were consistent with those observed in the combined pivotal phase 2 studies, with the exception of peripheral motor neuropathy,

which had a higher incidence (28% vs. 9% in the pivotal phase 2 studies) and was primarily Grade 2. Patients also had a higher incidence of arthralgia, Grade 3 anaemia, and back pain compared to patients observed in the combined pivotal phase 2 studies.

The safety data reported from the phase 1 dose escalation and clinical pharmacology studies (n=15 patients) and from the Named Patient Program (NPP; n = 26 patients), in patients with relapsed or refractory HL who had not received an ASCT (see section 5.1 Pharmacodynamic Properties, Clinical Trials), and were treated with the recommended dose of 1.8 mg/kg every three weeks, were consistent with the safety profile of the pivotal clinical studies.

Combination therapy

For safety information of agents given in combination with ADCETRIS (doxorubicin, vinblastine and dacarbazine [AVD]; or cyclophosphamide, doxorubicin, and prednisone [CHP]; or etoposide, cyclophosphamide, doxorubicin, dacarbazine, dexamethasone [BrECADD]), refer to their product information.

Combination therapy (ADCETRIS +AVD; ADCETRIS +CHP)

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

In patients receiving ADCETRIS combination therapy, serious adverse reactions occurred in 34% of patients. Serious adverse reactions occurring in ≥ 3% of patients included febrile neutropenia (15%), pyrexia (5%), infection (11%), and neutropenia (3%).

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

Tabulated list of adverse reactions

Adverse reactions for ADCETRIS are listed by MedDRA System Organ Class and Preferred Term (see Table 9). 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); Frequency not known (cannot be estimated from the available data).

Table 9 Adverse reactions for ADCETRIS

System organ class	Adverse reactions (monotherapy)	Adverse reactions (combination therapy, A+AVD; A+CHP)
Infections and infestations		
Very common:	Infection[a], upper respiratory tract infection	Infection[a], upper respiratory tract infection
Common:	Herpes zoster, herpes simplex, pneumonia, oral candidiasis	Pneumonia, oral candidiasis, sepsis/septic shock, herpes zoster
Uncommon:	Pneumocystis jiroveci pneumonia, staphylococcal bacteraemia, cytomegalovirus infection or reactivation, sepsis/septic shock	Herpes simplex, Pneumocystis jiroveci pneumonia
Frequency not known:	Progressive multifocal leukoencephalopathy	
Blood and lymphatic system disorders		
Very common:	Neutropenia	Neutropenia[a], anaemia, febrile neutropenia
Common:	Anaemia, thrombocytopenia	Thrombocytopenia
Uncommon:	Febrile neutropenia	

System organ class	Adverse reactions (monotherapy)	Adverse reactions (combination therapy, A+AVD; A+CHP)
Immune system disorders		
Uncommon:	Anaphylactic reaction	Anaphylactic reaction
Metabolism and nutrition disorders		
Very common:		Decreased appetite
Common:	Hyperglycaemia	Hyperglycaemia
Uncommon:	Tumour lysis syndrome	Tumour lysis syndrome
Nervous system disorders		
Very common:	Peripheral sensory neuropathy, peripheral motor neuropathy	Peripheral sensory neuropathy[a], peripheral motor neuropathy[a], dizziness
Common:	Dizziness	
Uncommon:	Demyelinating polyneuropathy	
Respiratory, thoracic and mediastinal disorders		
Very common:	Cough, dyspnoea	Cough, dyspnoea
Gastro-intestinal disorders		
Very common:	Diarrhoea, nausea, vomiting, constipation, abdominal pain	Nausea, constipation, vomiting, diarrhoea, abdominal pain, stomatitis
Uncommon:	Pancreatitis acute	Pancreatitis acute
Hepatobiliary disorders		
Common:	Alanine aminotransferase/aspartate aminotransferase (ALT/AST) increased	Alanine aminotransferase/aspartate aminotransferase (ALT/AST) increased
Skin and subcutaneous tissue disorders		
Very common:	Rash[a], pruritus	Alopecia, rash[a]
Common:	Alopecia	Pruritus
Uncommon:	Stevens-Johnson syndrome/toxic epidermal necrolysis	Stevens Johnson syndrome[b]
Frequency not known:	Drug reaction with eosinophilia and systemic symptoms (DRESS)	
Musculoskeletal and connective tissue disorders		
Very common:	Myalgia, arthralgia	Myalgia, bone pain, arthralgia, back pain
Common:	Back pain	
General disorders and administration site conditions		
Very common:	Fatigue, pyrexia, infusion-related reactions[a]	Fatigue, pyrexia
Common:	Chills	Infusion-related reactions[a], chills
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. Extravasation may result in skin redness, pain, swelling, blistering, exfoliation, or cellulitis at or surrounding the infusion site.

The most common adverse events (≥ 10%) for ADCETRIS in combination with CHP versus the comparator arm (CHOP) are listed in Table 10.

Table 10 Adverse Events Reported for ≥10% of Subjects in the Combination therapy of ADCETRIS with cyclophosphamide, doxorubicin, and prednisone [CHP] versus cyclophosphamide, doxorubicin, vincristine, and prednisone [CHOP] (Study SGN35-014)

Preferred Term	ADCETRIS+CHP (N=223) n (%)	CHOP (N=226) n (%)
Nausea	103 (46)	87 (38)
Peripheral sensory neuropathy	100 (45)	92 (41)
Diarrhoea	85 (38)	46 (20)
Neutropenia	85 (38)	85 (38)
Constipation	64 (29)	67 (30)
Alopecia	58 (26)	56 (25)
Pyrexia	58 (26)	42 (19)
Vomiting	57 (26)	39 (17)
Fatigue	54 (24)	46 (20)
Anaemia	46 (21)	36 (16)
Febrile neutropenia	41 (18)	33 (15)
Decreased appetite	39 (17)	27 (12)
Dyspnoea	32 (14)	24 (11)
Headache	31 (14)	31 (14)
Dizziness	28 (13)	20 (9)
Cough	27 (12)	22 (10)
Hypokalaemia	27 (12)	18 (8)
Stomatitis	27 (12)	27 (12)
Asthenia	26 (12)	16 (7)
Weight decreased	26 (12)	17 (8)
Insomnia	25 (11)	31 (14)
Myalgia	24 (11)	19 (8)
Oedema peripheral	24 (11)	18 (8)
Rash	22 (10)	15 (7)

Table 11 Adverse Events Reported for ≥10% of Subjects in the Combination therapy of ADCETRIS with doxorubicin, vinblastine, and dacarbazine (AVD) versus doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) (Study C25003)

Preferred Term	ADCETRIS+AVD (N=664) n (%)	ABVD (N=670) n (%)
Neutropenia	382 (58)	295 (45)
Nausea	348 (53)	371 (56)
Constipation	279 (42)	241 (37)
Vomiting	216 (33)	183 (28)
Fatigue	211 (32)	211 (32)
Peripheral sensory neuropathy	189 (29)	111 (17)
Diarrhoea	181 (27)	121 (18)
Pyrexia	179 (27)	147 (22)
Neuropathy peripheral	174 (26)	85 (13)
Alopecia	173 (26)	146 (22)
Weight decreased	148 (22)	40 (6)
Abdominal pain	142 (21)	65 (10)
Anaemia	140 (21)	67 (10)
Stomatitis	138 (21)	104 (16)
Febrile neutropenia	128 (19)	52 (8)
Bone pain	126 (19)	66 (10)
Insomnia	126 (19)	82 (12)
Decreased appetite	118 (18)	76 (12)
Cough	97 (15)	123 (19)
Headache	95 (14)	94 (14)
Arthralgia	89 (13)	78 (12)
Neutrophil count decreased	86 (13)	79 (12)
Dyspepsia	84 (13)	75 (11)
Paraesthesia	84 (13)	73 (11)
Back pain	83 (13)	49 (7)
Dyspnoea	82 (12)	124 (19)
Myalgia	81 (12)	71 (11)
Pain in extremity	81 (12)	67 (10)
Oropharyngeal pain	72 (11)	55 (8)
Upper respiratory tract infection	70 (11)	70 (11)
Alanine aminotransferase increased	68 (10)	26 (4)

In the clinical trial of ADCETRIS as combination therapy with AVD, 23 patients (3%) in the A+AVD arm experienced a second malignancy compared to 32 patients (5%) in the ABVD arm.

Combination therapy (BrECADD)

In the HD21 study, 747 patients received BrECADD, and 741 patients received eBEACOPP (escalated bleomycin [B], etoposide [E], doxorubicin [A], cyclophosphamide [C], vincristine [O], procarbazine [P] and prednisone [P]).

Serious adverse reactions occurred in 39.4% patients receiving BrECADD treatment, and 36.4% in patients who received eBEACOPP. The most common serious adverse reactions in patients who received BrECADD (>3%) were febrile neutropenia (19.3%), pyrexia (3.9%), neutropenia (3.2%).

Serious adverse events led to treatment discontinuation in 2% of patients in both BrECADD and eBEACOPP arms. The most common serious adverse event that led to discontinuation in the BrECADD arm were febrile neutropenia (0.3%) and cardiac failure (0.3%).

The most common treatment-emergent adverse events (≥ 10%) for BrECADD versus eBEACOPP are listed in Table 12 .

Table 12 Treatment-Emergent Adverse Events of Any Grade Reported for ≥10% of Subjects by CTCAE Toxicity or Preferred Term in the combination therapy of ADCETRIS with etoposide, cyclophosphamide, doxorubicin, dacarbazine, dexamethasone (BrECADD) versus escalated doses of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone (eBEACOPP) (Study HD21)[a]

No of patients (%)	**BrECADD N = 747 n (%)**	**eBEACOPP N = 741 n (%)**
At least 1 TEAE	745 (99.7)	741 (100)
CTCAE Toxicity	744 (99.6)	741 (100)
Anaemia	712 (95.3)	725 (97.8)
Leukopenia	697 (93.3)	724 (97.7)
Thrombocytopenia	645 (86.3)	689 (93.0)
Nausea/vomiting	411 (55.0)	464 (62.6)
Infection	400 (53.5)	372 (50.2)
GI disorders (except nausea, vomiting, mucositis)	398 (53.3)	334 (45.1)
Peripheral sensory neuropathy	291 (39.0)	362 (48.9)
Skin and subcutaneous tissue disorders	286 (38.3)	317 (42.8)
Respiratory, thoracic and mediastinal disorders	283 (37.9)	356 (48.0)
Mucositis	217 (29.0)	244 (32.9)
Febrile neutropenia	198 (26.5)	145 (19.6)
Nervous system disorders (except neuropathy)	193 (25.8)	208 (28.1)
Hepatobiliary disorders	172 (23.0)	152 (20.5)
Cardiac disorders	155 (20.7)	139 (18.8)
Renal and urinary disorders	71 (9.5)	95 (12.8)
Other Toxicities (Preferred Term)	468 (62.7)	513 (69.2)
Fatigue	223 (29.9)	206 (27.8)
Neutropenia	75 (10.0)	85 (11.5)

[a] In the HD21 study, adverse events were collected using either prespecified CTCAE toxicity terms or other toxicities. CTCAE toxicities were captured at higher classification levels (e.g., System Organ Class [SOC]) rather than at the Preferred Term (PT) level, whereas other toxicities were collected and coded at the MedDRA PT level. This approach differs from the standard methodology used in company-sponsored trials, including other combination-therapy studies (e.g., A+AVD vs ABVD and A+CHP vs CHOP), in which all adverse events were collected and coded at the MedDRA PT level. Given these methodological differences, the adverse event data from HD21 are not directly comparable with those from other studies, and the presentation format will necessarily differ.

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 was reported in <1% of the patients.

In the pivotal phase 2 population (SG035-0003 and SG035-0004), the median duration of Grade 3 or Grade 4 neutropenia was limited (1 week); 2% of patients had Grade 4 neutropenia that lasted ≥ 7 days. Less than half of the patients in the 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 C25003 (ADCETRIS + AVD) and SGN35-014 (ADCETRIS + CHP) 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% of patients discontinued one or more of the study drugs due to neutropenia.

Febrile neutropenia was reported in 20% of the patients who did not receive primary prophylaxis with G-CSF (see section 4.2). The frequency of febrile neutropenia was 13% in patients who received primary prophylaxis with G-CSF.

In the HD21 clinical trial (BrECADD) of ADCETRIS as combination therapy, neutropenia led to dose delays in 0.5% of patients. Grade 3 neutropenia was reported in 0.5% and Grade 4 neutropenia was reported in 9% of patients. A dose reduction was required in 1.1% of patients and there was no treatment discontinuation due to serious neutropenia. All patients received primary prophylaxis with G-CSF (see 4.2 Dose and Method of Administration). The frequency of febrile neutropenia was 26.5% in patients who received BrECADD.

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.

PML has been reported outside of the pivotal clinical trials described in this section (see 4.4 Special Warnings and Precautions for Use).

Combination therapy

In the clinical trials (C25003 [ADCETRIS + AVD] and SGN35-014 [ADCETRIS + CHP]) of ADCETRIS as combination therapy, serious infections, including opportunistic infections occurred in 15% of patients; sepsis, septic shock or bacteraemia occurred in 4% of the patients. The most commonly reported opportunistic infections were herpes viral infections.

In the clinical trial (HD21 [BrECADD]) of ADCETRIS as combination therapy, serious infections and infestations occurred in 14.3% of patients. The most commonly reported events were infection (2%), pneumonia (1.7%), and neutropenic infection (1.2%).

Peripheral Neuropathy

Monotherapy

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

Among patients who experienced peripheral neuropathy in the pivotal phase 2 studies (SG035-0003 and SG035-0004) and randomised phase 3 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, 82-85% of patients who experienced peripheral neuropathy had resolution or improvement of their peripheral neuropathy symptoms. The median time from onset to resolution or improvement for all events ranged from 16 to 23.4 weeks.

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

Combination therapy

In the clinical trial of ADCETRIS as combination therapy with AVD, treatment emergent neuropathy occurred in 67% of the population; peripheral motor neuropathy occurred in 11% of patients.

Peripheral neuropathy led to treatment discontinuation in 7%, dose reductions in 21%, and dose delays in 1% of patients. For patients who experienced peripheral neuropathy the median time of onset of peripheral neuropathy was 8 weeks. Patients who discontinued due to peripheral neuropathy received a median of 8 doses of ADCETRIS+AVD (A+AVD) before discontinuation of one or more agents.

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

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

Among patients who experienced peripheral neuropathy, the median follow up time from end of treatment until last evaluation was approximately 177 weeks. At the time of last evaluation, 64% who experienced peripheral neuropathy had resolution or improvement of their peripheral neuropathy symptoms. The median time from onset to resolution or improvement of peripheral neuropathy events was 19 weeks (ranged from 0 weeks to 195 weeks).

In the clinical trial (HD21 [BrECADD]) of ADCETRIS as combination therapy, treatment emergent peripheral sensory neuropathy occurred in 38.8% of the population; peripheral motor neuropathy occurred in 3.6% of patients. Peripheral sensory neuropathy as a serious adverse event did not lead to discontinuation in any patients, led to dose reduction in 4.7% and treatment delay in 1.5% of patients. Peripheral motor neuropathy as a serious adverse event did not lead to discontinuation in any patients, led to dose reduction in 0.7%, and treatment delay in 0.1% of patients.

Acute Pancreatitis

Acute pancreatitis (including fatal outcomes) has been reported outside of the pivotal clinical trials. Consider the diagnosis of acute pancreatitis for patients presenting with new or worsening abdominal pain (see 4.4 Special Warnings and Precautions for Use).

Infusion-related reactions

Monotherapy

Infusion-related reactions such as headache, rash, back pain, vomiting, chills, nausea, dyspnoea, pruritus, and cough were reported in 13% of patients.

Anaphylaxis has been reported. Symptoms of anaphylaxis may include, but are not limited to, urticaria, angioedema, hypotension and bronchospasm.

Combination therapy

In clinical trials (C25003 [ADCETRIS + AVD] and SGN35-014 [ADCETRIS + CHP]), infusion-related reactions, such as headache, rash, back pain, vomiting, chills, nausea, dyspnoea, pruritus, cough, infusion site pain and pyrexia were reported in 8% of patients. Dizziness, extravasation, hypoaesthesia, and hypoxia were reported in 4% of patients. Symptoms of an anaphylactic reaction may include, but are not limited to, urticaria, angioedema, hypotension and bronchospasm.

Immunogenicity

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

The presence of antibodies to brentuximab vedotin did not correlate with a clinically meaningful reduction in serum brentuximab vedotin levels and did not result in a decrease in the efficacy of ADCETRIS.

Immunogenicity assay results are highly dependent on several factors including assay sensitivity and specificity, assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of incidence of antibodies to brentuximab vedotin with the incidence of antibodies to other products may be misleading.

Elderly

Combination therapy

In older patients from clinical trials C25003 [ADCETRIS + AVD] and SGN35-014 [ADCETRIS + CHP] (≥ 60 years of age), the incidence of adverse events was similar across treatment arms. More serious adverse events and dose modifications (including dose delays, reductions, and discontinuations) were reported in the older patients compared with the overall study population. Advanced age was a risk factor for febrile neutropenia in patients in both arms. Older patients who received G-CSF primary prophylaxis had lower incidence of neutropenia and febrile neutropenia than those who did not receive G-CSF primary prophylaxis.

The safety and efficacy of ADCETRIS as part of the BrECADD regimen have not been established in patients over the age of 60 years.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at http://www.tga.gov.au/reporting-problems.

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 4.4 Special Warnings and Precautions for Use).

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Brentuximab vedotin is an ADC that delivers an antineoplastic agent that results in apoptotic cell death in CD30-expressing tumour cells (such as classical Hodgkin's lymphoma and systemic anaplastic large cell lymphoma). Nonclinical data suggest that the biological activity of brentuximab vedotin results from a multi-step process. Binding of the ADC to CD30 on the cell surface initiates internalisation of the ADC-CD30 complex, which then traffics to the lysosomal compartment. Within the cell, a single defined active species, MMAE, is released via proteolytic cleavage. Binding of MMAE to tubulin disrupts the microtubule network within the cell, induces cell cycle arrest and results in apoptotic death of the CD30-expressing tumour cell.

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

Cardiac electrophysiology

Forty-six (46) patients with CD30 expressing hematologic malignancies were evaluable of the 52 patients who received 1.8 mg/kg of brentuximab vedotin every 3 weeks as part of a phase 1, single-arm, open-label, multicentre cardiac safety study. The primary objective was to evaluate the effect of brentuximab vedotin on cardiac ventricular re-polarization and the predefined primary analysis was the change in QTc from baseline to multiple time points in Cycle 1.

The upper 90% confidence interval (CI) around the mean effect on QTc was <10 msec at each of the Cycle 1 and Cycle 3 post-baseline time points. These data indicate the absence of clinically relevant QT prolongation due to brentuximab vedotin administered at a dose of 1.8 mg/kg every 3 weeks in patients with CD30 expressing malignancies.

Clinical trials

Hodgkin lymphoma (HL)

Patients with previously untreated CD30+ Stage III or Stage IV Hodgkin lymphoma (HL) in combination with doxorubicin [A], vinblastine [V], and dacarbazine [D] (AVD) (Study C25003)

The efficacy and safety of ADCETRIS were evaluated in a randomised, open-label, 2-arm, multicentre trial in 1334 patients with previously untreated Stage III or Stage IV HL in combination with chemotherapy AVD. All patients had CD30-expressing HL. Sixty-two percent of patients had extranodal site involvement. Of the 1334 patients, 664 patients were randomised to the ADCETRIS + AVD arm and 670 patients were randomised to the ABVD (doxorubicin [A], bleomycin [B], vinblastine [V] and dacarbazine [D]) arm and stratified by the number of International Prognostic Factor Project (IPFP) risk factors and region. Patients were treated with 1.2 mg/kg of ADCETRIS administered as an intravenous infusion over 30 minutes on days 1 and 15 of each 28-day cycle + AVD. The median number of cycles received was 6 (range, 1 to 6 cycles). Table 13 provides a summary of the baseline patient and disease characteristics.

Table 13 Summary of baseline patient and disease characteristics in the phase 3 previously untreated HL study

Patient Characteristics	ADCETRIS + AVD n = 664	ABVD n = 670
Median age (range)	35 years (18-82)	37 years (18-83)
Patients ≥ 65 years old n (%)	60 (9)	62 (9)
Gender, n (%)	378M (57) 286F (43)	398M (59) 272F (41)
ECOG status, n (%)		
0	376 (57)	378 (57)
1	260 (39)	263 (39)
2	28 (4)	27 (4)
Missing	0	2
Disease Characteristics		
Median time from HL diagnosis to first dose (range)	0.92 mo (0.1-21.4)	0.89 mo (0.0-81.4)
Disease stage[a] at initial diagnosis of HL, n (%)		
III	237 (36)	246 (37)
IV	425 (64)	421 (63)
Not applicable	1 (< 1)	1 (< 1)
Missing	0	2 (< 1)
Extranodal involvement at time of diagnosis, n (%)	411 (62)	416 (62)
IPFP[b] risk factors, n (%)		
0-1	141 (21)	141 (21)
2-3	354 (53)	351 (52)
4-7	169 (25)	178 (27)
Bone marrow involvement at time of diagnosis or study entry, n (%)	147(22)	151 (23)
B symptoms[a],n (%)	400 (60)	381 (57)

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

The primary endpoint in Study C25003 was modified PFS per IRF, defined as time from randomisation 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. Timing of the modified event was the date of the first PET scan post completion of frontline therapy demonstrating the absence of CR, defined as Deauville score of ≥3. The median mPFS by IRF assessment was not estimable for either treatment arm. The results showed a statistically significant improvement in modified PFS for ADCETRIS+AVD, with a 2-sided p-value of 0.035 based on a stratified log-rank test. The stratified hazard ratio was 0.770 (95% CI, 0.603; 0.983), indicating a 23% reduction in the risk of modified PFS events for ADCETRIS+AVD versus ABVD. The results also showed a statistically significant improvement in OS in the ITT population for ADCETRIS + AVD at the second interim analysis for OS. Median OS was not reached for patients in either treatment arm. Table 14 provides the efficacy results for modified PFS and overall survival (OS).

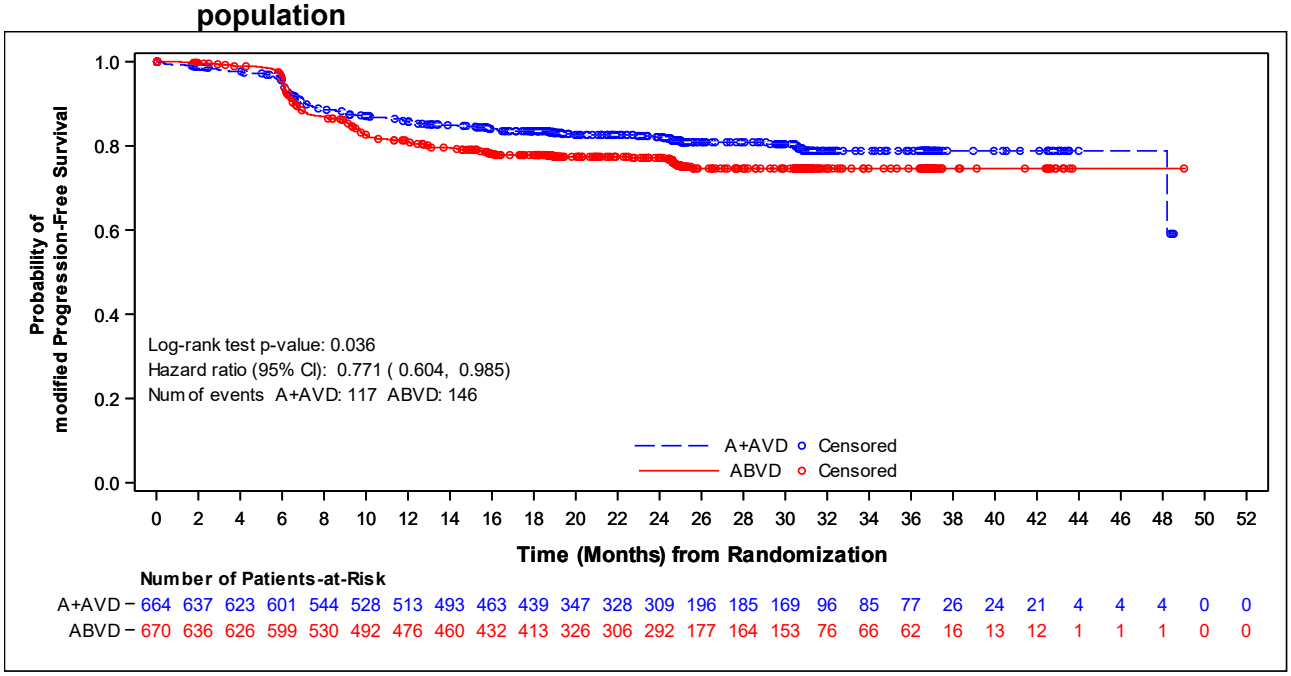
Table 14 Efficacy Results in Patients with Previously Untreated Stage III or Stage IV HL Treated with 1.2 mg/kg of ADCETRIS + AVD on Days 1 and 15 of a 28-Day Cycle

	ADCETRIS + AVD n = 664	ABVD n = 670	Stratified Hazard Ratio and p-value
	Modified Progression Free Survival (mPFS) Per IRF[a]		
Number of events (%)	117 (18)	146 (22)	0.77 (95% CI [0.60, 0.98]) p-value = 0.035
Estimated mPFS[a] per IRF at 2 Year (%)	82.1 (95% CI [78.8, 85.0])	77.2 (95% CI [73.7, 80.4])	
	Modified Progression Free Survival (mPFS) Per Investigator		
Number of events (%)	123 (19)	164 (24)	0.72 (95% CI [0.57, 0.91])
Number of Deaths at first pre-specified interim analysis(%)[b]	Overall Survival		
	28 (4)	39 (6)	0.73 (95% CI [0.45, 1.18]) p-value = 0.199
Number of Deaths at second interim analysis(%)[c]	39 (6)	64 (10)	0.59 (95% CI [0.396, 0.879] p-value = 0.009

a At the time of analysis, the median follow-up time for both arms was 24.6 months
b Data from first pre-specified interim OS analysis (median follow-up: 27.8 months for A + AVD; 27.4 months for ABVD)
c Data from the second interim OS analysis (median follow-up: 73.3 months for A+AVD; 72.4 months for ABVD)

Figure 1 below provides the Kaplan-Meier plot for the primary endpoint of mPFS per IRF.

Figure 1 Kaplan-Meier Plot modified Progression-Free Survival (mPFS) per IRF – ITT population



A+AVD: Brentuximab Vedotin (ADCETRIS) plus AVD (Doxorubicin [Adriamycin], Vinblastine, and Dacarbazine)
ABVD: ABVD (Doxorubicin (Adriamycin), Bleomycin, Vinblastine, and Dacarbazine)
Hazard ratio (A+AVD/ABVD) and 95% CI is based on a stratified Cox's proportional hazard regression model with stratification factors region and number of IPFP risk factors at baseline with treatment as the explanatory variable in the model. Hazard ratio <1 favors A+AVD arm.

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

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

Subgroup Analyses

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

Overall survival results in the stage III population for patients treated with ADCETRIS + AVD compared with patients treated with ABVD showed a HR = 0.86, 95% CI, (0.452; 1.648). Overall survival results in the stage IV population indicated a 52% reduction in the risk of death for patients treated with ADCETRIS + AVD compared with patients treated with ABVD [HR = 0.48, 95% CI (0.286, 0.799)].

Adult patients with previously untreated CD30+ Stage IIB with large mediastinal mass and/or extranodal disease, Stage III or Stage IV HL in combination with etoposide [E], cyclophosphamide [C], doxorubicin [A], dacarbazine [D], dexamethasone [D] (BrECADD) (Study HD21)

The safety and efficacy of ADCETRIS were evaluated in an open-label, prospective, multicentre phase III trial in 1500 patients with previously untreated Stage IIB with large mediastinal mass (mediastinal thoracic ratio [MTR] > 0.33) and/or extranodal lesions, Stage III, or Stage IV HL in combination with chemotherapy (etoposide [E], cyclophosphamide [C], doxorubicin [A], dacarbazine [D], dexamethasone [D] [BrECADD]). Of the 1500 patients, 751 patients were randomised to the BrECADD arm and 749 patients were randomised to eBEACOPP (escalated bleomycin [B], etoposide [E], doxorubicin [A], cyclophosphamide [C], vincristine [O], procarbazine [P] and prednisone [P]) arm and stratified by region of enrolment, age, sex, and International Prognostic Score (IPS). Patients in the BrECADD arm were treated on day 1 of each 21 day cycle with 1.8 mg/kg of ADCETRIS administered as an intravenous infusion over 30 minutes. Patients also received chemotherapy including cyclophosphamide 1250 mg/m^2, doxorubicin 40 mg/m^2, etoposide or etoposide phosphate 150 mg/m^2, dacarbazine 250 mg/m^2, and dexamethasone 40 mg.

All treated patients received primary prophylaxis with G-CSF (see 4.2 Dose and Method of Administration). After 2 cycles of treatment, restaging by PET was performed with PET negative patients to receive a total of 4 cycles and PET positive patients to receive a total of 6 cycles of therapy. The median number of cycles received in both arms was 4 (range, 1 to 6 cycles).
Table 15 provides a summary of the baseline patient and disease characteristics. There were no relevant differences in the patient and disease characteristics between the two arms.

Table 15 Summary of baseline patient and disease characteristics in the phase 3 previously untreated HL study

Patient Characteristics	BrECADD n = 751	eBEACOPP n = 749
Median age (range)	31 years (18-60)	31 years (18-60)
Patients < 45 years old, n (%)	590 (79)	584 (78)
Patients aged 45 to 60 years old, n (%)	161 (21)	165 (22)
Gender, n (%)		
Male	419 (56)	419 (56)
Female	332 (44)	330 (44)
ECOG status, n (%)		
0	514 (68)	521 (70)
1	223 (30)	205 (27)
2	11 (1)	18 (2)
Missing	3 (< 1)0	5 (< 1)
Disease Characteristics		
Median time from HL diagnosis to randomisation (range)	0.6 mo (0,12)	0.6 mo (0,10)
Disease stage[a] at initial diagnosis of HL, n (%)		
II	117 (16)	117 (16)
III	299 (40)	293 (39)
IV	332 (44)	334 (45)
Missing	3 (< 1)	5 (< 1)
IPS[b] Groups, n (%)		
0-2	394 (52)	403 (54)
3-7	357 (48)	346 (46)
B symptoms[a] n (%)	517 (69)	501 (67)

a. Per Ann Arbor Staging.

b. IPS = International Prognostic Score

The coprimary endpoints in Study HD21 were Treatment Related Morbidity [TRMB] and PFS [per investigator with central confirmation]. The first coprimary objective of the study was to demonstrate reduced toxicity of BrECADD compared with eBEACOPP, measured by TRMB. If reduced toxicity was shown by superiority test, the second coprimary objective was to further demonstrate noninferior efficacy of BrECADD compared with eBEACOPP in terms of PFS.

TRMB was defined as any Grade 3 or Grade 4 Common Terminology Criteria for Adverse Events (CTCAE) organ toxicity or Grade 4 haematological toxicity during primary chemotherapy, including the period of up to 30 days after the last chemotherapy dose.

At the time of the primary analysis, superiority was met for TRMB with BrECADD with an absolute risk reduction of -16.7 percentage points and with a statistically significant reduction in relative risk (stratified RR (95% CI): 0.712 (0.643, 0.789). The co-primary endpoint PFS regardless of missed visits and regardless of initialisation of new anticancer therapy met noninferiority with a statistically significant reduction in risk in the BrECADD treatment arm compared with eBEACOPP (unstratified HR=0.62 [multiplicity adjusted 95% CI, 0.369, 1.040]) (data cut off 31 December 2022).

Table 16 provides TRMB by treatment arm.

Table 16 Treatment Related Morbidity (TRMB) by treatment arm (Safety Population)

	BrECADD N = 747	eBEACOPP N = 741
Number of Patients with TRMB	314 (42)	435 (59)
Acute haematological toxicity Grade 4	233 (31)	386 (52)
Anemia	3 (< 1)	3 (< 1)
Thrombocytopenia	227 (30)	383 (52)
Infection	13 (2)	10 (1)
Acute Organ Toxicity; Grade 3 or Grade 4	139 (19)	129(17)
Cardiac Disorders	18 (2)	10 (1)
GI disorders (excluding vomiting, nausea, mucositis)	58 (8)	32 (4)
Hepatobiliary disorders	37 (5)	22 (3)
Nervous system disorders	20 (3)	40 (5)
Peripheral sensory neuropathy	9 (1)	17 (2)
Peripheral motor neuropathy	2 (< 1)	1 (< 1)
Nervous system disorder other than neuropathy	11 (2)	24 (3)
Renal or urinary disorders	7 (< 1)	10 (1)
Respiratory, thoracic, or mediastinal disorders	25 (3)	35 (5)
CMH p-value	< 0.0001	
Relative Risk - unstratified (BrECADD/eBEACOPP) (95% CI)	0.716 (0.646, 0.794)	
Relative Risk – stratified (BrECADD/eBEACOPP) (95% CI)	0.712 (0.643, 0.789)	
% Difference (BrECADD-eBEACOPP)	-16.7	
Exact 95% CI	-21.7, -11.5	

Incidence of TRMB was shown to be reduced in the BrECADD arm (42%) compared with eBEACOPP (58.7%) with a p-value < 0.0001. This was largely due to the reduction in Grade 4 haematological toxicities (31.2% in BrECADD and 52.1% in eBEACOPP).

Table 17 provides the efficacy results for PFS in the ITT population as of a data cut off of 31 December 2022.

Table 17 Efficacy results for previously untreated HL patients treated with 1.8 mg/kg of BrECADD on a 21 day cycle (PFS Primary Interim Analysis with data cut off of 31 December 2022)

	Intent to Treat (ITT) Population	
	BrECADD n = 751	**eBEACOPP n = 749**
Number of PFS events (%)	39 (5.2)	62 (8.3)
PFS[a] Hazard Ratio (98.87% CI[b])	0.619 (0.369, 1.040)	
Estimated PFS[c] (95% CI)		
At 3 Years	95.2 (93.3, 96.5)	92.3 (90.0, 94.0)
At 5 Years	91.5 (85.8, 94.9)	89.8 (86.8, 92.2)

a. PFS is per investigator with central confirmation.

b. CI was adjusted by the O'Brien-Fleming method with Lan-DeMets alpha-spending function and the actual information fraction of 66% observed at the interim analysis with the planned 154 PFS events at the final analysis.

c. Kaplan-Meier method is used to estimate the rates for PFS per investigator with central confirmation. The median PFS follow up time was 40.5 months.

OS showed comparable non-detrimental benefit in both BrECADD and eBEACOPP arms in the ITT population (HR 95% CI: 0.914 [0.403, 2.072] with 11 deaths in BrECADD [1.5%] and 12 in eBEACOPP [1.6%]). Other secondary efficacy endpoints including ORR, CR rate, duration of CR, and quality of life showed consistent evidence of non-inferiority in the BrECADD and eBEACOPP arms in the ITT population.

Prespecified subgroup analyses of PFS per Investigator assessment with central confirmation were performed for the ITT population including age, sex, enrolment region, IPS score, baseline Ann Arbor disease stage, baseline ECOG, baseline B symptoms, and Cycle 2 PET assessment. The analyses showed consistent evidence of non-inferiority for BrECADD arm patients compared with eBEACOPP group patients.

Patients with relapsed or refractory CD30+ HL following autologous stem cell transplant (ASCT) (Study SG035-0003)

The efficacy and safety of ADCETRIS as a single agent was evaluated in a pivotal open-label, single-arm, multicentre study (study SG035-0003) in 102 patients with relapsed or refractory HL. ADCETRIS was administered at a starting dose of 1.8 mg/kg (IV) infusion on day 1 of each 21-day cycle. See Table 18 below for a summary of baseline patient and disease characteristics.

Table 18 Summary of baseline patient and disease characteristics in the phase 2 relapsed or refractory CD30+ HL study (Study SG035-0003)

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

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

Eighteen (18) patients (18%) received 16 cycles of ADCETRIS; and the median number of cycles received was 9 (ranging from 1 to 16). Response to treatment with ADCETRIS was assessed by Independent Review Facility (IRF) using the Revised Response Criteria for Malignant Lymphoma (Cheson, 2007). Treatment response was assessed by spiral CT of chest, neck, abdomen and pelvis; PET scans and clinical data. Response assessments were performed at cycles 2, 4, 7, 10, 13, and 16 with PET at cycles 4 and 7.

The objective response rate (ORR) per IRF assessment was 75% (76 of 102 patients in the intent-to-treat [ITT] set). 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). 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 19.

Table 19 Efficacy results in relapsed or refractory CD30+ HL patients treated with 1.8 mg/kg of ADCETRIS every 3 weeks (Study SG035-0003)

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	**Median**	**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.

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

Tumour reduction was achieved in 94% of patients.

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.

Patients with relapsed or refractory CD30+ HL following at least two prior therapies when ASCT or multi-agent chemotherapy is not a treatment option

Data were collected from patients (n=15) in phase 1 dose escalation and clinical pharmacology studies, and from patients (n=26) in a Named Patient Program (NPP), with relapsed or refractory HL who had not received an ASCT, and who were treated with 1.8 mg/kg of ADCETRIS every 3 weeks. Baseline patient characteristics showed failure from multiple prior chemotherapy regimens (median of 3 with a range of 1 to 7) before first administration with brentuximab vedotin. Fifty nine percent (59%) of patients had advanced stage disease (stage III or IV) at initial diagnosis.

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

Patients with CD30+ HL at risk of relapse or progression following ASCT (Study SGN35-005)

The efficacy and safety of ADCETRIS were evaluated in a randomised, double-blinded, placebo controlled, 2-arm multicentre trial in 329 patients with HL at risk of relapse or progression following ASCT. The regulatory approval of this indication was based on an improvement in progression-free survival only; no improvement in overall survival has been demonstrated.

See Table 20 below for a summary of baseline patient characteristics. Of the 329 patients, 165 patients were randomised to the treatment arm and 164 patients were randomised to the placebo arm. The safety population in the ADCETRIS arm (N=167) included two additional patients who received at least one dose of ADCETRIS but were not randomised to the treatment arm. In the study, patients were to receive their first dose after recovery from ASCT (between days 30-45 following ASCT). Patients were treated with 1.8 mg/kg of ADCETRIS or matching placebo intravenously over 30 minutes every 3 weeks for up to 16 cycles. The median number of cycles received in both arms was 15 cycles.

In addition to other inclusion criteria, patients were also required to present with at least one of the following:

- 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 20 Summary of baseline patient and disease characteristics in the phase 3 CD30+ HL post-ASCT study (Study SGN35-005)

Patient Characteristics	ADCETRIS N =165	Placebo N=164
Age (median)	33 years (18-71)	32 years (18-76)
Gender	76M (46%)/89F (54%)	97M (59%)/67F (41%)
ECOG status		
0	87 (53%)	97 (59%)
1	77 (47%)	67 (41%)
2	1 (1%)	0
Disease Characteristics		
Number of prior chemotherapy regimens (median)	2 (2-8)	2 (2-7)
Time from HL diagnosis to first dose (median)	18.7 mo (6.1-204.0)	18.8 mo (7.4-180.8)
Disease stage at initial diagnosis of HL		
Stage I	1 (1%)	5 (3%)
Stage II	73 (44%)	61 (37%)
Stage III	48 (29%)	45 (27%)
Stage IV	43 (26%)	51 (31%)
Unknown	0	2 (1%)
PET scan Status prior to ASCT		
FDG-AVID	64 (39%)	51 (31%)
FDG-NEGATIVE	56 (34%)	57 (35%)
NOT DONE	45 (27%)	56 (34%)
Extranodal involvement at time of pre-ASCT relapse	54 (33%)	53 (32%)
B symptoms after failure of frontline therapy[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%)
Relapse occurred <12 months	53 (32%)	54 (33%)
Relapse occurred >=12	13 (8%)	13 (8%)

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

[b] Stratification factors at randomisation

Table 21 Efficacy results in CD30+ HL patients at risk of relapse or progression following ASCT treated with 1.8 mg/kg of ADCETRIS every 3 weeks (Study SGN35-005)

	ADCETRIS N=165	Placebo N=164	Stratified Hazard Ratio
Progression Free Survival (PFS)[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 using radiographic, biopsy, and clinical lymphoma assessments**		
	Not Reached (95% CI [-, -])	15.8 months (95% CI [8.5, -])	0.50 (95% CI [0.36, 0.70])[b]

[a]At the time of analysis, the median follow-up time for both arms was 30 months [range, 0 to 50]
[b]Stratified log-rank test was not performed for PFS per Investigator
* The primary efficacy analysis: PFS per IRF, defined as the time from randomisation to the first documentation of tumour progression or death.
**PFS per investigator using radiographic, biopsy, and clinical lymphoma assessments was a pre-specified sensitivity analysis

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.

Quality of life was assessed using the EQ-5D instrument. No clinically meaningful differences were observed between the treatment and placebo arms. Eighty-five patients in the placebo arm progressed and received subsequent treatments, of whom 72 (84.7%) received ADCETRIS.

Peripheral T-cell lymphoma (PTCL)

Patients with previously untreated CD30+ *PTCL in combination with cyclophosphamide [C], doxorubicin [H], and prednisone [P] (CHP) (Study SGN35-014)*

The efficacy and safety of ADCETRIS were evaluated in a randomised, double-blind, double-dummy, active-controlled, multicentre trial of 452 patients with previously untreated CD30+ PTCL in combination with cyclophosphamide [C], doxorubicin [H], and prednisone [P] (CHP). Of the 452 patients, 226 were randomised to treatment with ADCETRIS + CHP and 226 patients were randomised to treatment with CHOP (cyclophosphamide [C], doxorubicin [H], vincristine [O], and prednisone [P]). Randomisation was stratified by ALK-positive sALCL versus all other subtypes and by the International Prognostic Index (IPI) score. Patients were treated with 1.8 mg/kg of ADCETRIS administered as an intravenous infusion over 30 minutes on day 1 of each 21-day cycle 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 22 provides a summary of baseline patient and disease characteristics.

Table 22 Summary of baseline patient and disease characteristics in the phase 3 previously untreated 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 randomisation to the date of first documentation of progressive disease, death due to any cause, or receipt of subsequent anticancer chemotherapy to treat residual or progressive disease, whichever occurs first. Receipt of post treatment consolidative radiotherapy, post-treatment chemotherapy for the purpose of mobilising peripheral blood stem cells, or consolidative autologous or allogeneic stem cell transplant were not considered as disease progression or as having started new anticancer therapy.

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

The primary endpoint and alpha-protected, key secondary endpoints, which were evaluated hierarchically, were met. The median PFS per IRF 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 23 provides the efficacy results for PFS and other key secondary endpoints.

PFS per IRF for patients with centrally-confirmed sALCL was a pre-specified key secondary endpoint. The median PFS per IRF was 55.7 months on the ADCETRIS + CHP arm versus 54.2 months on the CHOP arm. The stratified hazard ratio was 0.59 (95% CI, 0.42; 0.84), compatible with a statistically

significant 41% reduction in the risk of PFS events for ADCETRIS + CHP versus CHOP (p value=0.003). No formal testing was performed in other histological subtypes, and no histological subtypes of PTCL were powered to detect a significant difference in treatment effect.

Table 23 Efficacy results in patients with previously untreated PTCL with 1.8 mg/kg of ADCETRIS on day 1 of a 3-week cycle (ITT population) (primary analysis)

	ADCETRIS + CHP n=226	CHOP n=226
PFS per IRF		
Number of patients with a PFS event, n (%)	95 (42)	125 (55)
Median PFS, months (95% CI)	48.2 (35.2, NE)	20.8 (12.7, 47.6)
Hazard ratio (95% CI)[a]	0.71 (0.54, 0.93)	
p-value[b]	0.0110	
OS[c]		
Number of deaths	51 (23)	73 (32)
Median OS, months (95% CI)	NE (NE, NE)	NE (54.2, NE)
Hazard ratio (95% CI)[a]	0.66 (0.46, 0.95)	
p-value[b]	0.0244	
CR Rate[d]		
% (95% CI)	68% (61.2, 73.7)	56% (49.0, 62.3)
p-value[e]	0.0066	
ORR[d]		
% (95% CI)	83% (77.7, 87.8)	72% (65.8, 77.9)
p-value[e]	0.0032	

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

a 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.

b p-value is calculated using a stratified log-rank test.

c Median OS follow-up in the ADCETRIS+CHP arm was 40.5 months; in the CHOP arm was 41.7 months.

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

e p-value is calculated using a stratified Cochran-Mantel-Haenszel test.

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.

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

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

Patients with relapsed or refractory sALCL (Study SG035-0004)

The efficacy and safety of ADCETRIS as a single agent was evaluated in an open-label, single-arm, multicentre study (study SG035-0004) in 58 patients with relapsed or refractory sALCL. Table 24 below for a summary of baseline patient and disease characteristics.

Table 24 Summary of baseline patient and disease characteristics in the phase 2 relapsed or refractory sALCL study (Study SG035-0004)

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 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 (of any degree) was achieved in 97% of patients. The estimated overall survival at 5 years was 60% (95% CI [47%, 73%]). The median observation time (time to death or last contact) from first dose was 71.4 months). The investigator assessments were generally consistent with the independent review of the scans. Of the patients treated, 9 responding patients went on to receive an allogeneic stem cell transplant and 9 responding patients went on to ASCT. For further efficacy results, see .

Table 25 Efficacy results in relapsed or refractory sALCL patients treated with 1.8 mg/kg of ADCETRIS every 3 weeks (Study SG035-0004)

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

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

b. Not estimable.

Tumour reduction was achieved in 97% of patients.

An exploratory intra-patient analysis showed that approximately 69% of the sALCL patients treated with ADCETRIS as part of the SG035-0004 clinical study experienced an improvement in clinical benefit as measured by longer progression free survival (PFS) compared with their most recent prior line of therapy.

Of the 17 patients (29%) who had B symptoms at baseline, 14 patients (82%) experienced resolution of all B symptoms in a median time from initiation of 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, multicentre 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 (CTCL)

Cutaneous T-cell Lymphoma (Study C25001)

The efficacy and safety of ADCETRIS as a single agent was evaluated in a pivotal phase 3, open-label, randomised, multicentre study in 128 patients with histologically confirmed CD30+ CTCL. Patients were stratified by disease subtype (mycosis fungoides [MF] or primary cutaneous anaplastic large cell lymphoma [pcALCL]) 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 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. provides a summary of the baseline patient and disease characteristics.

Table 26 Summary of Baseline Patient and Disease Characteristics in the Phase 3 CTCL Study (ITT Population)

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

The primary endpoint was objective response rate that lasts at least 4 months (ORR4) (duration from first response to last response ≥ 4 months), as determined by an independent review of the Global Response Score (GRS) consisting of skin evaluations (modified severity weighted assessment tool [mSWAT] assessment), nodal and visceral radiographic assessment, and detection of circulating

Sézary cells. The ORR4 was significantly higher in the ADCETRIS arm compared to the physician's choice arm (56.3% vs 12.5%, p<0.001). includes the results for ORR4 and other key secondary endpoints.

Table 27 Efficacy Results in CTCL Patients Treated with 1.8 mg/kg of ADCETRIS Every 3 Weeks (ITT Population)

	ADCETRIS (N=64)		Physician's Choice (Methotrexate or Bexarotene) N=64
Objective Response Rate lasting at least 4 months (ORR4) per IRF			
N (%)	36 (56.3)		8 (12.5)
Percent Difference (95% CI)		43.8 (29.1, 58.4)	
p-value		<0.001	
Complete Response (CR) per IRF			
N (%)	10 (15.6)		1 (1.6)
Percent Difference (95% CI)		14.1 (-4.0, 31.5)	
Adjusted p-value[a]		0.0046	
Progression Free Survival (PFS) per IRF			
Median (months)	16.7		3.5
Hazard Ratio		0.270	
95% CI		(0.17, 0.43)	
Adjusted p-value[a]		<0.001	
Skindex-29 Symptom Domain[b]			
Mean maximum reduction from baseline in disease symptoms (points)	-27.96		-8.62
Difference in maximum reduction (95% CI)		-18.9 (-26.6, -11.2)	
Adjusted p-value[a]		<0.001	

[a] Calculated from a weighted Holm's procedure

[b] Included the following components: skin hurts, skin condition burns or stings, skin itches, water bothers skin conditions (bathing, washing hands), skin is irritated, skin is sensitive and skin condition bleeds

Pre-specified subgroup analyses of ORR4 per IRF were performed by patients' CTCL subtype (MF, pcALCL), physicians' choice of treatment (methotrexate or bexarotene), baseline ECOG status, age, gender, and geographic region. The analyses showed a consistent trend towards benefit for patients who received ADCETRIS (56.3% ORR4) compared with patients who received physician's choice (12.5% ORR4). A higher percentage of patients with MF or pcALCL who were treated with ADCETRIS achieved ORR4 compared with the same patient population treated with physician's choice, with a difference of 39.8% (50% ADCETRIS vs. 10.2% physician's choice) for MF and 55.0% (75% ADCCETRIS vs. 20.0% physician's choice) for pcALCL.

Patient reported skin symptom burden was assessed using the symptom domain of Skindex-29 quality of life questionnaire. Symptom burden reduction from baseline was observed in both groups across the study duration, however significantly greater symptom burden reduction based on mean maximum reduction from baseline was observed in the ADCETRIS arm compared to the physician's choice arm. The difference between the treatment arms for the maximum reduction from baseline (- 18.9) exceeded all the estimated minimal important difference (MID) thresholds, demonstrating a clinically meaningful response.

5.2 PHARMACOKINETIC PROPERTIES

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

Absorption

Monotherapy

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 multi-exponential 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 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 brentuximab vedotin with approximately 50% to 80% of the exposure of the first dose being observed at subsequent doses. In the first cycle, higher MMAE exposure was associated with an absolute decrease in neutrophil count.

Combination therapy

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

After multiple-dose, IV infusion of 1.2 mg/kg brentuximab vedotin every two weeks, maximal serum concentrations of ADC were observed near the end of the infusion and elimination exhibited a multi-exponential decline with a $t_{1/2z}$ of approximately 4 to 5 days. Maximal plasma concentrations of MMAE were observed approximately 2 days after the end of infusion, and exhibited a mono-exponential decline with a $t_{1/2z}$ of approximately 3 to 4 days.

After multiple-dose, IV infusion of 1.2 mg/kg brentuximab vedotin every two weeks, steady-state trough concentrations of ADC and MMAE were achieved by Cycle 3. Once steady-state was achieved, the PK of ADC did not appear to change with time. ADC accumulation (as assessed by AUC_{14D} between Cycle 1 and Cycle 3) was 1.27-fold. The exposure of MMAE (as assessed by AUC_{14D} between Cycle 1 and Cycle 3) appeared to decrease with time by approximately 50%.

The pharmacokinetics of ADCETRIS in combination with CHP were evaluated in a single phase 3 study in 223 patients (SGN35-014). After multiple-dose IV infusion of 1.8 mg/kg ADCETRIS every 3 weeks, the pharmacokinetics of ADC and MMAE were similar to those of monotherapy.

The pharmacokinetics of ADCETRIS was not studied in the BrECADD regimen.

Distribution

In vitro, the binding of MMAE to human serum plasma proteins ranged from 68-82%. MMAE is not likely to displace or to be displaced by highly protein-bound medicines. *In vitro*, MMAE was a substrate of P-gp and was not an inhibitor of P-gp at clinical concentrations. In humans, the mean steady state volume of distribution was approximately 6-10 L for ADC. Based on population PK estimation the typical apparent volume of distribution of MMAE in the central compartment was 7.37 L and the typical apparent volume of distribution of MMAE in the peripheral compartment was 36.4 L.

Metabolism

The antibody component of the ADC is expected to be catabolised as a protein with component amino acids recycled or eliminated. *In vivo* data in animals and humans suggest that only a small fraction of MMAE released from brentuximab vedotin is metabolised. 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.

Excretion

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, with a typical apparent CL and half-life of MMAE of 19.99 L/day and 3-4 days respectively.

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

Pharmacokinetics in special populations

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

Hepatic impairment

The liver is a major route of elimination of the unchanged active metabolite MMAE.

A study evaluated the PK of brentuximab vedotin and MMAE after the administration of 1.2 mg/kg of ADCETRIS to patients with mild (Child-Pugh A; n=1), moderate (Child-Pugh B; n=5) and severe (Child-Pugh C; n=1) hepatic impairment. Compared to patients with normal hepatic function, MMAE exposure increased approximately 2.3-fold in patients with hepatic impairment (see 4.2 Dose and Method of Administration').

Renal impairment

The kidney is a route of excretion of the unchanged active metabolite MMAE.

A study evaluated the PK of brentuximab vedotin and MMAE after the administration of 1.2 mg/kg of ADCETRIS to patients with mild (n=4), moderate (n=3) and severe (n=3) renal impairment. Compared to patients with normal renal function, MMAE exposure increased approximately 1.9-fold in patients with severe renal impairment (creatinine clearance < 30 ml/min) (see 4.2 Dose and Method of Administration').

Elderly patients

The population pharmacokinetics of brentuximab vedotin were examined from several studies, including data from 380 patients up to 87 years old. The influence of age on pharmacokinetics was investigated and it was not a significant covariate. The safety profile in elderly patients with CTCL was consistent with that of younger patients, therefore no dosage adjustment is recommended for patients aged 65 and older.

Paediatric population

Clinical studies of brentuximab vedotin did not include sufficient numbers of patients below 18 years of age to determine whether the PK profile differs from adult patients.

5.3 PRECLINICALSAFETY DATA

Genotoxicity

MMAE was genotoxic in the rat bone marrow micronucleus study through an aneugenic mechanism. This effect is consistent with the pharmacological effect of MMAE as a microtubule disrupting agent. MMAE was not mutagenic in the bacterial reverse mutation assay (Ames test) or the L5178Y mouse lymphoma forward mutation assay.

Carcinogenicity

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

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

The reconstituted product contains trehalose dihydrate, sodium citrate dihydrate, citric acid monohydrate, and polysorbate 80 and water for injection.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

After reconstitution

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 ADCETRIS at 2°C-8°C. Refrigerate. Do not freeze. Keep the vial in the original carton in order to protect from light. Do not use beyond the expiry date included on the carton/vial.

6.5 NATURE AND CONTENTS OF CONTAINER

ADCETRIS is supplied in a glass vial with a butyl rubber stopper and an aluminium/plastic flip-off seal, containing 50 mg ADCETRIS as a white to off-white lyophilized cake or powder. Each pack of ADCETRIS contains 1 vial.

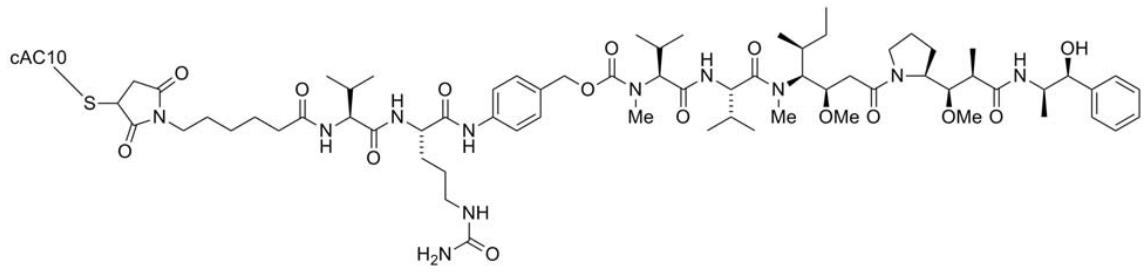
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

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

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

ADCETRIS (brentuximab vedotin) is a CD30-directed antibody-drug conjugate (ADC) consisting of three components: 1) the chimeric IgG1 antibody cAC10, specific for human CD30, 2) the microtubule disrupting agent MMAE, and 3) a protease-cleavable linker that covalently attaches MMAE to cAC10.



Brentuximab vedotin has an approximate molecular weight of 153 kDa. Approximately 4 molecules of MMAE are attached to each antibody molecule. Brentuximab vedotin is produced by chemical conjugation of the antibody and small molecule components. The antibody is produced by mammalian (Chinese hamster ovary) cells, and the small molecule components are produced by chemical synthesis.

CAS number

914088-09-8

7 PATIENT COUNSELLING INFORMATION

Patients should be provided with a copy of the Consumer Medicine Information (available at https://www.ebs.tga.gov.au/).

Patients should be advised to contact their treating physician if they experience signs and symptoms of adverse reactions with the use ADCETRIS as described in the CMI.

Patients should be reminded to inform all treating healthcare professionals that they are receiving ADCETRIS.

8 MEDICINE SCHEDULE (POISONS STANDARD)

Prescription Only Medicine (Schedule 4)

9 SPONSOR

Takeda Pharmaceuticals Australia Pty Ltd
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Ph: 1800 012 612
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10 DATE OF FIRST APPROVAL

20 December 2013

11 DATE OF REVISION

17 December 2025

Summary table of changes

Section changed	Summary of new information
4.1, 4.2, 4.4, 4.5, 4.8, 5.1	Update to include new indication and information relating the treatment of adult patients with previously untreated CD30+ Stage IIB with large mediastinal mass and/or extranodal disease, Stage III or Stage IV HL in combination with etoposide, cyclophosphamide, doxorubicin, dacarbazine, dexamethasone (BrECADD).