Product Monograph

Including Patient Medication Information

Pr**ADCETRIS®**

brentuximab vedotin for injection

Lyophilized powder for reconstitution, 50 mg/vial

Intravenous infusion

USP

Antineoplastic agent

Pfizer Canada ULC
17300 Trans-Canada Highway
Kirkland, QC H9J 2M5

Date of Authorization:
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Control Number: 301092

Recent Major Label Changes

Not applicable	

Table of Contents

Part 1: Healthcare Professional Information

1. Indications

Hodgkin Lymphoma (HL):

ADCETRIS (brentuximab vedotin for injection) is indicated for:

- the treatment of previously untreated patients with Stage IV HL, in combination with doxorubicin, vinblastine, and dacarbazine.
- the post autologous stem cell transplant (ASCT) consolidation treatment of patients with HL at increased risk* of relapse or progression (* see 14 Clinical Trials).
- the treatment of patients with HL after failure of ASCT or after failure of at least two multi-agent chemotherapy regimens in patients who are not ASCT candidates.

Clinical effectiveness in relapsed or refractory HL was based on promising response rates demonstrated in single-arm trials (see 14 Clinical Trials).

Systemic Anaplastic Large Cell Lymphoma (sALCL), CD30-Expressing Peripheral T-cell Lymphoma-Not Otherwise Specified (PTCL-NOS) or CD30-Expressing Angioimmunoblastic T-cell lymphoma (AITL):

ADCETRIS is indicated for the treatment of previously untreated adult patients with systemic anaplastic large cell lymphoma (sALCL), peripheral T-cell lymphoma-not otherwise specified (PTCL-NOS) or angioimmunoblastic T-cell lymphoma (AITL), whose tumours express CD30, in combination with cyclophosphamide, doxorubicin, and prednisone (CHP) (see 14 Clinical Trials).

Systemic Anaplastic Large Cell Lymphoma (sALCL):

ADCETRIS is indicated for the treatment of patients with sALCL after failure of at least one multi-agent chemotherapy regimen.

Clinical effectiveness in relapsed or refractory sALCL was based on promising response rates demonstrated in single-arm trials (see 14 Clinical Trials). No survival benefits have been established.

Primary Cutaneous Anaplastic Large Cell Lymphoma (pcALCL) or CD30-Expressing Mycosis Fungoides (MF):

ADCETRIS is indicated for the treatment of adult patients with pcALCL or CD30-expressing MF who have received prior systemic therapy.

1.1. Pediatrics

Pediatrics (<18 years of age): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of ADCETRIS in pediatric patients has not been established; therefore, Health Canada has not authorized an indication for pediatric use.

1.2. Geriatrics

Geriatrics (≥65 years of age): In the clinical trial of ADCETRIS in combination with doxorubicin, vinblastine, and dacarbazine (AVD) for previously untreated patients with advanced HL, (Study 5: ECHELON-1), older age was a risk factor for febrile neutropenia (see 8.2 Clinical Trial Adverse Reactions).

In the clinical trial of ADCETRIS in combination with cyclophosphamide [C], doxorubicin [H], and prednisone [P] (CHP) for treatment of previously untreated patients with CD30-expressing Peripheral T-Cell Lymphoma (PTCL) (Study 6: ECHELON-2), patients age 65 and older had a higher incidence of adverse reactions ≥ Grade 3 and serious adverse reactions compared with younger patients. Older age was a risk factor for febrile neutropenia (see 7 Warnings and Precautions, 7.1 Special Populations).

The safety and efficacy of ADCETRIS monotherapy have not been established in geriatric patients with HL at increased risk of relapse or geriatric patients with relapsed/refractory HL or relapsed/refractory sALCL. No meaningful differences in safety or efficacy were reported between patients age 65 and older and younger patients who have pcALCL or CD30-expressing MF.

2. Contraindications

- ADCETRIS is contraindicated for patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 Dosage Forms, Strengths, Composition, and Packaging.
- ADCETRIS is contraindicated for patients receiving concomitant bleomycin due to pulmonary toxicity.
- ADCETRIS is contraindicated for patients who have or have had progressive multifocal leukoencephalopathy (PML) (see 7 Warnings and Precautions, Neurologic, Progressive multifocal leukoencephalopathy).

3. Serious Warnings and Precautions Box

Clinically significant and/or life-threatening adverse events include:

- John Cunningham virus (JCV) infection resulting in progressive multifocal leukoencephalopathy (PML) and death (see 7 Warnings and Precautions, Neurologic, Progressive multifocal leukoencephalopathy)
- Stevens-Johnson syndrome and toxic epidermal necrolysis (see 7 Warnings and Precautions, Skin)
- Serious and opportunistic infections (see 7 Warnings and Precautions, Infections)
- Acute pancreatitis (see 7 Warnings and Precautions, Gastrointestinal)
- Gastrointestinal complications (see 7 Warnings and Precautions, Gastrointestinal)
- Pulmonary toxicity (see 7 Warnings and Precautions, Respiratory)

In addition to above, clinically significant and/or life-threatening adverse events in combination therapy with doxorubicin, vinblastine and dacarbazine (AVD) include:

- Febrile neutropenia (see 7 Warnings and Precautions, Hematologic)

ADCETRIS should only be administered by a qualified healthcare professional experienced in the use of antineoplastic therapy.

4. Dosage and Administration

4.1. Dosing Considerations

- ADCETRIS is for intravenous infusion and must be reconstituted and diluted prior to administration. **Do not administer as an intravenous push or bolus.**
- **Do not mix ADCETRIS with, or administer as an infusion with, other medicinal products.**

Dosing modification may be needed in the following situations (see 4.2 Recommended Dose and Dosage Adjustment section for details);

- Peripheral Neuropathy
- Neutropenia
- Thrombocytopenia
- Severe renal insufficiency
- Hepatic insufficiency

4.2. Recommended Dose and Dosage Adjustment

The recommended ADCETRIS dosage is provided in Table 1.

Table 1: Recommended ADCETRIS Dosage

Indication	Recommended Dose*	Administration	Frequency and Duration
Previously Untreated Stage IV Hodgkin Lymphoma	1.2 mg/kg up to a maximum of 120 mg in combination with AVD	Intravenous infusion over 30 minutes	Administer (along with G-CSF prophylaxis – see 7 Warnings and Precautions) every 2 weeks for a maximum of 12 doses or until disease progression or unacceptable toxicity.
Hodgkin Lymphoma Consolidation	1.8 mg/kg up to a maximum of 180 mg	Intravenous infusion over 30 minutes	Initiate ADCETRIS treatment within 4–6 weeks post-ASCT or upon recovery from ASCT. Administer every 3 weeks until a maximum of 16 cycles, disease progression, or unacceptable toxicity.
Relapsed/Refractory Hodgkin Lymphoma	1.8 mg/kg up to a maximum of 180 mg	Intravenous infusion over 30 minutes	Administer every 3 weeks until disease progression or unacceptable toxicity. In the absence of disease progression or unacceptable toxicity, patients who achieve stable disease or better should continue to receive ADCETRIS for a minimum of 8 cycles and up to a maximum of 16 cycles. Treatment beyond 16 cycles should be administered only when agreed to by the patient and their healthcare professional after consideration of the risks associated with prolonged treatment.
Previously Untreated Systemic Anaplastic Large Cell Lymphoma, CD30-Expressing Peripheral T-Cell Lymphoma-Not Otherwise Specified, or CD30-expressing Angioimmunoblastic T-cell lymphoma	1.8 mg/kg up to a maximum of 180 mg in combination with CHP	Intravenous infusion over 30 minutes	Administer every 3 weeks for 6 or 8 cycles, or until disease progression or unacceptable toxicity.

Indication	Recommended Dose*	Administration	Frequency and Duration
Relapsed/Refractory Systemic Anaplastic Large Cell Lymphoma	1.8 mg/kg up to a maximum of 180 mg	Intravenous infusion over 30 minutes	Administer every 3 weeks until disease progression or unacceptable toxicity. In the absence of disease progression or unacceptable toxicity, patients who achieve stable disease or better should continue to receive ADCETRIS for a minimum of 8 cycles and up to a maximum of 16 cycles. Treatment beyond 16 cycles should be administered only when agreed to by the patient and their healthcare professional after consideration of the risks associated with prolonged treatment.
Primary Cutaneous Anaplastic Large Cell Lymphoma or CD30-Expressing Mycosis Fungoides	1.8 mg/kg up to a maximum of 180 mg	Intravenous infusion over 30 minutes	Administer every 3 weeks for a maximum of 16 cycles or until disease progression or unacceptable toxicity.

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

The recommended dose for patients with renal or hepatic impairment is provided in Table 2 (see 10.3 Pharmacokinetics, Special Populations and Conditions: Hepatic insufficiency).

Table 2: Recommended Dose for Patients with Renal or Hepatic Impairment

Recommended Dose	Degree of Impairment	Recommended Dose
Renal Impairment		
ADCETRIS + AVD		
1.2 mg/kg up to a maximum of 120 mg* every 2 weeks	Normal Mild (CrCL >50-80 mL/min) Moderate (CrCL= 30-50 mL/min)	1.2 mg/kg up to a maximum of 120 mg* every 2 weeks
	Severe (CrCL < 30 mL/min)	Avoid use (see 7 Warnings and Precautions)
ADCETRIS Monotherapy or ADCETRIS + CHP		
1.8 mg/kg up to a maximum of 180 mg* every 3 weeks	Normal Mild (CrCL >50-80 mL/min) Moderate (CrCL = 30-50 mL/min)	1.8 mg/kg up to a maximum of 180 mg* every 3 weeks

Recommended Dose	Degree of Impairment	Recommended Dose
	Severe (CrCL < 30 mL/min)	Avoid use (see 7 Warnings and Precautions
Hepatic Impairment		
ADCETRIS + AVD		
1.2 mg/kg up to a maximum of 120 mg* every 2 weeks	Normal	1.2 mg/kg up to a maximum of 120 mg* every 2 weeks
	Mild (Child-Pugh A)	0.9 mg/kg up to a maximum of 90 mg* every 2 weeks
	Moderate (Child-Pugh B) Severe (Child-Pugh C)	Avoid use (see 7 Warnings and Precautions)
ADCETRIS Monotherapy or ADCETRIS + CHP		
1.8 mg/kg up to a maximum of 180 mg* every 3 weeks	Normal	1.8 mg/kg up to a maximum of 180 mg* every 3 weeks
	Mild (Child-Pugh A)	1.2 mg/kg up to a maximum of 120 mg* every 3 weeks
	Moderate (Child-Pugh B) Severe (Child-Pugh C)	Avoid use (see 7 Warnings and Precautions)

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

The recommended dose modifications for patients with peripheral neuropathy, neutropenia or thrombocytopenia are provided in Table 3.

Table 3: Dose Modifications for Peripheral Neuropathy, Neutropenia, and Thrombocytopenia

Recommended ADCETRIS dose	Severity	Dose Modification
Peripheral Neuropathy		
ADCETRIS + AVD		
1.2 mg/kg up to a maximum of 120 mg* every 2 weeks	Grade 2	Reduce ADCETRIS to 0.9 mg/kg up to a maximum of 90 mg* every 2 weeks
	Grade 3	Hold ADCETRIS until improvement to Grade 2 or lower and then, Reduce ADCETRIS to 0.9 mg/kg up to a maximum of 90 mg* every 2 weeks for the remaining duration of treatment If already at 0.9 mg/kg, consider discontinuing ADCETRIS
	Grade 4	Discontinue ADCETRIS

Recommended ADCETRIS dose	Severity	Dose Modification
ADCETRIS + CHP		
1.8 mg/kg up to a maximum of 180 mg* every 3 weeks	Grade 2	Sensory neuropathy: Continue treatment at same dose level Motor neuropathy: Reduce dose to 1.2 mg/kg, up to a maximum of 120 mg every 3 weeks
	Grade 3	Sensory neuropathy: Reduce dose to 1.2 mg/kg up to a maximum of 120 mg every 3 weeks Motor neuropathy: Discontinue dosing
	Grade 4	Sensory neuropathy: Discontinue dosing Motor neuropathy: Discontinue dosing
ADCETRIS Monotherapy		
1.8 mg/kg up to a maximum of 180 mg* every 3 weeks	New or worsening Grade 2 or 3	Hold ADCETRIS until improvement to baseline or Grade 1 and then, Reduce ADCETRIS to 1.2 mg/kg up to a maximum of 120 mg* every 3 weeks for the remaining duration of treatment
	Grade 4	Discontinue ADCETRIS
Neutropenia		
ADCETRIS + AVD		
1.2 mg/kg up to a maximum of 120 mg* every 2 weeks	Grade 3 or 4	Continue G-CSF prophylaxis
	Recurrent Grade 4 despite G-CSF prophylaxis	Consider discontinuing ADCETRIS or reducing the dose to 0.9 mg/kg up to a maximum of 90 mg* every 2 weeks
ADCETRIS + CHP		
1.8 mg/kg up to a maximum of 180 mg* every 3 weeks	Grade 3 or 4	Administer G-CSF prophylaxis for subsequent cycles for patients not receiving primary G-CSF prophylaxis
	Recurrent Grade 4 despite G-CSF prophylaxis	Consider discontinuing ADCETRIS or reducing the dose to 1.2 mg/kg, up to a maximum of 120 mg* every 3 weeks.
ADCETRIS Monotherapy		
1.8 mg/kg up to a maximum of 180 mg* every 3 weeks	Grade 3 or 4	Hold ADCETRIS until improvement to Grade 2 or lower Consider GCSF prophylaxis for subsequent- cycles
	Recurrent Grade 4 despite G-CSF prophylaxis	Consider discontinuing ADCETRIS or reducing the dose to 1.2 mg/kg up to a maximum of 120 mg* every 3 weeks upon improvement to Grade 2 or lower for the remaining duration of treatment
Thrombocytopenia		
Any dose	Grade 3 or 4	Monitor closely and consider platelet transfusions or dose delays.

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

- Do not administer as an intravenous push or bolus.
- Health Canada has not authorized an indication for pediatric use.

4.3. Reconstitution

Use appropriate aseptic technique for reconstitution and preparation of dosing solutions.

- Calculate the dose (mg) and determine the number of 50 mg vials of ADCETRIS required. The dose for patients with a weight of >100 kg should be calculated based on a weight of 100 kg.
- Reconstitute each 50 mg vial of ADCETRIS with 10.5 mL of Sterile Water for Injection, USP, to yield a single-use solution containing 5 mg/mL brentuximab vedotin.
- Direct the stream toward wall of vial and not directly at the cake or powder.
- Gently swirl the vial to aid dissolution. **DO NOT SHAKE.**
- Inspect the reconstituted solution for particulates and discoloration. The reconstituted solution should be clear to slightly opalescent, colorless, and free of visible particulates.

Dilution:

- Calculate the required volume of 5 mg/mL reconstituted ADCETRIS solution needed
- Withdraw this amount from the vials. The dose for patients weighing greater than 100 kg should be calculated based on a weight of 100 kg. Immediately add the reconstituted solution to an infusion bag containing a minimum volume of 100 mL to achieve a final concentration of 0.4 mg/mL to 1.8 mg/mL brentuximab vedotin. ADCETRIS can be diluted into 0.9% Sodium Chloride Injection, 5% Dextrose Injection or Lactated Ringer's Injection.
- Gently invert the bag to mix the solution. ADCETRIS contains no bacteriostatic preservatives.
- Following dilution, infuse the ADCETRIS solution immediately, or store the solution at 2–8°C and use within 24 hours of reconstitution. **DO NOT FREEZE.**
- Discard any unused portion left in the vial.

Do not mix ADCETRIS with, or administer as an infusion with, other medicinal products.

4.4. Administration

Follow procedures for proper handling and disposal of anticancer drugs.

4.5. Missed Dose

A missed dose should be administered as soon as possible. Subsequent doses should not be administered less than 2 weeks apart for combination therapy with AVD or less than 3 weeks apart for monotherapy.

5. Overdose

There is no known antidote for overdosage of ADCETRIS. In case of overdosage, the patient should be closely monitored for adverse reactions, particularly neutropenia, and supportive treatment should be administered.

For management of a suspected drug overdose, contact your regional poison control center. For the most recent information in the management of a suspected drug overdose, contact your regional poison control centre or Health Canada’s toll-free number, 1-844 POISON-X (1-844-764-7669).

6. Dosage Forms, Strengths, Composition, and Packaging

To help ensure the traceability of biologic products, healthcare professionals should record both the brand name and the non-proprietary (active ingredient) name as well as other product-specific identifiers such as the Drug Identification Number (DIN) and the batch/lot number of the product supplied.

Table 4: Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Intravenous infusion	Lyophilized powder, 50 mg	citric acid monohydrate, polysorbate 80, sodium citrate dihydrate, and trehalose dihydrate

ADCETRIS (brentuximab vedotin) for Injection is supplied as a single-use vial containing 50 mg of brentuximab vedotin as a sterile, white to off-white lyophilized, preservative-free cake or powder. Prior to administration, the contents of the ADCETRIS vial are reconstituted with 10.5 mL of Sterile Water for Injection, USP resulting in a clear to slightly opalescent, colorless solution containing 5 mg/mL brentuximab vedotin. The pH of the reconstituted solution is approximately 6.6. Non-medicinal ingredients include citric acid monohydrate, polysorbate 80, sodium citrate dihydrate, and trehalose dihydrate.

Description

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 potent microtubule-disrupting agent monomethyl auristatin E (MMAE), and 3) a protease-cleavable linker that covalently attaches MMAE to cAC10. The biological activity of brentuximab vedotin results from a multi-step process. Binding of the ADC to CD30 on the cell surface initiates internalization of the ADC-CD30 complex, which then traffics to the lysosomal compartment. Within the cell, MMAE is released via proteolytic cleavage. Binding of MMAE to tubulin disrupts the microtubule network within the cell, induces cell cycle arrest, and results in apoptotic death of the CD30-expressing tumor cell.

7. Warnings and Precautions

Please see 3 Serious Warnings and Precautions Box.

General

Infusion reactions

Immediate and delayed infusion-related reactions, as well as anaphylaxis, have been reported. Carefully monitor patients during and after infusion of ADCETRIS. Symptoms of an infusion reaction include chills, nausea, cough, and itching within 2 days after a dose. Symptoms of a severe infusion reaction include wheezing, difficulty breathing, syncope, hives, itching, and swelling. If anaphylaxis occurs, immediately and permanently discontinue administration of ADCETRIS and administer appropriate medical therapy. If an infusion-related reaction occurs, the infusion should be interrupted and appropriate medical management instituted. Patients who have experienced a prior infusion-related reaction should be premedicated for subsequent infusions. Premedication may include

acetaminophen, an antihistamine and a corticosteroid. In clinical trials, IRRs were reported more frequently and with more severity in patients who developed anti-drug antibodies (see 8 ADVERSE REACTIONS, 8.2 Clinical Trial Adverse Reactions, 10.4 Immunogenicity).

Cardiovascular

Cardiac Ventricular Repolarization

QT shortening was observed in CD30-positive patients treated with ADCETRIS. The clinical significance of QT shortening is unknown.

Endocrine and Metabolism

Hyperglycemia

Hyperglycemia has been reported during clinical trials in patients with an elevated body mass index (BMI) with or without a history of diabetes mellitus. If hyperglycemia develops, monitor the patient's serum glucose and administer anti-diabetic treatment as appropriate.

Tumor Lysis Syndrome

Tumor lysis syndrome (TLS) has been reported. Patients with rapidly proliferating tumor and high tumor burden may be at increased risk of TLS. Symptoms of TLS include nausea, vomiting, edema (swelling), shortness of breath, heart rhythm disturbances, and acute renal failure. Monitor at-risk patients closely and take prophylactic or treatment measures, as appropriate. Prophylaxis and treatment for TLS may include hydration, correction of electrolyte abnormalities, and anti-hyperuricemic agents. In severe cases of TLS, hemodialysis or hemofiltration may be required.

Gastrointestinal

Acute pancreatitis

Acute pancreatitis, including fatal outcomes, has been reported in patients treated with ADCETRIS. Consider the diagnosis of acute pancreatitis for patients presenting with new or worsening abdominal pain. Hold ADCETRIS for any suspected case of acute pancreatitis and discontinue if a diagnosis of acute pancreatitis is confirmed.

Gastrointestinal (GI) complications

GI complications, including intestinal obstruction, ileus, enterocolitis, neutropenic colitis, erosion, ulcer, perforation and hemorrhage, some with fatal outcomes, have been reported in patients treated with ADCETRIS. Lymphoma with preexisting GI involvement may increase the risk of perforation. In the event of new or worsening GI symptoms, including severe abdominal pain, perform a prompt diagnostic evaluation and treat appropriately.

Hematologic

Anemia

Grade 3 or 4 anemia can occur with ADCETRIS. Complete blood counts should be monitored prior to administration of each dose of ADCETRIS.

Neutropenia and Febrile Neutropenia

Prolonged (≥1 week) severe neutropenia and febrile neutropenia can occur with ADCETRIS. In clinical trials, neutropenia of any grade occurred in the majority of ADCETRIS-treated patients (see 8 Adverse Reactions, 8.2 Clinical Trial Adverse Reactions). Serious cases of febrile neutropenia, including fatal outcomes, have been reported with ADCETRIS.

An increased incidence of febrile neutropenia was reported in patients treated with ADCETRIS + AVD compared to patients treated with ADCETRIS monotherapy in clinical trials. Primary prophylaxis with G-CSF is recommended beginning in Cycle 1 for patients who receive treatment with ADCETRIS + AVD for previously untreated Stage IV HL, and for patients who receive treatment with ADCETRIS + CHP for CD30-expressing PTCL.

Monitor complete blood counts prior to each dose of ADCETRIS and consider more frequent monitoring for patients with Grade 3 or 4 neutropenia. Patients with Grade 3 or 4 neutropenia should be closely monitored for fever and managed by growth factor support, dose delays, reductions or discontinuations (see 4 Dosage and Administration and 8 Adverse Reactions, 8.2 Clinical Trial Adverse Reactions).

Thrombocytopenia

Prolonged (≥1 week) severe thrombocytopenia can occur with ADCETRIS. If Grade 3 or 4 thrombocytopenia develops, monitor closely and consider platelet transfusions or dose delays.

Hepatic/Biliary/Pancreatic

Hepatotoxicity

Serious cases of hepatotoxicity, including fatal outcomes, have occurred in patients receiving ADCETRIS. Cases were consistent with hepatocellular injury, including elevations of transaminases and/or bilirubin. Cases have occurred after the first dose of ADCETRIS or after ADCETRIS rechallenge. Preexisting liver disease, elevated baseline liver enzymes, and concomitant medications may also increase the risk. Monitor liver enzymes and bilirubin. Patients experiencing new, worsening, or recurrent hepatotoxicity may require a delay, change in dose, or discontinuation of ADCETRIS.

Hepatic impairment

Avoid use of ADCETRIS in patients with moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment. Dose reduction is required in patients with mild (Child-Pugh A) hepatic impairment (see 4 Dosage and Administration). MMAE exposure is increased in patients with hepatic impairment. Due to higher MMAE exposure, ≥Grade 3 adverse reactions and deaths may be more frequent in patients with moderate and severe hepatic impairment compared to patients with normal hepatic function (see 4 Dosage and Administration and 10 Clinical Pharmacology).

Immune

The efficacy and safety of, and ability to generate a primary or anamnestic response to immunization with, live attenuated or inactivated vaccines during or following ADCETRIS treatment have not been established; therefore, patients should be observed for failure to respond to a vaccine. The risks and

benefits of vaccinating patients with live attenuated, or inactivated, vaccines during or following ADCETRIS therapy should be considered.

Infections

Serious and opportunistic infections such as pneumonia, bacteremia, sepsis/septic shock (including fatal outcomes), herpes zoster, cytomegalovirus (reactivation), Pneumocystis jiroveci pneumonia, and oral candidiasis have been reported in patients treated with ADCETRIS. Symptoms of infection include fever (≥38°C), sore throat, difficulty breathing, painful sores (ulcers) around the mouth and/or anus, or pain on urination. Patients should be carefully monitored during treatment for the emergence of possible bacterial, fungal, or viral infections.

Monitoring and Laboratory Tests

Complete blood counts should be monitored prior to each dose of ADCETRIS, and more frequent monitoring should be considered for patients with Grade 3 or 4 neutropenia or thrombocytopenia. Primary prophylaxis with G-CSF beginning with Cycle 1 is recommended for all patients who receive ADCETRIS in combination with AVD for previously untreated Stage IV HL.

Neurologic

Peripheral Neuropathy

ADCETRIS treatment can cause peripheral neuropathy, both sensory and motor. Monitor patients for symptoms of neuropathy, such as hypoesthesia, hyperesthesia, paresthesia, discomfort, a burning sensation, neuropathic pain or weakness. Patients experiencing new or worsening peripheral neuropathy may require a delay, change in dose, or discontinuation of ADCETRIS (see 4 Dosage and Administration).

In clinical trials of ADCETRIS as monotherapy or in combination with chemotherapy, over half of ADCETRIS-treated patients experienced any grade of neuropathy. ADCETRIS-induced peripheral neuropathy is typically associated with cumulative exposure and is often reversible following cessation of treatment. The majority of patients who developed peripheral neuropathy experienced partial improvement or complete resolution at the end of treatment or during long-term follow-up. Time from onset to improvement or resolution increased with greater severity of neuropathy (see 8 Adverse Reactions, 8.2 Clinical Trial Adverse Reactions).

The trial of ADCETRIS in combination with AVD for previously untreated HL excluded patients with any form of baseline neuropathy, including asymptomatic Grade 1 neuropathy. Careful consideration of the benefits and risks, including alternative therapies, should be weighed prior to using ADCETRIS in combination with AVD for previously untreated patients with Stage IV HL who have pre-existing neuropathy.

Progressive multifocal leukoencephalopathy

John Cunningham virus (JCV) infection resulting in progressive multifocal leukoencephalopathy (PML) and death has occurred in ADCETRIS-treated patients. Contributing factors may include prior therapies and underlying disease that may cause immunosuppression.

Closely monitor patients for any new or worsening neurological, cognitive, or psychiatric signs or symptoms suggestive of PML. First onset of symptoms occurred at various times from initiation of ADCETRIS therapy, with some cases occurring within 3 months of initial exposure. Hold ADCETRIS

dosing for any suspected case of PML and initiate neurology consultation for evaluation of PML, which includes magnetic resonance imaging of the brain and cerebrospinal fluid analysis or a brain biopsy for evidence of JCV. Discontinue ADCETRIS dosing if a diagnosis of PML is confirmed.

Renal

Renal impairment

Avoid use of ADCETRIS in patients with severe renal impairment [creatinine clearance (CrCL) <30 mL/min]. MMAE exposure is increased in patients with severe renal impairment. Due to higher MMAE exposure, ≥Grade 3 adverse reactions may be more frequent in patients with severe renal impairment compared to patients with normal renal function (see 4 Dosage and Administration and 10 Clinical Pharmacology).

Reproductive Health

- **Fertility**

It is not known if ADCETRIS will affect human spermatogenesis. In non-clinical studies, brentuximab vedotin resulted in testicular toxicity which was partially resolved 16-weeks post last dose administration. Therefore, due to this potential risk, men should be advised not to impregnate their partner during treatment with ADCETRIS. Men of reproductive potential should use an appropriate method of barrier contraception throughout treatment with ADCETRIS and for at least 6 months after completing therapy (see Reproductive and Developmental Toxicology: Impairment of Fertility).

Respiratory

Cases of pulmonary toxicity, including pneumonitis, interstitial lung disease, and acute respiratory distress syndrome, some with fatal outcomes, have been reported in ADCETRIS-treated patients, either as single-agent or in combination with bleomycin. Concomitant use of ADCETRIS and bleomycin is contraindicated. Patients typically reported cough and dyspnea. Interstitial infiltration and/or inflammation were observed on radiographs and computed tomographic imaging of the chest. In the event of new or worsening pulmonary symptoms, a prompt diagnostic evaluation should be performed and patients should be treated appropriately. Consider holding ADCETRIS dosing during evaluation and until symptomatic improvement.

Skin

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN)

Cases of SJS and TEN, including fatal outcomes, have been reported with ADCETRIS. The symptoms of SJS and TEN include unexplained widespread skin pain, blisters on the skin and mucous membranes, hives, tongue swelling, a red or purple skin rash that spreads, or unexplained shedding of the skin. If SJS or TEN occurs, discontinue ADCETRIS and administer appropriate medical therapy.

7.1. Special Populations

7.1.1. Pregnancy

There are no adequate and well-controlled studies performed 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. In animal reproduction studies, brentuximab vedotin caused embryo-fetal toxicities including increased early resorption, post-implantation loss, decreased numbers of live fetuses, and external malformations (i.e., umbilical hernias and malrotated hindlimbs) at maternal exposures that were similar to human exposures at the recommended doses for patients. Brentuximab vedotin and MMAE were both shown to cross the placenta in this study (see 16 Non-Clinical Toxicology, Reproductive and Developmental Toxicology).

For women of childbearing potential, precautions should be taken to avoid pregnancy and at least two contraceptive methods should be used while taking ADCETRIS and for 6 months after completing therapy. If pregnancy occurs, the physician should be immediately informed. ADCETRIS should not be administered to pregnant women unless the possible benefits to the mother outweigh the risks to the fetus. If this drug is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus.

See the fertility section under 7 Warnings and Precautions, Reproductive Health: Female and Male Potential pertaining to advice for women whose male partners are being treated with ADCETRIS.

7.1.2. Breastfeeding

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

7.1.3. Pediatrics

Pediatrics (<18 years of age): Clinical trials of ADCETRIS did not include a sufficient number of pediatric patients to determine whether they respond differently than adult patients (see 10 Clinical Pharmacology). Based on the data submitted and reviewed by Health Canada, the safety and efficacy of ADCETRIS in pediatric patients has not been established; therefore, Health Canada has not authorized an indication for pediatric use.

7.1.4. Geriatrics

Geriatrics (≥65 years of age): In the clinical trial of ADCETRIS in combination with AVD for patients with advanced HL (Study 5: ECHELON-1), 9% of ADCETRIS-treated patients were age 65 or older. Older age was a risk factor for febrile neutropenia, occurring in 39% of patients age 65 or older versus 17% of patients less than age 65, who received ADCETRIS + AVD (see 8 Adverse Reactions, Previously Untreated Advanced Hodgkin Lymphoma (HL) (Study 5: ECHELON-1)).

In a clinical trial of ADCETRIS in combination with CHP as treatment for previously untreated patients with CD30-expressing PTCL (Study 6: ECHELON-2), 31% of ADCETRIS + CHP-treated patients were age 65 or older. Among patients who were age 65 or older, 29% experienced febrile neutropenia, 74% had adverse reactions ≥ Grade 3 and 49% had serious adverse reactions. Among patients younger than age 65, 14% experienced febrile neutropenia, 62% had adverse reactions ≥ Grade 3 and 34% had serious adverse reactions (see 14.1 Clinical Trials by Indication, Hodgkin Lymphoma (HL)).

The safety and efficacy of ADCETRIS monotherapy have not been established in geriatric patients with HL at high risk of relapse or geriatric patients with relapsed/refractory HL or relapsed/refractory sALCL (Studies 3, 1, and 2, respectively). Clinical trials of ADCETRIS in these indications included a total of 17

geriatric patients and this number is not sufficient to determine whether they respond differently than younger patients. In the clinical trial of ADCETRIS in pcALCL or CD30-expressing MF (Study 4: ALCANZA), 42% of ADCETRIS-treated patients were aged 65 or older. No meaningful differences in safety or efficacy were observed between these patients and younger patients (see 14.1 Clinical Trials by Indication, T-Cell Lymphoma).

8. Adverse Reactions

8.1. Adverse Reaction Overview

Across studies, the most common adverse reactions (≥20%), regardless of causality, were neutropenia, anemia, leukopenia, peripheral sensory neuropathy, nausea, upper respiratory tract infection, fatigue, constipation, thrombocytopenia, diarrhea, pyrexia, vomiting, alopecia, lymphopenia, peripheral neuropathy, rash, peripheral motor neuropathy, weight decreased, abdominal pain, cough, and stomatitis.

8.2. Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. Therefore, the frequencies of adverse reactions observed in the clinical trials may not reflect frequencies observed in clinical practice and should not be compared to frequencies reported in clinical trials of another drug.

Previously Untreated Advanced Hodgkin Lymphoma (HL) (Study 5: ECHELON-1)

ADCETRIS in combination with AVD was evaluated for the treatment of previously untreated patients with Stage III or IV HL in a randomized, open-label, multicenter clinical trial of 1334 patients. Patients were randomized to receive up to 6 cycles of ADCETRIS + AVD or ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) on Days 1 and 15 of each 28-day cycle. The recommended starting dose of ADCETRIS was 1.2 mg/kg intravenously over 30 minutes, administered approximately 1 hour after completion of AVD therapy. A total of 1321 patients received at least one dose of study treatment (662 ADCETRIS + AVD, 659 ABVD). The median number of treatment cycles in each study arm was 6 (range, 1-6) (see 14 Clinical Trials).

Nine patients on the ADCETRIS + AVD arm and 13 patients on the ABVD arm died within 30 days of last study treatment. Of the 9 on-study deaths among ADCETRIS + AVD-treated patients, 8 were considered treatment-related, of which 7 deaths were associated with neutropenia; none of these patients had received G-CSF primary prophylaxis prior to developing neutropenia. Of the 13 on-study deaths among ABVD treated patients, 11 were associated with pulmonary-related events and 6 of the 7 deaths considered treatment-related were associated with pneumonia or pneumonitis.

Adverse reactions that led to dose delays of one or more drugs in more than 5% of ADCETRIS + AVD-treated patients were neutropenia (21%) and febrile neutropenia (8%) (see 4 Dosage and Administration). Adverse reactions led to treatment discontinuation of one or more drugs in 13% of ADCETRIS + AVD-treated patients. Those that occurred in ≥1% of patients on the ADCETRIS + AVD arm were peripheral sensory neuropathy (3% of patients), peripheral neuropathy and peripheral motor neuropathy (2% each), and febrile neutropenia (1%). Adverse reactions that led to treatment discontinuation of one or more study drugs in ≥1% of patients on the ABVD arm were dyspnea (4%), pulmonary toxicity, cough, and decreased carbon monoxide diffusing capacity (2% each), and pneumonitis (1%).

In this study, 67% (n=443) of ADCETRIS + AVD-treated patients experienced any grade of neuropathy compared to 43% (n=286) of ABVD-treated patients. For patients treated with ADCETRIS + AVD, the median time to onset of any grade was 8 weeks (range, 0-29), of Grade 2 was 14 weeks (range, 0-28), and of Grade 3 was 16 weeks (range, 1-29). The median time from onset to resolution or improvement of any grade was 10 weeks (range, 0-139), of Grade 2 was 12 weeks (range, 0-123), and of Grade 3 was 17 weeks (range, 0-139). At the time of the primary analysis (median follow up 24.6 months), 43% of the patients who experienced peripheral neuropathy had complete resolution, 24% had improvement (a decrease in severity by one or more grades from highest grade) and 33% had no improvement at the time of their last evaluation. Of 443 patients who experienced any grade of neuropathy, 251 patients had residual neuropathy at the time of their last evaluation.

Serious adverse reactions, regardless of causality, were reported in 43% of ADCETRIS + AVD-treated patients compared to 27% in patients treated with ABVD. The most common serious adverse reactions following ADCETRIS + AVD treatment (≥2% of patients) were febrile neutropenia (17%), pyrexia (7%), neutropenia and pneumonia (3% each), and abdominal pain, sepsis, constipation, diarrhea, pulmonary embolism, vomiting, and dehydration (2% each).

Infusion-related reactions were reported in 57 patients (9%) in the ADCETRIS + AVD arm and 100 patients (15%) in the ABVD arm. Grade 3 events were reported in 3 of the 57 patients treated with ADCETRIS + AVD who experienced infusion-related reactions. The most common adverse reaction (≥2%) associated with infusion-related reactions was nausea (2%).

Table 5: Adverse Reactions Reported in ≥10% of ADCETRIS + AVD-Treated Patients in Study 5 (ECHELON-1)

	ADCETRIS + AVD Total N = 662 % of patients			**ABVD Total N = 659 % of patients**		
Adverse Reaction	**Any Grade**	**Grade 3**	**Grade 4**	**Any Grade**	**Grade 3**	**Grade 4**
Blood and lymphatic system disorders						
Anemia[1]	98	11	<1	92	6	<1
Neutropenia[1]	91	20	62	89	31	42
Febrile neutropenia[2]	19	13	6	8	6	2
Gastrointestinal disorders						
Constipation	42	2	-	37	<1	<1
Vomiting	33	3	-	28	1	-
Diarrhea	27	3	<1	18	<1	-
Stomatitis	21	2	-	16	<1	-
Abdominal pain	21	3	-	10	<1	-
Abdominal pain upper	10	<1	-	5	-	-
Nervous system disorders						
Peripheral sensory neuropathy	65	10	<1	41	2	-
Peripheral motor neuropathy	11	2	-	4	<1	-
General disorders and administration site conditions						
Pyrexia	27	3	<1	22	2	-
Musculoskeletal and connective tissue disorders						
Bone pain	19	<1	-	10	<1	-

	ADCETRIS + AVD Total N = 662 % of patients			ABVD Total N = 659 % of patients		
Adverse Reaction	**Any Grade**	**Grade 3**	**Grade 4**	**Any Grade**	**Grade 3**	**Grade 4**
Back pain	13	<1	-	7	-	-
Respiratory, thoracic and mediastinal disorders						
Dyspnea	12	1	-	19	2	-
Investigations						
Decreased weight	22	<1	-	6	<1	-
Increased alanine aminotransferase	10	3	-	4	<1	-
Metabolism and nutrition disorders						
Decreased appetite	18	<1	-	12	<1	-
Psychiatric disorders						
Insomnia	19	<1	-	12	<1	-

[1] Derived from laboratory values and adverse reaction data; data are included for clinical relevance irrespective of rate between arms

[2] In a subset of 83 patients who also received primary prophylaxis with granulocyte colony-stimulating factor (G-CSF), the rate of febrile neutropenia was 11%.

AVD = doxorubicin, vinblastine, and dacarbazine
ABVD = doxorubicin, bleomycin, vinblastine, and dacarbazine
Events were graded using the National Cancer Institute Common Terminology for Adverse Events (NCI CTCAE) Version 4.03
Events listed are those having a ≥5% difference in rate between treatment arms

At the 6-year post-treatment follow up analysis (median follow up 65.7 months), 72% (n=318) of the patients who experienced peripheral neuropathy had complete resolution, 14% (n=61) had partial improvement, and 14% (n=64) had no improvement. Of the patients who experienced peripheral neuropathy, 16% (n=71) had Grade 1, 9% (n=38) had Grade 2, 3% (n=15) had Grade 3, and <1% (n=1) had Grade 4 neuropathy.

Hodgkin Lymphoma (HL) Consolidation Trial (Study 3: AETHERA)

ADCETRIS was studied in 329 patients with HL at high risk of relapse or progression post-ASCT in a phase 3 randomized, double-blind, placebo-controlled clinical trial in which the recommended starting dose and schedule was 1.8 mg/kg of ADCETRIS administered intravenously over 30 minutes every 3 weeks or placebo for up to 16 cycles. Of the 329 enrolled patients, 327 (167 ADCETRIS, 160 placebo) received at least one dose of study treatment. In the ADCETRIS-treatment arm, median duration of treatment was 48 weeks (range, 3–60); mean duration of treatment was 38 weeks. In the placebo arm, median duration of treatment was 47 weeks (range, 3–62); mean duration of treatment was 34 weeks. The median number of treatment cycles in each study arm was 15 (range, 1–16) and 80 patients (48%) in the ADCETRIS-treatment arm received 16 cycles (see 14 Clinical Trials).

In this HL consolidation study, 67% of ADCETRIS-treated patients experienced any grade of neuropathy. The median time to first onset of any grade was 14 weeks (range, 0.1–47), of Grade 2 was 27 weeks (range, 0.4–52) and of Grade 3 was 34 weeks (range, 7–106). The median time from onset to resolution

or improvement of any grade was 23 weeks (range, 0.1–138), of Grade 2 was 24 weeks (range, 1–108) and of Grade 3 was 25 weeks (range, 2–98). Of the patients who reported neuropathy, 59% had complete resolution, 26% had partial improvement, and 15% had no improvement at the time of their last evaluation. Of the patients who reported neuropathy, 41% had residual neuropathy at the time of their last evaluation [Grade 1 (28%), Grade 2 (10%), Grade 3 (4%)].

In the ADCETRIS–treated arm, the most common treatment emergent adverse reactions (≥20%), regardless of causality, were neutropenia, peripheral sensory neuropathy, thrombocytopenia, anemia, upper respiratory tract infection, fatigue, peripheral motor neuropathy, nausea, cough, and diarrhea. Serious adverse reactions, regardless of causality, were reported in 25% of ADCETRIS-treated patients. The most common serious adverse reactions were pneumonia (4%), pyrexia (4%), vomiting (3%), nausea (2%), hepatotoxicity (2%) and peripheral sensory neuropathy (2%).

One patient in the ADCETRIS arm died within 30 days of last study treatment due to treatment-related acute respiratory distress syndrome associated with pneumonitis.

Adverse reactions that led to dose delays in more than 5% of ADCETRIS-treated patients were neutropenia (22%), peripheral sensory neuropathy (16%), upper respiratory tract infection (6%), and peripheral motor neuropathy (6%). Adverse reactions led to treatment discontinuation in 32% of ADCETRIS-treated patients. Adverse reactions that led to treatment discontinuation in 2 or more patients were peripheral sensory neuropathy (14%), peripheral motor neuropathy (7%), acute respiratory distress syndrome (1%), paresthesia (1%) and vomiting (1%).

Infusion-related reactions were reported in 25 patients (15%) in the ADCETRIS-treated arm and 3 patients (2%) in the placebo arm. Grade 3 events were reported in 3 of the 25 ADCETRIS-treated patients who experienced infusion-related reactions. No Grade 4 infusion-related reactions were reported. The most common adverse reactions (≥2%) associated with infusion-related reactions reported in ADCETRIS-treated patients were nausea (4%), chills (4%), dyspnea (2%), headache (2%), pruritus (2%), rash (2%), back pain (2%), and vomiting (2%).

Adverse reactions, regardless of causality, occurring in ≥5% of patients in the ADCETRIS arm and at a higher rate than the placebo arm, regardless of causality, using the NCI CTCAE Version 4.0, are shown in Table 6.

Table 6: Commonly Reported Adverse Reactions (≥5% of Patients and at a Higher Rate in the ADCETRIS Arm in Study 3: AETHERA)

	ADCETRIS Total N =167 n (%) of patients			**Placebo Total N = 160 n (%) of patients**		
Adverse Reaction	**Any Grade**	**Grade 3**	**Grade 4**	**Any Grade**	**Grade 3**	**Grade 4**
Blood and lymphatic system disorders	148 (89)	51 (31)	20 (12)	89 (56)	14 (9)	10 (6)
Neutropenia[a]	130 (78)	50 (30)	15 (9)	55 (34)	10 (6)	7 (4)
Thrombocytopenia[a]	68 (41)	4 (2)	7 (4)	32 (20)	5 (3)	3 (2)
Anemia[a]	45 (27)	7 (4)	-	31 (19)	3 (2)	-
Leukopenia	9 (5)	6 (4)	-	3 (2)	1 (1)	-
Nervous system disorders	116 (69)	25 (15)	-	48 (30)	5 (3)	-
Peripheral sensory neuropathy	94 (56)	17 (10)	-	25 (16)	2 (1)	-
Peripheral motor neuropathy	38 (23)	10 (6)	-	3 (2)	1 (1)	-

	ADCETRIS Total N =167 n (%) of patients			Placebo Total N = 160 n (%) of patients		
Adverse Reaction	**Any Grade**	**Grade 3**	**Grade 4**	**Any Grade**	**Grade 3**	**Grade 4**
Headache	19 (11)	3 (2)	-	13 (8)	1 (1)	-
Paresthesia	16 (10)	3 (2)	-	2 (1)	-	-
Infections and infestations	100 (60)	10 (6)	1 (1)	80 (50)	8 (5)	-
Upper respiratory tract infection	44 (26)	-	-	37 (23)	2 (1)	-
Herpes zoster	12 (7)	1 (1)	-	4 (3)	2 (1)	-
Bronchitis	10 (6)	-	-	10 (6)	-	-
Pneumonia	9 (5)	4 (2)	1 (1)	4 (3)	4 (3)	-
Pharyngitis	8 (5)	-	-	4 (3)	-	-
Gastrointestinal disorders	91 (54)	16 (10)	1 (1)	50 (31)	4 (3)	-
Nausea	36 (22)	5 (3)	-	12 (8)	-	-
Diarrhea	33 (20)	3 (2)	-	16 (10)	1 (1)	-
Vomiting	27 (16)	4 (2)	-	11 (7)	-	-
Abdominal pain	23 (14)	3 (2)	-	5 (3)	-	-
Constipation	21 (13)	4 (2)	-	5 (3)	-	-
Dyspepsia	11 (7)	-	-	6 (4)	-	-
General disorders and administration site conditions	80 (48)	8 (5)	-	66 (41)	5 (3)	-
Fatigue	40 (24)	3 (2)	-	29 (18)	4 (3)	-
Pyrexia	31 (19)	3 (2)	-	25 (16)	-	-
Chills	17 (10)	-	-	8 (5)	-	-
Asthenia	13 (8)	1 (1)	-	7 (4)	1 (1)	-
Pain	9 (5)	-	-	5 (3)	-	-
Musculoskeletal and connective tissue disorders	75 (45)	2 (1)	-	50 (31)	2 (1)	-
Arthralgia	30 (18)	1 (1)	-	15 (9)	-	-
Muscle spasms	18 (11)	-	-	9 (6)	-	-
Myalgia	18 (11)	1 (1)	-	6 (4)	-	-
Pain in extremity	11 (7)	-	-	8 (5)	-	-
Muscular weakness	8 (5)	-	-	1 (1)	-	-
Respiratory, thoracic and mediastinal disorders	67 (40)	4 (2)	2 (1)	53 (33)	1 (1)	1 (1)
Cough	35 (21)	-	-	26 (16)	-	-
Dyspnea	21 (13)	-	-	10 (6)	-	1 (1)
Skin and subcutaneous tissue disorders	62 (37)	2 (1)	-	61 (38)	-	-
Pruritus	20 (12)	1 (1)	-	12 (8)	-	-
Rash	13 (8)	1 (1)	-	5 (3)	-	-
Dry skin	10 (6)	-	-	7 (4)	-	-
Investigations	45 (27)	8 (5)	1 (1)	31 (19)	6 (4)	-
Weight decreased	32 (19)	1 (1)	-	9 (6)	-	-
Metabolism and nutrition disorders	40 (24)	10 (6)	1 (1)	20 (13)	4 (3)	1 (1)
Decreased appetite	20 (12)	1 (1)	-	9 (6)	-	-
Hypokalemia	10 (6)	5 (3)	-	6 (4)	2 (1)	1 (1)

	ADCETRIS Total N =167 n (%) of patients			Placebo Total N = 160 n (%) of patients		
Adverse Reaction	**Any Grade**	**Grade 3**	**Grade 4**	**Any Grade**	**Grade 3**	**Grade 4**
Psychiatric disorders	34 (20)	-	1 (1)	22 (14)	2 (1)	1 (1)
Insomnia	14 (8)	-	-	5 (3)	-	-
Vascular disorders	28 (17)	2 (1)	1 (1)	18 (11)	2 (1)	-
Hypotension	10 (6)	2 (1)	-	4 (3)	1 (1)	-
Cardiac disorders	18 (11)	3 (2)	1 (1)	12 (8)	1 (1)	-
Sinus tachycardia	10 (6)	1 (1)	-	3 (2)	-	-

[a] Includes adverse reactions and laboratory abnormalities
Events were graded using the NCI CTCAE Version 4

Relapsed/Refractory Hodgkin Lymphoma (HL) Trial (Study 1)

ADCETRIS was studied in 102 patients with HL (Study 1) in a single arm phase 2 trial in which the recommended starting dose and schedule was 1.8 mg/kg intravenously every 3 weeks for a maximum of 16 cycles. Median duration of treatment was 27 weeks (range, 3 to 56 weeks) (see 14 Clinical Trials).

The treatment-emergent adverse reactions that occurred in ≥20% of HL patients in Study 1 were: leukopenia (61%), neutropenia (54%), peripheral sensory neuropathy (52%), upper respiratory tract infection (47%), fatigue (46%), nausea (42%), diarrhea (36%), anemia (33%), pyrexia (29%), thrombocytopenia (28%), lymphopenia (24%), vomiting (22%), and cough (21%). Grade 3 treatment-emergent adverse reactions that occurred in more than 2% of patients included neutropenia (15%), peripheral sensory neuropathy (9%), anemia (8%), thrombocytopenia (7%), lymphopenia (7%), leukopenia (6%), peripheral motor neuropathy (4%), and hyperglycemia (4%). Grade 4 treatment-emergent adverse reactions included neutropenia (6%), thrombocytopenia (2%), anemia (2%), abdominal pain (1%), and lymphopenia (1%).

Serious adverse reactions, regardless of causality, were reported in 25 (25%) of patients receiving ADCETRIS. The serious adverse reactions experienced by at least 2 HL patients were abdominal pain, pulmonary embolism, demyelinating polyneuropathy, pneumonitis, pneumothorax, pyelonephritis, and pyrexia.

Peripheral neuropathy was experienced by 55% of the patients. The median time to first onset of any grade was 12 weeks (range, 0.1–41), of Grade 2 was 27 weeks (range, 0.1–52) and of Grade 3 was 38 weeks (range, 24–57). The median time from onset to resolution or improvement of any grade was 20 weeks (range, 1–107), of Grade 2 was 22 weeks (range, 1–94), and of Grade 3 was 15 weeks (range, 2–59). Of the patients who reported neuropathy, 61% had complete resolution, 25% had partial improvement, and 14% had no improvement. Of the patients who reported neuropathy, 39% had residual neuropathy at the time of their last evaluation [Grade 1 (27%), Grade 2 (13%)].

Adverse reactions that led to dose reductions in at least 2 HL patients included peripheral sensory neuropathy (10%). Adverse reactions that led to dose delays in at least 2 HL patients included neutropenia (16%), peripheral sensory neuropathy (13%), thrombocytopenia (4%), upper respiratory tract infection, alanine aminotransferase increased, herpes zoster, influenza, lymphadenopathy and pyelonephritis (2%). Adverse reactions that led to treatment discontinuation in at least 2 patients with

HL were peripheral sensory neuropathy (6%), peripheral motor neuropathy (3%) and Hodgkin disease recurrent (2%).

One ADCETRIS-treated patient died 40 days after last study treatment due to ARDS considered not treatment-related and after a prior episode of treatment-related acute pancreatitis; and one ADCETRIS-treated patient died 706 days after last study treatment due to myelodysplastic syndrome considered treatment related.

Grade 1 or 2 infusion-related reactions were reported for 12 HL patients (12%). The adverse reactions that were associated with infusion-related reactions in HL patients in Study 1 were chills (5%), nausea (4%), dyspnea (4%), pruritus (4%), cough (3%), erythema (2%), flushing (2%), throat tightness (2%) and in 1 patient each, dizziness, pyrexia, rash, vomiting, back pain, dyspepsia, dysphagia, hypoesthesia facial, oropharyngeal pain, and urticaria.

Table 7: Commonly Reported Adverse Reactions (≥ 5% of Patients in Study 1)

	HL Total N = 102 n (%) of patients		
System Organ Class Preferred Term	**Any Grade**	**Grade 3**	**Grade 4**
Blood and lymphatic system disorders[a]	*41 (40)*		
Leukopenia	62 (61)	6 (6)	-
Neutropenia	55 (54)	15 (15)	6 (6)
Anemia	34 (33)	8 (8)	2 (2)
Thrombocytopenia	29 (28)	7 (7)	2 (2)
Lymphopenia	24 (24)	7 (7)	1 (1)
Lymphadenopathy	11 (11)	-	-
Nervous system disorders	*66 (65)*		
Peripheral sensory neuropathy[b]	53 (52)	9 (9)	-
Headache	19 (19)	-	-
Peripheral motor neuropathy[c]	16 (16)	4 (4)	-
Dizziness	11 (11)	-	-
General disorders and administration site conditions	*72 (71)*		
Fatigue	47 (46)	2 (2)	-
Pyrexia	30 (29)	2 (2)	-
Chills	13 (13)	-	-
Pain	7 (7)	-	-
Gastrointestinal disorders	*77 (75)*		
Nausea	43 (42)	-	-
Diarrhea	37 (36)	1 (1)	-
Vomiting	22 (22)	-	-
Abdominal pain	17 (17)	1 (1)	1 (1)
Constipation	16 (16)	-	-

	HL Total N = 102 n (%) of patients		
System Organ Class Preferred Term	**Any Grade**	**Grade 3**	**Grade 4**
Dyspepsia	5 (5)	-	-
Abdominal pain upper	6 (6)	1 (1)	-
Infections and infestations	*65 (64)*		
Upper respiratory tract infection[d]	48 (47)	-	-
Bronchitis	9 (9)	-	-
Urinary tract infection	6 (6)	1 (1)	-
Herpes zoster	7 (7)	-	-
Respiratory, thoracic and mediastinal disorders	*56 (55)*		
Cough	21 (21)	-	-
Dyspnea	13 (13)	1 (1)	-
Oropharyngeal pain	11 (11)	-	-
Productive cough	6 (6)	-	-
Nasal congestion	6 (6)	-	-
Skin and subcutaneous tissue disorders	*64 (63)*		
Rash	14 (14)	-	-
Pruritus	16 (16)	-	-
Alopecia	13 (13)	-	-
Night sweats	12 (12)	-	-
Hyperhidrosis	6 (6)	-	-
Musculoskeletal and connective tissue disorders	*63 (62)*		
Myalgia	17 (17)	-	-
Arthralgia	19 (19)	-	-
Back pain	14 (14)	-	-
Pain in extremity	10 (10)	-	-
Muscle spasms	9 (9)	-	-
Neck pain	6 (6)	-	-
Bone pain	8 (8)	1 (1)	-
Musculoskeletal pain	5 (5)	-	-
Psychiatric disorders	*27 (26)*		
Insomnia	14 (14)	-	-
Anxiety	11 (11)	2 (2)	-
Depression	8 (8)	-	-
Metabolism and nutrition disorders	*23 (23)*		
Decreased appetite	11 (11)	-	-
Hyperglycemia	6 (6)	4 (4)	-
Investigations	*17 (17)*		

	HL Total N = 102 n (%) of patients		
System Organ Class Preferred Term	**Any Grade**	**Grade 3**	**Grade 4**
Weight decreased	6 (6)	-	-
Vascular disorders	*13 (13)*		
Hot flush	5 (5)	-	-
Neoplasms benign, malignant and unspecified (including cysts and polyps)	*11 (11)*		
Hodgkin's disease recurrent	7 (7)	1 (1)	-

[a] Includes adverse reactions and laboratory abnormalities

[b] Includes peripheral sensory neuropathy, paresthesia, neuralgia, hyperesthesia, hypoesthesia, and burning sensation

[c] Includes peripheral motor neuropathy, demyelinating polyneuropathy, muscular weakness, and polyneuropathy

[d] Includes terms upper respiratory tract infection, sinusitis, nasopharyngitis, rhinitis, viral upper respiratory tract infection, and acute sinusitis

Events were graded using the NCI CTCAE Version 3.0

Previously Untreated Systemic Anaplastic Large Cell Lymphoma (sALCL), CD30-Expressing Peripheral T-Cell Lymphoma-Not Otherwise Specified (PTCL-NOS) or CD30-Expressing Angioimmunoblastic T-cell lymphoma (AITL) (Study 6, ECHELON 2)

ADCETRIS in combination with CHP was evaluated for the treatment of patients with previously untreated CD30-expressing PTCL in a multicenter, randomized, double-blind, double-dummy, active-controlled trial. Patients were randomized to receive ADCETRIS + CHP or CHOP (cyclophosphamide [C], doxorubicin [H], vincristine [O], and prednisone [P]) for 6 or 8, 21-day cycles. ADCETRIS was administered on Day 1 of each cycle, with a starting dose of 1.8 mg/kg intravenously over 30 minutes, approximately 1 hour after completion of CHP.

A total of 449 patients were treated (223 with ADCETRIS + CHP, 226 with CHOP), with 6 cycles planned in 81%. In the ADCETRIS + CHP arm, 70% of patients received 6 cycles, and 18% received 8 cycles. Primary prophylaxis with G-CSF was administered to 34% of ADCETRIS + CHP-treated patients and 27% of CHOP-treated patients.

In the Adcetris-treated arm, adverse reactions that occurred in ≥20% of patients were anemia (66%), neutropenia (59%), nausea (46%), peripheral sensory neuropathy (45%), diarrhea (38%), constipation (29%), vomiting (26%), pyrexia (26%), alopecia (26%), and fatigue (24%). Grade 3 treatment-emergent adverse reactions that occurred in >2% of patients included neutropenia (17%), febrile neutropenia (16%), anemia (13%), diarrhea (6%), pneumonia (5%), leukopenia (4%), hypokalemia (4%), peripheral sensory neuropathy (3%) and thrombocytopenia (3%). Grade 4 treatment-emergent adverse reactions that occurred in ≥2% of patients included neutropenia (22%), leukopenia (4%), thrombocytopenia (3%) and febrile neutropenia (2%) (Table 8). Serious adverse reactions were reported in 39% of ADCETRIS + CHP-treated patients and 38% of CHOP-treated patients. Serious adverse reactions occurring in ≥2% of

ADCETRIS + CHP-treated patients included febrile neutropenia (14%), pneumonia (5%), pyrexia (4%), neutropenia, (4%), pneumonitis (2%), sepsis (2%) and diarrhea (2%).

Fatal adverse reactions occurred in 8 (4%) patients in the A+CHP arm and in 16 (7%) patients in the CHOP arms. The cause of death of the Adcetris-treated patients was cardiac arrest, ventricular fibrillation, pneumonia, pneumonia aspiration, pulmonary cavitation, sepsis, acute kidney injury and PTCL-NOS (1 patient each). Among them, sepsis, pneumonia, pneumonia aspiration and ventricular fibrillation were considered related to Adcetris and CHP.

On the Adcetris + CHP arm, 52% of patients experienced new or worsening peripheral neuropathy of any grade (by maximum grade, 34% Grade 1, 15% Grade 2, 4% Grade 3, < 1% Grade 4). The peripheral neuropathy was predominantly sensory (94% sensory, 16% motor) and had a median onset time of 9 weeks (range, <1–21). At last evaluation, 50% had complete resolution of neuropathy, 12% had partial improvement, and 38% had no improvement. The median time to resolution or improvement overall was 17 weeks (range, 0–195). Of patients with residual neuropathy at their last evaluation, the neuropathy was Grade 1 in 72%, Grade 2 in 25%, and Grade 3 in 3%.

In recipients of ADCETRIS + CHP, adverse reactions led to dose delays of ADCETRIS in 26% of patients (neutropenia 5%), dose reduction in 9% (peripheral sensory neuropathy 5%; peripheral motor neuropathy 2%), and discontinuation of ADCETRIS with or without the other components in 2% (peripheral sensory neuropathy 1%). Adverse reactions led to discontinuation of all components of study treatment in 6% of patients in the Adcetris + CHP arm (peripheral sensory neuropathy 1% and others occurring in 1 patient each) and 7% in the CHOP arm.

Infusion-related reactions were reported in 10 patients (4%) in the ADCETRIS + CHP arm: 2 patients (1%) with events that were Grade 3 or higher.

Table 8: Adverse Reactions Reported in ≥10% of ADCETRIS + CHP-Treated Patients in Study 6 (ECHELON-2)

	ADCETRIS + CHP Total N = 223 % of patients			**CHOP Total N = 226 % of patients**		
Adverse Reaction	**Any Grade**	**Grade 3**	**Grade 4**	**Any Grade**	**Grade 3**	**Grade 4**
Blood and lymphatic system disorders						
Anemia[a]	66	13	<1	59	12	1
Neutropenia[a]	59	17	22	58	14	21
Febrile neutropenia	18	16	2	15	12	3
Thrombocytopenia[a]	17	3	3	13	3	2
Gastrointestinal disorders						
Nausea	46	2	-	38	2	-
Diarrhea	38	6	-	20	1	-
Constipation	29	<1	<1	30	1	-
Vomiting	26	1	-	17	2	-
Stomatitis	12	1	-	12	1	-
Nervous system disorders						
Peripheral sensory neuropathy	45	3	<1	41	3	-
Headache	14	<1	-	14	<1	-

	ADCETRIS + CHP Total N = 223 % of patients			CHOP Total N = 226 % of patients		
Adverse Reaction	**Any Grade**	**Grade 3**	**Grade 4**	**Any Grade**	**Grade 3**	**Grade 4**
Dizziness	13	-	-	9	1	-
General disorders and administration site conditions						
Pyrexia	26	1	<1	19	-	-
Fatigue	24	1	-	20	2	-
Asthenia	12	1	-	7	-	-
Edema peripheral	11	-	-	8	1	-
Skin and subcutaneous						
Alopecia	26	-	-	25	1	-
Rash	10	1	-	7	<1	-
Respiratory, thoracic and mediastinal disorders						
Dyspnea	14	2	-	11	2	-
Cough	12	1	-	10	-	-
Musculoskeletal and connective tissue disorders						
Myalgia	11	-	-	8	-	-
Metabolism and nutrition disorders						
Decreased appetite	17	1	-	12	1	-
Hypokalemia	12	4	-	8	<1	1
Investigations						
Weight decreased	12	<1	-	8	<1	-
Psychiatric disorders						
Insomnia	11	-	-	14	-	-

CHP = cyclophosphamide, doxorubicin, and prednisone; CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone

[a] Derived from laboratory values and adverse reaction data. Laboratory values were obtained at the start of each cycle and end of treatment.

Events were graded using the NCI CTCAE Version 4.03

Relapsed/Refractory Anaplastic Large Cell Lymphoma (sALCL) Trial (Study 2)

ADCETRIS was studied in 58 patients with sALCL (Study 2) in a single arm phase 2 trial in which the recommended starting dose and schedule was 1.8 mg/kg intravenously every 3 weeks for a maximum of 16 cycles. The median duration of treatment was 23.5 weeks (range, 3 to 75 weeks) (see 14 Clinical Trials).

The treatment-emergent adverse reactions that occurred in ≥20% of sALCL patients in Study 2 were: neutropenia (64%), leukopenia (52%), peripheral sensory neuropathy (52%), nausea (40%), fatigue (38%), pyrexia (34%), anemia (33%), diarrhea (29%), upper respiratory tract infection (28%), lymphopenia (26%), rash (24%), thrombocytopenia (24%), and constipation (22%). Grade 3 treatment-emergent adverse reactions that occurred in more than 3% of patients included neutropenia (16%), peripheral sensory neuropathy (16%), lymphopenia (10%), thrombocytopenia (9%), anemia (7%) and peripheral motor neuropathy (7%). Grade 4 treatment-emergent adverse reactions included

neutropenia (9%), thrombocytopenia (5%), fatigue, leukopenia, lymphopenia, pain in extremity, and pain (1 patient, 2% each).

Serious adverse reactions, regardless of causality, were reported in 25 (43%) of patients receiving ADCETRIS. The serious adverse reactions experienced by at least 2 sALCL patients were ALCL recurrent in 3 patients, and septic shock, supraventricular arrhythmia, pain in extremity, and urinary tract infection each in 2 patients.

In Study 2, 57% of patients experienced peripheral neuropathy. The median time to first onset of any grade was 15 weeks (range, 0.1–52), of Grade 2 was 17 weeks (range, 2–45) and of Grade 3 was 36 weeks (range, 6–52). The median time from onset to resolution or improvement of any grade was 3 weeks (range, 0.3-49), of Grade 2 was 6 weeks (range, 0.7–47), and of Grade 3 was 17 weeks (range, 1–49). Of the patients who reported neuropathy, 48% had complete resolution, 30% had partial improvement, and 21% had no improvement. Of the patients who reported neuropathy, 52% had residual neuropathy at the time of their last evaluation [Grade 1 (27%), Grade 2 (15%), Grade 3 (9%)].

Adverse reactions that led to dose reductions in at least 2 sALCL patients included peripheral sensory neuropathy (10%). Adverse reactions that led to dose delays in at least 2 sALCL patients included peripheral sensory neuropathy (14%), neutropenia (12%), and thrombocytopenia (5%). The adverse reaction that led to treatment discontinuation in patients with sALCL was peripheral sensory neuropathy (12%).

Six deaths occurred within 30 days of the last study treatment and were due to ALCL recurrent (3 patients), acute myocardial infarction and acute renal failure not related to disease (both in 1 patient), respiratory failure secondary to progressive sALCL (1 patient) and sudden death (1 patient).

Grade 1 or 2 infusion-related reactions were reported for 5 sALCL patients (9%). The adverse reactions that were associated with infusion-related reactions in sALCL patients in Study 2 were chills, nausea, dizziness, pyrexia, rash, vomiting, diarrhea and local neck swelling each of which occurred in 1 patient.

Four patients experienced serious cardiac adverse events. Of these, one patient with a history of severe cardiac disease experienced a myocardial infarction while on study therapy. The potential cardiac toxicity of ADCETRIS is unknown, and patients with significant pre-existing cardiac conditions should be monitored closely as these patients were excluded from clinical studies with ADCETRIS.

Table 9: Commonly Reported Adverse Reactions (≥ 5% of Patients in Study 2)

	sALCL Total N = 58 n (%) of patients		
System Organ Class Preferred Term	**Any Grade**	**Grade 3**	**Grade 4**
Blood and lymphatic system disorders[a]	*22 (38)*		
Leukopenia	30 (52)	2 (3)	1 (2)
Neutropenia	37 (64)	9 (16)	5 (9)
Anemia	19 (33)	4 (7)	-
Thrombocytopenia	14 (24)	5 (9)	3 (5)
Lymphopenia	15 (26)	6 (10)	1 (2)
Lymphadenopathy	6 (10)	-	-

	sALCL Total N = 58 n (%) of patients		
System Organ Class Preferred Term	**Any Grade**	**Grade 3**	**Grade 4**
Nervous system disorders	*42 (72)*		
Peripheral sensory neuropathy[b]	30 (52)	9 (16)	-
Headache	11 (19)	1 (2)	-
Peripheral motor neuropathy[c]	5 (9)	4 (7)	-
Dizziness	9 (16)	-	-
Memory impairment	3 (5)	-	-
General disorders and administration site conditions	*44 (76)*		
Fatigue	22 (38)	2 (3)	1 (2)
Pyrexia	20 (34)	1 (2)	-
Chills	8 (14)	-	-
Pain	6 (10)	-	1 (2)
Edema peripheral	8 (14)	-	-
Asthenia	5 (9)	-	-
Gastrointestinal disorders	*40 (69)*		
Nausea	23 (40)	1 (2)	-
Diarrhea	17 (29)	2 (3)	-
Vomiting	10 (17)	2 (3)	-
Abdominal pain	5 (9)	1 (2)	-
Constipation	13 (22)	1 (2)	-
Dyspepsia	5 (9)	-	-
Abdominal distension	3 (5)	-	-
Oral pain	5 (9)	-	-
Gastroesophageal reflux disease	3 (5)	-	-
Hemorrhoids	3 (5)	-	-
Infections and infestations	*33 (57)*		
Upper respiratory tract infection[d]	16 (28)	-	-
Bronchitis	3 (5)	-	-
Urinary tract infection	3 (5)	2 (3)	-
Folliculitis	5 (9)	-	-
Respiratory, thoracic and mediastinal disorders	*29 (50)*		
Cough	10 (17)	-	-
Dyspnea	11 (19)	1 (2)	-
Oropharyngeal pain	4 (7)	-	-
Productive cough	3 (5)	-	-
Skin and subcutaneous tissue disorders	*33 (57)*		
Rash	14 (24)	-	-
Pruritus	11 (19)	-	-

	sALCL Total N = 58 n (%) of patients		
System Organ Class Preferred Term	**Any Grade**	**Grade 3**	**Grade 4**
Alopecia	8 (14)	-	-
Night sweats	4 (7)	-	-
Dry skin	6 (10)	-	-
Rash pruritic	4 (7)	-	-
Dermatitis	4 (7)	1 (2)	-
Musculoskeletal and connective tissue disorders	*29 (50)*		
Myalgia	9 (16)	1 (2)	-
Arthralgia	5 (9)	-	-
Back pain	5 (9)	1 (2)	-
Pain in extremity	8 (14)	1 (2)	1 (2)
Muscle spasms	8 (14)	1 (2)	-
Neck pain	5 (9)	1 (2)	-
Groin pain	5 (9)	-	-
Musculoskeletal pain	4 (7)	1 (2)	-
Psychiatric disorders	*16 (28)*		
Insomnia	9 (16)	-	-
Anxiety	4 (7)	-	-
Depression	4 (7)	1 (2)	-
Confusional state	3 (5)	1 (2)	-
Metabolism and nutrition disorders	*20 (34)*		
Decreased appetite	9 (16)	1 (2)	-
Hyperglycemia	3 (5)	1 (2)	-
Hypokalemia	5 (9)	2 (3)	-
Dehydration	3 (5)	1 (2)	-
Hypomagnesemia	3 (5)	-	-
Investigations	*16 (28)*		
Weight decreased	8 (14)	2 (3)	-
Vascular disorders	*8 (14)*		
Hot flush	3 (5)	-	-
Neoplasms benign, malignant and unspecified (including cysts and polyps)	*9 (16)*		
Tumor flare	5 (9)	-	1 (2)
Anaplastic large cell lymphoma t- and null-cell types recurrent	3 (5)	-	-
Cardiac disorders	*6 (10)*		
Tachycardia	3 (5)	-	-

	sALCL Total N = 58 n (%) of patients		
System Organ Class Preferred Term	**Any Grade**	**Grade 3**	**Grade 4**
Injury, poisoning and procedural complications	*7 (12)*		
Excoriation	3 (5)	-	-

[a] Includes adverse reactions and laboratory abnormalities

[b] Includes peripheral sensory neuropathy, paresthesia, neuralgia, hyperesthesia, hypoesthesia, and burning sensation

[c] Includes peripheral motor neuropathy, demyelinating polyneuropathy, muscular weakness, and polyneuropathy

[d] Includes terms upper respiratory tract infection, sinusitis, nasopharyngitis, rhinitis, viral upper respiratory tract infection, and acute sinusitis

Events were graded using the NCI CTCAE Version 3.0

Primary Cutaneous Anaplastic Large Cell Lymphoma (pcALCL) or CD30-Expressing Mycosis Fungoides Trial (Study 4: ALCANZA)

ADCETRIS was studied in 66 patients with either pcALCL or CD30-expressing MF who had received prior systemic therapy in a randomized, open-label, multicenter clinical trial. In the control arm, 65 patients were randomized to physician's choice of either bexarotene or methotrexate. Patients received either ADCETRIS 1.8 mg/kg intravenously over 30 minutes every 3 weeks or physician's choice of either methotrexate 5 to 50 mg orally weekly or bexarotene 300 mg/m^2 orally daily.

Of the 131 enrolled patients, 128 patients comprised the safety population (66 in ADCETRIS-treated arm and 62 in the physician's choice arm) as 3 patients in the physician's choice arm did not receive treatment. The median number of treatment cycles in the ADCETRIS-treatment arm was 12 (range, 1-16) compared to 3 (range, 1-16) and 6 (range, 1-16) in the methotrexate and bexarotene arms, respectively. Twenty-four (24) patients (36%) in the ADCETRIS-treatment arm received 16 cycles compared to 5 patients (8%) in the physician's choice arm (see 14 Clinical Trials).

The treatment-emergent adverse reactions that occurred in ≥20% of patients in the ADCETRIS-treated arm were: anemia (62%), peripheral sensory neuropathy (45%), nausea (36%), fatigue and diarrhea (29% each), and neutropenia (21%). Adverse reactions, regardless of causality, occurring in ≥5% of patients in the ADCETRIS-treated arm and at a higher rate than the physician's choice arm, regardless of causality, using the NCI CTCAE Version 4.03, are shown in Table 10.

Grade 3 treatment-emergent adverse reactions that occurred in more than 3% of patients in the ADCETRIS-treated arm included peripheral sensory neuropathy (5%), fatigue (5%), and hyperglycemia (5%). Grade 4 treatment-emergent adverse events included neutropenia and thrombocytopenia, occurring in one patient each (2%). Serious adverse reactions were reported in 29% of ADCETRIS-treated patients. The most common serious adverse reactions were cellulitis (3%) and pyrexia (3%).

Adverse reactions that led to dose delays in more than 5% of ADCETRIS-treated patients were peripheral sensory neuropathy (15%) and neutropenia (6%). Adverse reactions led to treatment discontinuation in 24% of ADCETRIS-treated patients. The most common adverse reactions that led to treatment discontinuation in at least 2 patients were peripheral sensory neuropathy (8%) and neuropathy peripheral (3%).

Four patients in the ADCETRIS arm died within 30 days of last study treatment. Causes of death were reported as lymphoma progression, sepsis, multiorgan dysfunction syndrome, and pulmonary embolism.

Infusion-related reactions were reported in 9 patients (14%) in the ADCETRIS-treated arm. Grade 3 events were reported in 2 of the 9 ADCETRIS-treated patients who experienced infusion-related reactions (urticarial and drug hypersensitivity) and 1 infusion-related reaction led to study drug discontinuation (Grade 3 urticaria). None of the infusion-related reactions were considered to be serious. No Grade 4 infusion-related reactions were reported. The most common adverse reaction reported in 2 or more patients (≥3%) associated with infusion-related reactions was pruritus (5%).

Table 10: Commonly Reported Adverse Reactions (≥5% of Patients and at a Higher Rate in the ADCETRIS Arm in Study 4: ALCANZA)

	ADCETRIS Total N = 66 n (%) of patients			**Physician's Choice[a] Total N = 62 n (%) of patients**		
Adverse Reaction	**Any Grade**	**Grade 3**	**Grade 4**	**Any Grade**	**Grade 3**	**Grade 4**
Blood and lymphatic system disorders	*45 (68)*	*2 (3)*	*3 (5)*	*48 (77)*	*6 (10)*	-
Thrombocytopenia*	10 (15)	1 (2)	1 (2)	1 (2)	-	-
Nervous system disorders	*47 (71)*	*7 (11)*	-	*12 (19)*	-	-
Peripheral sensory neuropathy[b]	38 (58)	3 (5)	-	3 (5)	-	-
Peripheral motor neuropathy[c]	7 (11)	2 (3)	-	1 (2)	-	-
Neuropathy peripheral	3 (5)	1 (2)	-	-	-	-
Dysgeusia	5 (8)	-	-	-	-	-
Dizziness	5 (8)	2 (3)	-	1 (2)	-	-
Gastrointestinal disorders	*40 (61)*	*4 (6)*	*1 (2)*	*23 (37)*	-	*1 (2)*
Nausea	24 (36)	1 (2)	-	8 (13)	-	-
Diarrhea	19 (29)	2 (3)	-	4 (6)	-	-
Vomiting	11 (17)	1 (2)	-	3 (5)	-	-
General disorders and administration site conditions	*39 (59)*	*4 (6)*	-	*36 (58)*	*3 (5)*	*1 (2)*
Fatigue	19 (29)	3 (5)	-	17 (27)	1 (2)	-
Edema peripheral	7 (11)	-	-	6 (10)	-	-
Asthenia	7 (11)	1 (2)	-	5 (8)	-	1 (2)
Chills	4 (6)	-	-	2 (3)	-	-
Skin and subcutaneous tissue disorders	*34 (52)*	*3 (5)*	*1 (2)*	*20 (3)*	*2 (3)*	-
Pruritus	11 (17)	1 (2)	-	8 (13)	2 (3)	-
Alopecia	10 (15)	-	-	2 (3)	-	-
Rash maculo-papular	7 (11)	1 (2)	-	3 (5)	-	-
Pruritus generalized	7 (11)	1 (2)	-	1 (2)	-	-
Urticaria	5 (8)	1 (2)	-	1 (3)	-	-
Dermatitis acneiform	3 (5)	-	-	-	-	-
Infections and Infestations	*29 (44)*	*9 (14)*	-	*32 (52)*	*9 (15)*	*3 (5)*
Upper respiratory tract infection	4 (6)	-	-	2 (3)	-	-
Nasopharyngitis	3 (5)	-	-	1 (2)	-	-

	ADCETRIS Total N = 66 n (%) of patients			Physician's Choice[a] Total N = 62 n (%) of patients		
Adverse Reaction	**Any Grade**	**Grade 3**	**Grade 4**	**Any Grade**	**Grade 3**	**Grade 4**
Impetigo	3 (5)	1 (2)	-	1 (2)	-	-
Urinary tract infection	5 (8)	1 (2)	-	4 (6)	1 (2)	-
Cellulitis	3 (5)	2 (3)	-	2 (3)	1 (2)	-
Metabolism and nutrition disorders	*21 (32)*	*4 (6)*	-	*18 (29)*	*6 (10)*	*4 (6)*
Decreased appetite	10 (15)	-	-	3 (5)	-	-
Hyperglycemia	6 (9)	3 (5)	-	-	-	-
Hyperuricemia	4 (6)	-	-	2 (3)	1 (2)	1 (2)
Investigations	*15 (23)*	-	-	*21 (34)*	*5 (8)*	-
Weight decreased	6 (9)	-	-	2 (3)	-	-
Blood triglyceride increased	-	-	-	5 (8)	2 (3)	-
Musculoskeletal and connective tissue disorders	*22 (33)*	*2 (3)*	-	*14 (23)*	-	-
Arthralgia	8 (12)	-	-	4 (6)	-	-
Myalgia	8 (12)	-	-	2 (3)	-	-
Pain in extremity	6 (9)	1 (2)	-	4 (6)	-	-
Muscle spasms	4 (6)	-	-	3 (5)	-	-
Respiratory, thoracic and mediastinal disorders	*13 (20)*	*1 (2)*	-	*7 (11)*	-	-
Dyspnea	7 (11)	-	-	-	-	-
Vascular disorders	*10 (15)*	*3 (5)*	-	*3 (5)*	*1 (2)*	-
Hypertension	6 (9)	2 (3)	-	-	-	-
Hot flush	3 (5)	-	-	-	-	-
Eye disorders	*6 (9)*	-	-	*6 (10)*	-	-
Vision blurred	3 (5)	-	-	-	-	-

* Derived from laboratory values and adverse reaction data

[a] Physician's choice of either methotrexate or bexarotene

[b] Includes peripheral sensory neuropathy, paresthesia, neuralgia, hyperesthesia, hypoesthesia, and burning sensation.

[c] Includes peripheral motor neuropathy, demyelinating polyneuropathy, muscular weakness, and polyneuropathy.

Events were graded using the NCI CTCAE Version 4.03

Additional Clinical Trial Experience in HL and sALCL

Limited studies have investigated retreatment (N=29) and extended treatment (N=19) with ADCETRIS 1.8 mg/kg intravenously every 3 weeks in patients with HL or sALCL. Median duration of retreatment was 23 weeks (range, 6 to 167 weeks) and the median number of cycles was 7 (range, 2 to 37 cycles). Median duration of extended treatment was 90 weeks (range, 59 to 139 weeks) and the median number of cycles was 24 (range, 17 to 42 cycles). In these studies, the types of adverse events observed were similar to those observed in the phase 2 clinical trials.

Among retreated HL (n=21) and sALCL (n=8) patients, the incidences of peripheral motor neuropathy (HL: 29%, sALCL: 25%) were increased compared to the incidences observed in the phase 2 trials.

Extended treatment of patients with HL (n=13) or sALCL (n=6) was associated with higher incidences of peripheral sensory neuropathy (HL: 77%, sALCL: 67%), peripheral motor neuropathy (HL: 23%, sALCL 17%) and upper respiratory tract infections (HL: 62%, sALCL: 67%) when compared to the incidences of these events in the phase 2 trials.

8.3. Less Common Clinical Trial Adverse Reactions

Less Common Clinical Trial Adverse Drug Reactions for ADCETRIS Monotherapy (<5%, all grades), ADCETRIS + AVD (<10%, all grades), and for ADCETRIS + CHP (<5%, all grades)

The following adverse reactions, regardless of relationship to ADCETRIS, were reported in <5% of patients treated with ADCETRIS monotherapy in either the relapsed/refractory HL or sALCL trial (Studies 1 and 2), in ADCETRIS-treated patients at a rate of <5% and at a rate ≥1% higher than placebo in the HL consolidation trial (Study 3: AETHERA), or the ADCETRIS-treated patients at a rate of <5% and at a rate ≥1% higher than patients receiving physician's choice treatment in the pcALCL or CD30-expressing MF trial (Study 4: ALCANZA). These adverse reactions, regardless of relationship to ADCETRIS, were reported in patients treated with ADCETRIS + AVD at a rate of <10% and at a rate ≥1% higher than patients treated with ABVD (Study 5: ECHELON-1), and in patients treated with ADCETRIS + CHP at a rate of <5% (Study 6: ECHELON-2). These reactions are presented in alphabetical order according to MedDRA system organ classes (SOCs).

Blood and lymphatic system disorders: Anemia of chronic disease, coagulopathy, eosinophilia, febrile bone marrow aplasia, febrile neutropenia, hemolysis, hemolytic uremic syndrome, idiopathic thrombocytopenic purpura, leukocytosis, leukopenia, lymphadenopathy, lymph node pain, lymphopenia, macrocytosis, neutrophilia, pancytopenia, splenomegaly, thrombocytopenia, thrombocytosis

Cardiac disorders: Acute myocardial infarction, angina pectoris, arrhythmia supraventricular, atrial fibrillation, atrioventricular block complete, bradycardia, cardiac arrest, cardiac failure congestive, cyanosis, left ventricular dysfunction, left ventricular hypertrophy, myocardial infarction, palpitations, sinus bradycardia, sinus tachycardia, supraventricular tachycardia, systolic dysfunction, tachycardia, ventricular fibrillation

Congenital, familial and genetic disorders: fibrous dysplasia of bone, porokeratosis, trisomy 21, vertebral artery hypoplasia

Ear and labyrinth disorders: Deafness, deafness unilateral, ear congestion, ear discomfort, ear pain, ear pruritus, hypoacusis, middle ear effusion, otorrhea, tinnitus, vertigo, vestibular disorder

Endocrine disorders: Addison's disease, adrenal insufficiency, hypogonadism, hypothyroidism**,** secondary adrenocortical insufficiency, steroid withdrawal syndrome

Eye disorders: Astigmatism, blepharospasm, cataract, conjunctival hyperemia, diabetic retinopathy, diplopia, dry eye, episcleritis, eye discharge, eye irritation, eye pain, eye pruritus, eye swelling, glare, lacrimal disorder, lacrimation increased, ocular hyperemia, periorbital edema, photophobia, photopsia, retinal vascular disorder, retinal vein occlusion, visual acuity reduced, vision blurred, visual impairment

Gastrointestinal disorders: Abdominal discomfort, abdominal distension, abdominal hernia, abdominal pain, abdominal pain lower, abdominal pain upper, abdominal tenderness, anal fissure, anal inflammation, aphthous ulcer, ascites, Barrett's esophagus, cheilitis, colitis, defecation urgency, dental caries, diverticulum, dry mouth, duodenal ulcer hemorrhage, duodenitis hemorrhagic, dyspepsia, dysphagia, enteritis, enterocolitis, epigastric discomfort, epiglotic appendagitis, erosive duodenitis,

esophageal pain, esophageal spasm, esophageal stenosis, esophagitis, fecal incontinence, flatulence, gastric hemorrhage, gastric ulcer, gastric ulcer hemorrhage, gastritis, gastroduodenitis, gastroesophageal reflex disease, gastrointestinal disorder, gastrointestinal hemorrhage, gastrointestinal inflammation, gastrointestinal pain, gastrointestinal ulcer, gingival bleeding, gingival pain, hematemesis, hematochezia, hemorrhoidal hemorrhage, hemorrhoids, hiatus hernia, ileus, impaired gastric emptying, inguinal hernia, inguinal hernia strangulated, intestinal obstruction, intestinal perforation, large intestine polyp, lip dry, lip exfoliation, lip pain, lip swelling, lip ulceration, loose tooth, melena, mouth hemorrhage, mouth ulceration, odynophagia, , oral disorder, oral dysesthesia, oral mucosal blistering, oral pain, pancreatitis, pancreatitis acute, paresthesia oral, periodontal disease, proctalgia, rectal hemorrhage, rectal tenesmus, retching, salivary hypersecretion, sensitivity of teeth, stomatitis, swollen tongue, tongue coated, tongue discoloration, tongue ulceration, tooth discoloration, toothache, tooth disorder, tooth loss, upper gastrointestinal hemorrhage, umbilical hernia

General disorders and administration site conditions: Application site erythema, axillary pain, catheter site inflammation, catheter site pain, catheter site pruritus, catheter site related reaction, chest discomfort, chest pain, chills, cyst, disease progression, drug withdrawal syndrome, edema, extravasation, face edema, feeling cold, feeling hot, fibrosis, gait disturbance, general physical health deterioration, generalized edema, hernia, hyperthermia, inflammation, influenza-like illness, infusion site erythema, injection site erythema, localized edema, local swelling, malaise, mucosal inflammation, multiple organ dysfunction syndrome, non-cardiac chest pain, pain, peripheral swelling, sudden death, suprapubic pain, temperature intolerance, tenderness, thirst, ulcer

Hepatobiliary disorders: Drug-induced liver injury, hepatic mass, hepatic function abnormal, hepatic failure, hepatic steatosis, hepatomegaly, hepatocellular injury, hepatotoxicity

Immune system disorders: Allergy to arthropod bite, contrast media allergy, drug hypersensitivity, hypersensitivity, hypogammaglobulinemia, seasonal allergy

Infections and infestations: Abscess, abscess soft tissue, acute hepatitis B, acute sinusitis, acute tonsillitis, anal fistula infection, angular cheilitis, appendicitis, atypical pneumonia, bacteremia, bacterial infection, bacterial pyelonephritis, bacterial sepsis, bronchitis, bronchopulmonary aspergillosis, candida infection, candidiasis, catheter site cellulitis, catheter site infection, cellulitis, chronic hepatitis B, clostridium difficile colitis, clostridium difficile infection, conjunctivitis, conjunctivitis infective, cystitis, cystitis Escherichia, cytomegalovirus infection, device-related infection, diverticulitis, ear infection, endocarditis staphylococcal, enterococcal infection, enterocolitis infectious, Epstein-Barr virus infection, Escherichia bacteremia, Escherichia infection, esophageal infection, external ear cellulitis, eye infection, folliculitis, fungal infection, fungal skin infection, furuncle, gardnerella infection, gastroenteritis, gastroenteritis viral, gastrointestinal infection, genital infection, gingival abscess, gingivitis, groin abscess, groin infection, h1n1 influenza, hepatic candidiasis, herpes dermatitis, herpes simplex, herpes virus infection, herpes zoster, hordeolum, impetigo, infection, infected skin ulcer, infection, influenza, injection site infection, klebsiella bacteremia, klebsiella infection, laryngitis, localized infection, lower respiratory tract infection, lower respiratory tract infection fungal, lung infection, Lyme disease, lymph gland infection, metapneumovirus infection, mucosal infection, myelitis, , nasopharyngitis, neutropenic infection, oral candidiasis, oral herpes, oropharyngeal candidiasis, otitis externa, otitis media, otitis media acute, paronychia, parotitis, perineal infection, perirectal abscess, peritonsillar abscess, pharyngitis, Pneumocystis jiroveci pneumonia, pneumonia, pneumonia staphylococcal, pyelonephritis, rash pustular, respiratory infection, respiratory syncytial virus infection, rhinitis, sepsis, sinusitis, scrotal infection, septic shock,

skin infection, soft tissue infection, staphylococcal bacteremia, staphylococcal infection, staphylococcal skin infection, subcutaneous abscess, superinfection bacterial, tinea cruris, tinea infection, tonsillitis, tonsillitis bacterial, tooth abscess, tooth infection, tracheitis, urinary tract infection, urinary tract infection enterococcal, urinary tract infection pseudomonal, urethritis, urinary tract infection staphylococcal, viral infection, viral pharyngitis, viral upper respiratory tract infection, vulvovaginal candidiasis, vulvovaginal mycotic infection

Injury, poisoning and procedural complications: Animal bite, ankle fracture, arthropod bite, contusion, fall, foot fracture, fracture, joint sprain, ligament sprain, limb injury, lip injury, lower limb fracture, muscle strain, nail injury, open wound, procedural pain, road traffic accident, radiation injury, radiation pneumonitis, rib fracture, skin abrasion, splenic rupture, thermal burn, transfusion reaction, wrist fracture, wound, wound complication

Investigations: Activated partial thromboplastin time prolonged, alanine aminotransferase increased, aspartate aminotransferase increased, biopsy bronchus, biopsy liver, blood alkaline phosphatase increased, blood cholesterol increased, blood creatinine increased, blood creatinine phosphokinase increased, blood glucose increased, blood lactate dehydrogenase increased, blood thyroid stimulating hormone decreased, blood triglycerides increased, blood uric acid increased, body temperature increased, brain natriuretic peptide increased, breath sound abnormal, c-reactive protein increased, cardiac murmur, catheter culture positive, cortisol decreased, ejection fraction decreased, gallop rhythm present, gamma-glutamyltransferase increased, hepatic enzyme increased, human papilloma virus test positive, international normalized ratio increased, liver function test abnormal, lymphocyte count decreased, nerve conduction studies abnormal, platelet count decreased, respiratory rate increased, scan abdomen abnormal, staphylococcus test positive, thyroxine increased, transaminases increased, urine leukocyte esterase positive, weight increased, white blood cell count decreased, white blood cell count increased

Metabolism and nutrition disorders: Cachexia, dehydration, diabetes mellitus, failure to thrive, fluid overload, folate deficiency, gout, hypercalcemia, hypercholesterolemia, hypercreatinemia, hyperglycemia, hyperkalemia, hypernatremia, hyperphosphatemia, hyperuricemia, hypoalbuminemia, hypocalcemia, hypoglycemia, hypokalemia, hypomagnesemia, hyponatremia, hypophagia, hypophosphatemia, iron deficiency, lactic acidosis, metabolic acidosis, polydipsia, tumor lysis syndrome, type 2 diabetes mellitus, vitamin B1 deficiency, vitamin D deficiency

Musculoskeletal and connective tissue disorders: Amyotrophy, arthritis, arthropathy, back pain, bursitis, exostosis, fistula, flank pain, foot deformity, joint effusion, joint hyperextension, joint stiffness, joint swelling, limb discomfort, muscle atrophy, muscle spasms, muscle twitching, muscular weakness, musculoskeletal chest pain, musculoskeletal discomfort, musculoskeletal pain, musculoskeletal stiffness, myositis, neck pain, osteoarthritis, osteoporosis, pain in jaw, periarthritis, sensation of heaviness, spinal disorder, synovial cyst, tendonitis

Neoplasms benign, malignant and unspecified (including cysts and polyps): Bladder cancer, colon adenoma, diffuse large b-cell lymphoma, lung neoplasm malignant, lymphoma, malignant pleural effusion, mycosis fungoides, myelodysplastic syndrome, pancreatic carcinoma, papillary thyroid cancer, peripheral T-cell lymphoma unspecified, squamous cell carcinoma, tumor hemorrhage, urethral papilloma

Nervous system disorders: Ageusia, amnesia, anosmia, aphasia, areflexia, ataxia, balance disorder, basilar migraine, burning sensation, carpal tunnel syndrome, cluster headache, cognitive disorder, convulsion, decreased vibratory sense, demyelinating polyneuropathy, diabetic coma, dysesthesia,

dysgeusia, dyspraxia, encephalopathy, extrapyramidal disorder, facial palsy, facial paralysis, hemorrhage intracranial, hyperesthesia, hypoesthesia, hyporeflexia, intercostal neuralgia, Lhermitte's sign, lethargy, lumbar radiculopathy, loss of consciousness, memory impairment, migraine, migraine with aura, nerve compression, paresthesia, Parkinson's disease, parosmia, peripheral motor neuropathy, peripheral sensorimotor neuropathy, peroneal nerve palsy, presyncope, polyneuropathy, post herpetic neuralgia, presyncope, restless leg syndrome, retinal migraine, seizure, sensory disturbance, sensory loss, sinus headache, somnolence, spinal cord compression, syncope, tremor, tunnel vision

Product Issues: Device infusion issue, device occlusion

Psychiatric disorders: Agitation, anger, anticipatory anxiety, anxiety, confusional state, delirium, depressed mood, depression, disorientation, irritability, libido decreased, mental status changes, mood swings, panic attack, restlessness, sleep disorder, stress, suicidal ideation

Renal and urinary disorders: Acute kidney injury, bladder pain, chromaturia, diabetic nephropathy, dysuria, hematuria, hydronephrosis, micturition disorder, nephrolithiasis, pollakiuria, polyuria, renal cyst, renal failure, renal failure acute, renal pain, urinary hesitation, urinary incontinence, urinary retention, urinary tract pain, urine odor abnormal

Reproductive system and breast disorders: Amenorrhea, artificial menopause, benign prostatic hyperplasia, breast mass, breast tenderness, dysmenorrhea, edema genital, erectile dysfunction, genital erythema, menometrorrhagia, menopausal symptoms, menorrhagia, menstruation irregular, nipple disorder, ovarian cyst, ovarian vein thrombosis, pelvic pain, penile pain, penile swelling, scrotal swelling, testicular pain, vaginal discharge, vaginal hemorrhage, vulvovaginal burning sensation, vulvovaginal dryness, vulvovaginal erythema, vulvovaginal pruritus

Respiratory, thoracic and mediastinal disorders: Acute respiratory failure, allergic cough, asthma exercise induced, atelectasis, bronchial hyperreactivity, bronchospasm, chronic obstructive pulmonary disease, dysphonia, dyspnea exertional, emphysema, epistaxis, hiccups, hemoptysis, hyperventilation, hypoxia, increased upper airway secretion, increased bronchial secretion, laryngeal edema, lung consolidation, lung disorder, nasal congestion, nasal discomfort, nasal dryness, paranasal cyst, paranasal sinus hypersecretion, pharyngeal edema, pharyngeal erythema, pleural effusion, pleuritic pain, pneumonia aspiration, pneumonitis, pneumothorax, postnasal drip, productive cough, pulmonary cavitation, pulmonary edema, pulmonary embolism, pulmonary fibrosis, pulmonary toxicity, respiratory distress, respiratory failure, respiratory tract congestion, rhinorrhea, rhinitis allergic, sinus congestion, sinus disorder, sneezing, sputum increased, tachypnea, throat irritation, tonsillar disorder, tonsillar hypertrophy, throat tightness, tonsillar inflammation, tracheal disorder, tracheal pain, upper respiratory tract inflammation, upper-airway cough syndrome, wheezing

Skin and subcutaneous tissue disorders: Acne, actinic keratosis, alopecia areata, blister, blood blister, dapsone syndrome, decubitus ulcer, dermal cyst, dermatitis acneiform, dermatitis allergic, dermatitis atopic, dermatitis bullous, dermatitis contact, dermatitis exfoliative, drug eruption, dry skin, ecchymosis, eczema, erythema, erythema nodosum, exfoliative rash, hangnail, hyperhidrosis, hypoesthesia facial, in-growing nail, miliaria, nail discoloration, nail disorder, nail ridging, night sweats, onychoclasis, onychomadesis, pain of skin, palmar-plantar erythrodysesthesia syndrome, periorbital edema, petechiae, pruritus, pruritus generalized, rash, rash erythematous, rash generalized, rash macular, rash maculo-papular, rash morbilliform, rash papular, rash pruritic, scar, skin discoloration, skin exfoliation, skin fissures, skin lesion, skin nodule, skin ulcer, Stevens-Johnson syndrome, telangiectasia, urticaria, vascular purpura, vitiligo, yellow skin

Surgical and medical procedures: Cataract operation, sinus operation

Vascular disorders: Deep vein thrombosis, embolism, flushing, hot flush, hypertension, hypotension, orthostatic hypotension, peripheral artery aneurysm, phlebitis, poor venous access, Raynaud's phenomenon, superior vena cava syndrome, thrombophlebitis, vascular pain, vasculitis, venous thrombosis

8.4. Abnormal Laboratory Findings: Hematologic, Clinical Chemistry, and Other Quantitative Data

Clinical Trial Findings

Abnormal Hematologic and Clinical Chemistry Findings in Study 5 (ECHELON-1)

Among patients treated with ADCETRIS + AVD, clinical laboratory abnormalities reported for ≥5% of patients with a post-baseline maximum of Grade 3 included leukocytes (24%), neutrophils (20%), GGT (7%), and hemoglobin (5%). ADCETRIS + AVD-treated patients experienced post-baseline maximum of Grade 4 laboratory abnormalities for neutrophils (31%) leukocytes (5%), and GGT, glucose, potassium, sodium, and platelets (1% each). ABVD-treated patients experienced post-baseline maximum of Grade 4 laboratory abnormalities for neutrophils (27%), leukocytes (4%), glucose and potassium (1% each), and AST, creatinine, GGT, and sodium (<1% each).

Table 11: Post-Baseline Maximum ≥ Grade 3 Laboratory Abnormality in Study 5 (ECHELON-1)

	ADCETRIS Total N = 662 Highest Grade		**ABVD Total N = 659 Highest Grade**	
	Grade 3 n (%)	**Grade 4 n (%)**	**Grade 3 n (%)**	**Grade 4 n (%)**
	Hematology			
Hemoglobin	33 (5)	-	15 (2)	-
Leukocytes	157 (24)	33 (5)	184 (28)	24 (4)
Neutrophils	135 (20)	204 (31)	186 (28)	177 (27)
Platelets	1 (<1)	1 (<1)	1 (<1)	-
	Biochemistry			
ALT	8 (1)	-	4 (<1)	-
Alkaline phosphatase	3 (<1)	-	-	-
AST	6 (1)	-	3 (<1)	1 (<1)
Bilirubin	-	-	1 (<1)	-
Creatinine	-	-	-	1 (<1)
GGT	45 (7)	5 (1)	29 (4)	1 (<1)
Glucose	28 (4)	7 (1)	20 (3)	6 (1)
Magnesium	1 (<1)	-	1 (<1)	-
Phosphate	19 (3)	-	8 (1)	-
Potassium	15 (2)	3 (<1)	10 (2)	9 (1)
Sodium	11 (2)	2 (<1)	11 (2)	2 (<1)

Abnormal Hematologic and Clinical Chemistry Findings in Study 3 (AETHERA)

The clinical laboratory parameters for which ADCETRIS-treated patients (≥5%) reported a post-baseline maximum of Grade 3 were low neutrophils (20%), low leukocytes (11%), and low lymphocytes (11%). ADCETRIS-treated patients experienced a post-baseline maximum of Grade 4 for high urate (4%), low neutrophils (2%), low platelets (2%), low calcium (2%), high ALT (1%), high AST (1%), high glucose (1%), and low potassium (1%). Patients on the placebo arm experienced a post-baseline maximum of Grade 4 for low neutrophils (2%), low lymphocytes (1%), low platelets (1%), and high urate (1%).

Table 12: Post-baseline Maximum ≥Grade 3 Laboratory Abnormalities in Study 3 (AETHERA)

	ADCETRIS Total N =167 Highest Grade		**Placebo Total N = 160 Highest Grade**	
	Grade 3 n (%)	**Grade 4 n (%)**	**Grade 3 n (%)**	**Grade 4 n (%)**
Hematology				
Hemoglobin (low)	1 (1)	-	1 (1)	-
Leukocytes (low)	19 (11)	-	7 (4)	-
Lymphocytes (low)	18 (11)	-	6 (4)	2 (1)
Neutrophils (low)	34 (20)	4 (2)	6 (4)	3 (2)
Platelets (low)	5 (3)	3 (2)	6 (4)	1 (1)
Biochemistry				
ALT (high)	4 (2)	1 (1)	-	-
Albumin (low)	2 (1)	-	-	-
AST (high)	3 (2)	1 (1)	-	-
Bilirubin (high)	1 (1)	-	-	-
Calcium (low)	1 (1)	3 (2)	2 (1)	-
Creatinine (high)	1 (1)	-	-	-
Glucose (high)	4 (2)	1 (1)	1 (1)	-
Glucose (low)	1 (1)	-	-	-
Phosphate (low)	2 (1)	-	3 (2)	-
Potassium (high)	1 (1)	-	-	-
Potassium (low)	4 (2)	2 (1)	3 (2)	-
Sodium (high)	1 (1)	-	-	-
Sodium (low)	2 (1)	-	1 (1)	-
Urate (high)	-	6 (4)	-	2 (1)

Abnormal Hematologic and Clinical Chemistry Findings in Study 1

The clinical laboratory parameters for which patients (≥5%) had new or worsening shifts to Grade 3 were low neutrophils (12%), low lymphocytes (9%), low platelets (6%), high glucose (6%), and low leukocytes (6%). New or worsening shifts to Grade 4 occurred for high urate low lymphocytes, and low hemoglobin (1% each). One patient in the trial had Grade 3 high ALT and AST.

Table 13: Incidence of New or Worsening ≥Grade 3 Laboratory Abnormalities in Study 1

	HL Total N=102 Highest Grade	
	Grade 3 n (%)	**Grade 4 n (%)**
Hematology		
Hemoglobin (low)	4 (4)	1 (1)
Leukocytes (low)	6 (6)	0
Lymphocytes (low)	7 (9)	1 (1)
Neutrophils (low)	12 (12)	0
Platelets (low)	6 (6)	0
Biochemistry		
ALT (high)	1 (1)	0
Albumin (low)	1 (1)	0
Calcium (low)	1 (1)	0
Glucose (high)	6 (6)	0
Potassium (low)	2 (2)	0
Sodium (high)	1 (1)	0
Urate (high)	0	1 (1)

Abnormal Hematologic and Clinical Chemistry Findings in Study 6 (ECHELON-2)

Among patients treated with ADCETRIS + CHP, clinical laboratory abnormalities reported for ≥5% of patients with a post-baseline maximum of Grade 3 included low lymphocytes (22%), low neutrophils (6%), and low leukocytes (5%). ADCETRIS + CHP-treated patients experienced post-baseline maximum of Grade 4 laboratory abnormalities for high urate (2%), low lymphocytes (1%), low neutrophils (1%), and high glucose (<1%).

Table 14: Post-baseline maximum ≥Grade 3 laboratory abnormality in Study 6 (ECHELON-2)

	ADCETRIS + CHP Total N = 223 Highest Grade		CHOP Total N = 226 Highest Grade	
	Grade 3 n (%)	**Grade 4 n (%)**	**Grade 3 n (%)**	**Grade 4 n (%)**
	Hematology			
Hemoglobin (high)	1 (<1)	0	0	0
Hemoglobin (low)	9 (4)	0	13 (6)	0
Leukocytes (low)	12 (5)	0	21 (9)	0
Lymphocytes (low)	50 (22)	2 (1)	56 (25)	5 (2)
Neutrophils (low)	14 (6)	3 (1)	15 (7)	4 (2)
Platelets (low)	1 (<1)	0	1 (<1)	0
	Biochemistry			
ALT (high)	3 (1)	0	1 (<1)	0
Albumin (low)	2 (1)	0	3 (1)	0

	ADCETRIS + CHP Total N = 223 Highest Grade		CHOP Total N = 226 Highest Grade	
	Grade 3 n (%)	Grade 4 n (%)	Grade 3 n (%)	Grade 4 n (%)
Alkaline phosphatase (high)	1 (<1)	0	0	0
Calcium (low)	1 (<1)	0	1 (<1)	0
Glucose (high)	7 (3)	1 (<1)	6 (3)	0
Phosphate (low)	4 (2)	0	3 (1)	0
Potassium (low)	3 (1)	0	2 (1)	0
Sodium (high)	1 (<1)	0	0	0
Sodium (low)	4 (2)	0	6 (3)	0
Urate (high)	0	5 (2)	0	2 (1)

CHP = cyclophosphamide, doxorubicin, and prednisone; CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone

Abnormal Hematologic and Clinical Chemistry Findings in Study 2

The clinical laboratory parameters for which patients (≥5%) had new or worsening shifts to Grade 3 were low neutrophils (11%), low lymphocytes (12%), low platelets (5%), and high glucose (5%). New or worsening shifts to Grade 4 occurred for high urate (4%), low calcium and low lymphocytes (2% each).

Table 15: Incidence of New or Worsening ≥Grade 3 Laboratory Abnormalities in Study 2

	ALCL Total N=58 Highest Grade	
	Grade 3 n (%)	Grade 4 n (%)
Hematology		
Leukocytes (low)	2 (4)	0
Lymphocytes (low)	6 (12)	1 (2)
Neutrophils (low)	6 (11)	0
Platelets (low)	3 (5)	0
Biochemistry		
AST (high)	1 (2)	0
Calcium (low)	2 (4)	1 (2)
Glucose (high)	3 (5)	0
Sodium (low)	1 (2)	0
Urate (high)	0	2 (4)

Abnormal Hematologic and Clinical Chemistry Findings in Study 4 (ALCANZA)

The clinical laboratory parameters for which ADCETRIS-treated patients reported a post-baseline maximum of Grade 3 were low lymphocytes (8%) and low platelets (2%). The biochemistry laboratory parameter for which ADCETRIS-treated patients reported a post-baseline maximum of Grade 3 was high ALT (2%). ADCETRIS-treated patients experienced a post-baseline maximum of Grade 4 for low lymphocytes (2%) and low platelets (2%). Patients on the physician's choice-treated arm reported a

post-baseline maximum of Grade 3 for low lymphocytes (10%), low neutrophils (5%), low hemoglobin (3%) and high ALT (2%).

Table 16: Post-baseline Maximum ≥Grade 3 Laboratory Abnormalities in Study 4 (ALCANZA)

	ADCETRIS Total N = 66 Highest Grade		Physician's Choice[a] Total N = 62 Highest Grade	
	G3 n (%)	G4 n (%)	G3 n (%)	G4 n (%)
Hematology				
Hemoglobin (low)	-	-	2 (3)	-
Lymphocytes (low)	5 (8)	1 (2)	6 (10)	-
Neutrophils (low)	-	-	3 (5)	-
Platelets (low)	1 (2)	1 (2)	-	-
Biochemistry				
ALT (high)	1 (2)	-	1 (2)	-

[a] Physician's choice of either methotrexate or bexarotene

8.5. Post-Market Adverse Reactions

The following adverse reactions have been identified during post-approval use of ADCETRIS. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Gastrointestinal disorders: Acute pancreatitis (including fatal outcomes). Consider the diagnosis of pancreatitis for patients presenting with severe abdominal pain (see 7 Warnings and Precautions).

Hepatobiliary disorders: Hepatotoxicity, including fatal outcome (see 7 Warnings and Precautions).

Infections and infestations: Progressive Multifocal Leukoencephalopathy (PML) has been reported in patients receiving ADCETRIS (see 7 Warnings and Precautions).

Respiratory, thoracic and mediastinal disorders: Pulmonary toxicity (see 7 Warnings and Precautions).

Skin and subcutaneous tissue disorders: Toxic epidermal necrolysis (TEN), including fatal outcomes (see 7 Warnings and Precautions).

9. Drug Interactions

9.2. Drug Interactions Overview

In vitro data indicate that monomethyl auristatin E (MMAE) is a substrate and an inhibitor of CYP3A4/5. In vitro data indicate that MMAE is also a substrate of the efflux transporter P-glycoprotein (P-gp).

9.3. Drug-Behaviour Interactions

No drug-behavioural interactions have been established.

9.4. Drug-Drug Interactions

The drugs listed in Table 17 are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Table 17 – Established or Potential Drug-Drug Interactions

	Source of evidence	Effect	Clinical comment
Bleomycin	CT	Pulmonary toxicity	
CYP3A4 and P-gp Inhibitors/Inducers: - ketoconazole (potent CYP3A4 and P-gp inhibitor) - rifampin (potent CYP3A4 inducer)	CT	 ↑ exposure to MMAE by approximately 34% ↓ exposure to MMAE by approximately 46%	MMAE is primarily metabolized by CYP3A (see 10 Clinical Pharmacology). Patients who are receiving strong CYP3A4 and P-gp inhibitors concomitantly with ADCETRIS should be closely monitored for adverse reactions.

CT = Clinical Trial;

Co-administration of ADCETRIS did not affect exposure to midazolam, a CYP3A4 substrate. MMAE does not inhibit other CYP enzymes at relevant clinical concentrations (see 10 Clinical Pharmacology). ADCETRIS is not expected to alter the exposure to drugs that are metabolized by CYP3A4 enzymes.

9.5. Drug-Food Interactions

Grapefruit has CYP3A4 inhibitory activity. Therefore, ingestion of grapefruit while on ADCETRIS therapy may increase MMAE plasma concentrations. Patients receiving concomitant administration of ADCETRIS with grapefruit, grapefruit juice, products containing grapefruit extract, star fruit, pomegranate, Seville oranges, and other similar fruits that are known to inhibit CYP3A4 should be closely monitored for adverse reactions.

9.6. Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7. Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10. Clinical Pharmacology

10.1. Mechanism of Action

CD30 is a member of the tumor necrosis factor receptor family and is expressed on the surface of Hodgkin Reed-Sternberg (HRS) cells in cHL and on sALCL cells. CD30 is variably expressed in other T-cell

lymphomas. Expression of CD30 on healthy tissues and cells is limited. In vitro data suggest that signaling through CD30-CD30L binding may affect cell survival and proliferation.

Brentuximab vedotin is an ADC (antibody-drug conjugate). The antibody is a chimeric IgG1 directed against CD30. The small molecule, MMAE, is a potent microtubule disrupting agent. MMAE is covalently attached to the antibody via a linker. Nonclinical data suggest that the anticancer activity of ADCETRIS is due to the binding of the ADC to CD30-expressing cells, followed by internalization of the ADC-CD30 complex, and the release of MMAE via proteolytic cleavage. Binding of MMAE to tubulin disrupts the microtubule network within the cell, subsequently inducing cell cycle arrest and apoptotic death of the cells. Additionally, in vitro data provide evidence of antibody-dependent cellular phagocytosis (ADCP). MMAE release by CD30-independent mechanisms and contributions to the mechanism of action by other antibody-associated functions have not been excluded.

10.2. Pharmacodynamics

Electrocardiography

Administration of brentuximab vedotin did not prolong the QTc interval from baseline; however, small increases in QTc interval cannot be excluded because of study limitations. The ECG study also showed a brentuximab vedotin-associated decrease from baseline in the QTc interval (maximum mean decrease from baseline approximately 7 ms [90% CI: 3.5, 11.2]). The clinical significance of this finding is unknown.

10.3. Pharmacokinetics

The pharmacokinetics of brentuximab vedotin administered as monotherapy were evaluated in phase 1 trials and in a population pharmacokinetic analysis of data from 314 patients with HL. The pharmacokinetics of three analytes were determined: the ADC, MMAE, and total antibody. Total antibody had the greatest exposure and had a PK profile similar to that of the ADC. Data on the pharmacokinetics of the ADC and MMAE are summarized in Table 18.

Table 18: Pharmacokinetic Parameters for ADC and MMAE

	Dose (mg/kg)	N	$AUC_{0\text{-}21d}$ (day·mcg/mL)	C_{max} (mcg/mL)	$t_{1/2}$ (day)	CL (L/day)	V_{ss} (L)
ADC	1.2	4	45.21 (63)	18.89 (27)	3.79 (11)	1.96 (105)	5.85 (260)
	1.8	12	76.65 (31)	31.98 (29)	4.43 (38)	1.76 (17)	8.21 (24)

	Dose* (mg/kg)	N	$AUC_{0\text{-}21d}$ (day·ng/mL)	C_{max} (ng/mL)	$t_{1/2}$ (day)
MMAE	1.2	4	20.05 (215)	2.72 (272)	3.13 (28)
	1.8	12	36.07 (47)	4.97 (43)	3.60 (25)

Data are based on non-compartmental analysis of data obtained in study SG035-0001 (the phase I dose-escalation study) and all PK parameters are summarized by the geometric mean (% CV).
* Dose of brentuximab vedotin.

Absorption

Maximum concentrations of ADC were typically observed close to the end of infusion. A multiexponential decline in ADC serum concentrations was observed with a terminal half-life of

approximately 4 to 6 days. Exposures were approximately dose proportional from 1.2 to 2.7 mg/kg. Steady-state of the ADC was achieved within 21 days with every 3-week dosing of ADCETRIS, consistent with the terminal half-life estimate. Minimal to no accumulation of ADC was observed with multiple doses at the every 3-week schedule.

The time to maximum concentration for MMAE ranged from approximately 1 to 3 days. Similar to the ADC, steady state of MMAE was achieved within 21 days with every 3-week dosing of ADCETRIS. MMAE exposures decreased with continued administration of ADCETRIS with approximately 50% to 80% of the exposure of the first dose being observed at subsequent doses.

Distribution

In vitro, the binding of MMAE to human plasma proteins ranged from 68%–82%. MMAE is not likely to displace or to be displaced by highly protein-bound drugs. In vitro, MMAE was a substrate of P-gp and was not a potent inhibitor of P-gp.

In humans, the mean steady state volume of distribution was approximately 6–10 L for ADC. The typical apparent volume of distribution for MMAE, an estimate based on population PK modeling, was 44 L. The organ distribution of MMAE in humans is unknown..

Metabolism

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

Intact MMAE was the primary species excreted in humans, suggesting a low propensity for metabolism based biotransformations. MMAE was excreted in both feces (72%) and urine (28%) in patients with CD30-positive hematologic malignancies, though mass balance was not achieved with approximately 23.5% of the equivalent amount of MMAE administered being recovered in excreta. A metabolite not previously observed was detected in humans in both feces and urine, but this metabolite was a combination of two biotransformations that were observed in humans.

Elimination

MMAE appeared to follow metabolite kinetics, with the elimination of MMAE appearing to be limited by its rate of release from ADC. An excretion study was undertaken in patients who received a dose of 1.8 mg/kg of ADCETRIS. Approximately 24% of the total MMAE administered as part of the ADC during an ADCETRIS infusion was recovered in both urine and feces over a 1-week period. Of the recovered MMAE, approximately 72% was recovered in the feces and the majority of the excreted MMAE was unchanged.

<u>Pharmacokinetics in Combination Therapy</u>

The pharmacokinetics of brentuximab vedotin (ADC, MMAE, and total antibody) in combination with AVD were evaluated in a single phase 3 study in 661 patients. Population pharmacokinetic analysis indicated that the pharmacokinetics of brentuximab vedotin were similar to that in monotherapy.

The pharmacokinetics of brentuximab vedotin in combination with CHP were evaluated in a single phase 3 study in 217 subjects. The pharmacokinetic parameters of ADC administered as the combination therapy were similar to those following the monotherapy. There was insufficient data for

the comparison of the pharmacokinetic profile of MMAE between the combination therapy and the monotherapy.

Special populations and conditions

- **Pediatrics:** The pharmacokinetics, safety, and efficacy in children aged less than 18 years have not been established.
- **Geriatrics:** The population pharmacokinetics of ADCETRIS 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.
- **Sex:** Based on the population pharmacokinetic analysis, sex does not have a meaningful effect on the pharmacokinetics of brentuximab vedotin.
- **Hepatic Insufficiency:** The liver is a route of clearance for MMAE. A study evaluated the pharmacokinetics 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.
- **Renal Insufficiency:** The kidney is a route of excretion for MMAE. A study evaluated the pharmacokinetics 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).

10.4. Immunogenicity

All therapeutic proteins have the potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of incidence of antibodies in the studies described below with the incidences of antibodies in other studies or to other products may be misleading.

Anti-therapeutic antibodies (ATA) to brentuximab vedotin were measured using a sensitive chemiluminescence assay.

In Study 5 (ECHELON-1), patients were tested for ATA at Cycle 1 pre-dose (baseline) and at Cycle 2 through Cycle 6 or through treatment termination. Of 632 evaluable patients, 568 (90%) were ATA negative at baseline, and 64 (10%) were ATA positive at baseline. Most patients (83%) were ATA negative post-baseline, and 17% were ATA positive at some time point post-baseline. Among those ATA positive, 4 patients were persistently positive, and 2 of these 4 patients were positive at baseline.

In Studies 1-3, patients were tested for antibody to brentuximab vedotin every 3 weeks.

In Study 1, 6 patients (6%) tested ATA positive at baseline; 35 patients (34%) tested positive at least once post-baseline. Overall, the incidence of ATA was highest at Cycle 2 (30 patients [30%]) and decreased in subsequent cycles of treatment. Four patients tested ATA positive at their end-of-treatment visit.

Of 56 immunogenicity-evaluable patients in Study 2, 2 patients (4%) tested ATA positive at baseline; 22 patients (36%) tested ATA positive post-baseline. Overall, the incidence of ATA positivity was highest at Cycle 2 and decreased in subsequent cycles of treatment; 2 patients were ATA positive at the end of treatment.

In Study 3 (AETHERA), 138 patients (88%) were ATA negative at baseline, 92 (59%) were ATA negative post-baseline, 36 (23%) were transiently ATA positive post-baseline, and 10 (6%) were persistently ATA positive. Of 19 patients (12%) who were ATA positive at baseline, 7 (4%) were ATA negative post-baseline, 9 (6%) were transiently ATA positive post-baseline, and 3 (2%) were persistently ATA positive.

A higher incidence of infusion-related reactions was associated with patients who were ATA positive compared to those who tested transiently positive or negative. The presence of ATA did not correlate with a substantial reduction in serum brentuximab vedotin levels and did not result in a decrease in efficacy.

11. Storage, Stability, and Disposal

Store vial at 2–8°C in the original carton to protect from light.

12. Special Handling Instructions

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

Part 2: Scientific Information

13. Pharmaceutical Information

Drug Substance

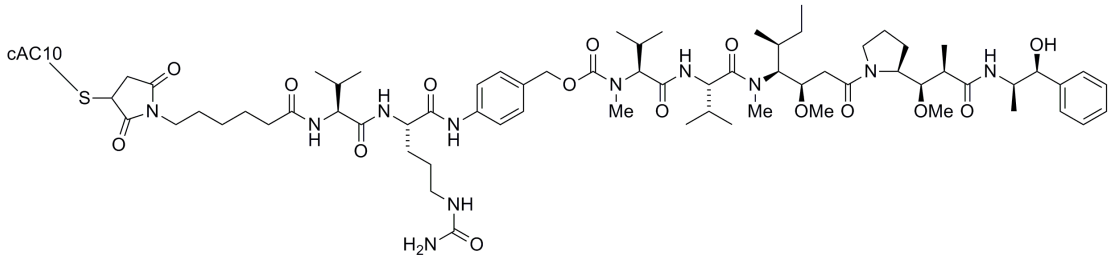
Proper name: Brentuximab vedotin

Chemical name: Chimeric IgG_1 cAC10 covalently linked to vcMMAE

Molecular formula and molecular mass: $C_{6860}H_{10532}N_{1740}O_{2168}S_{40}$

Average mass: 153,352 Da

Structural formula:



Physicochemical properties: The brentuximab vedotin bulk drug substance is colorless and slightly opalescent.

Average drug-to-antibody molar ratio (MRD): 4

Product Characteristics:

Brentuximab vedotin is an ADC (antibody-drug conjugate) composed of a CD30-directed monoclonal antibody (cAC10) covalently linked, via an enzyme-cleavable linker, to the potent antimitotic small molecule monomethyl auristatin E (MMAE). cAC10 is produced by Chinese hamster ovary cell culture. The small molecule, MMAE, attached to an enzyme-cleavable linker (maleimidolcaproyl-valine-citrulline-p-aminobenzyloxycarbonyl-MMAE, vcMMAE) is produced by chemical synthesis. Brentuximab vedotin is produced via the chemical conjugation of cAC10 to vcMMAE.

14. Clinical Trials

14.1. Clinical Trials by Indication

Hodgkin Lymphoma (HL)

Previously Untreated Stage III or IV HL

Table 19 – Summary of Patient Demographics for Clinical Trials in Previously Untreated Stage III or IV HL

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Age[a] (range)	Sex
Study 5: ECHELON-1	Randomized, open-label, phase 3 trial of A+AVD versus ABVD as frontline therapy in patients with advanced classical Hodgkin Lymphoma	ADCETRIS + AVD: 1.2 mg/kg of ADCETRIS IV + AVD every 2 weeks for up to 12 doses	n=664	35 (18-82) years	57% M 43% F
		ABVD: every 2 weeks for up to 12 doses of ABVD	n=670	37 (18-83) years	59% M 41% F

[a] Median age; M=Male; F=Female; ADCETRIS + AVD= ADCETRIS + doxorubicin (A), vinblastine (V), and dacarbazine (D); ABVD= doxorubicin (A), bleomycin (B), vinblastine (V), and dacarbazine (D).

The efficacy of ADCETRIS in combination with AVD for the treatment of previously untreated patients with Stage III or IV HL was evaluated in a randomized, open-label, 2-arm, multicenter trial. Of 1334 total patients, 664 patients were randomized to ADCETRIS + doxorubicin (A), vinblastine (V), and dacarbazine (D) [ADCETRIS + AVD]; and 670 patients were randomized to A + bleomycin (B) + V + D [ABVD]. Patients on the ADCETRIS + AVD arm were treated with 1.2 mg/kg of ADCETRIS administered as an intravenous infusion over 30 minutes every 2 weeks for up to 12 doses + AVD. Patients on the ABVD arm were treated every 2 weeks for up to 12 doses of ABVD. The primary endpoint was modified progression-free survival (mPFS) per independent review facility (IRF). A mPFS event is defined as progression, death, or receipt of additional anticancer therapy for patients who are not in complete remission (CR) after completion of therapy. The key secondary endpoint was overall survival (OS).

Patients had Stage III (36%) or IV disease (64%), and 62% had extranodal involvement at diagnosis. Most patients were male (58%) and white (84%). The median age was 36 years (range, 18-83); 122 patients (9%) were 65 years or older.

Table 20: Summary of Baseline Patient and Disease Characteristics in Study 5 (ECHELON-1)

	ADCETRIS + AVD N=664	ABVD N=670
Age, years		
Median (range)	35 (18-82)	37 (18-83)
≥ 65, n (%)	60 (9)	62 (9)

ECOG status, n (%)		
0	376 (57)	378 (57)
1	259 (39)	262 (39)
2	28 (4)	26 (4)
Missing	1	4
Disease stage 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
Extranodal involvement at time of diagnosis, n (%)	411 (62)	416 (62)
IPFP 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	147 (22)	151 (23)
B symptoms	399 (60)	381 (57)

The efficacy results for Study 5 are summarized in Table 21. Study 5 (ECHELON 1) demonstrated a statistically significant improvement in IRF-assessed mPFS with a 23% reduction in the risk of mPFS events in the ADCETRIS + AVD arm compared with the ABVD arm (p-value=0.035). The median mPFS by IRF assessment was not reached for either treatment arm. At 2 years, the mPFS rate was 82.1% (95% CI: 78.8, 85.0) on the ADCETRIS + AVD arm compared with 77.2% on the ABVD arm (95% CI: 73.7, 80.4). In patients with Stage IV disease, improvement in IRF-assessed mPFS demonstrated a 29% reduction in risk of mPFS events in the ADCETRIS + AVD arm compared with the ABVD arm. The median mPFS by IRF assessment was not reached for either treatment arm. At 2 years, the mPFS rate was 82% (95% CI: 77.8, 85.5) on the ADCETRIS + AVD arm compared with 75.3% on the ABVD arm (95% CI: 70.6, 79.3).

Table 21: Efficacy Results per IRF in Patients with Previously Untreated Stage III or IV HL (Study 5: ECHELON-1)

	Overall Population			**Patients with Stage IV Disease**		
	ADCETRIS + AVD N=664	**ABVD N=670**	**Stratified Hazard Ratio[2] and p-value[3]**	**ADCETRIS + AVD N=425**	**ABVD N=421**	**Unstratified Hazard Ratio**
mPFS[1] Number of events (%)	117 (18)	146 (22)	0.77 (95% CI [0.60, 0.98]) p-value=0.035	77 (18)	102 (24)	0.71 (95% CI [0.53, 0.96])
Median months (95% CI)	NE*	NE*		NE*	NE*	

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

2 Hazard ratio (ADCETRIS + AVD/ABVD) and 95% confidence intervals are based on a stratified Cox's proportional hazard regression model with stratification factors region and number of International Prognostic Factor Project (IPFP) risk factors at baseline with treatment as explanatory variable in the model. Hazard ratio <1 favors ADCETRIS + AVD arm.

3 P-value is from a stratified log-rank test with stratification factors IPFP group and region; alpha = 0.05.

* NE=not estimable

Figure 1: Hazard Ratio for mPFS per IRF Overall and by Stage III and Stage IV Disease Subgroups (Study 5: ECHELON-1)

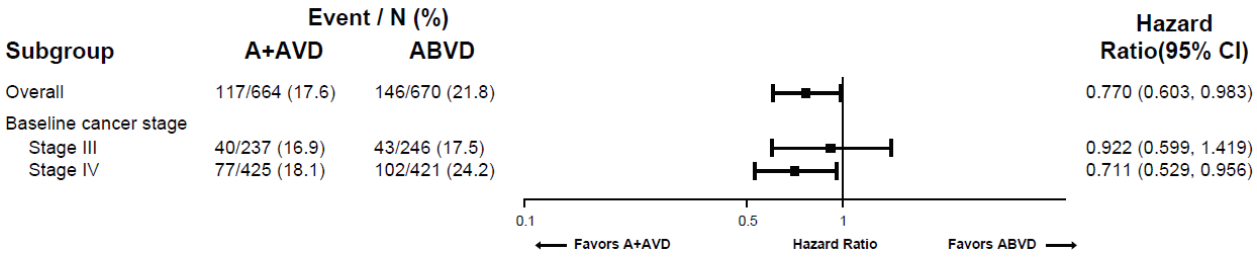
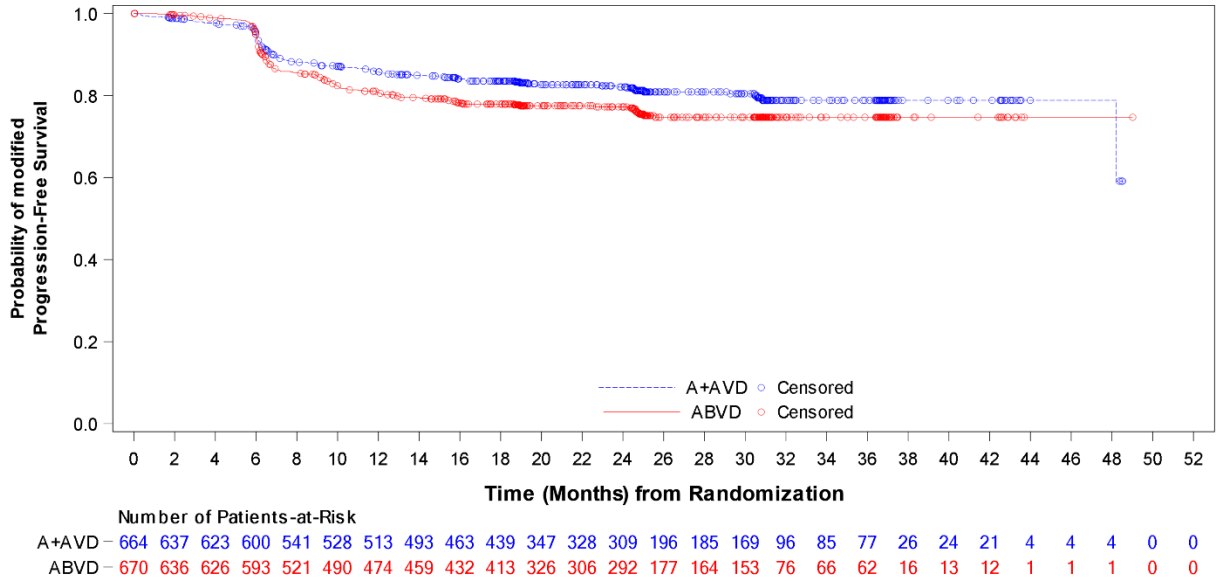
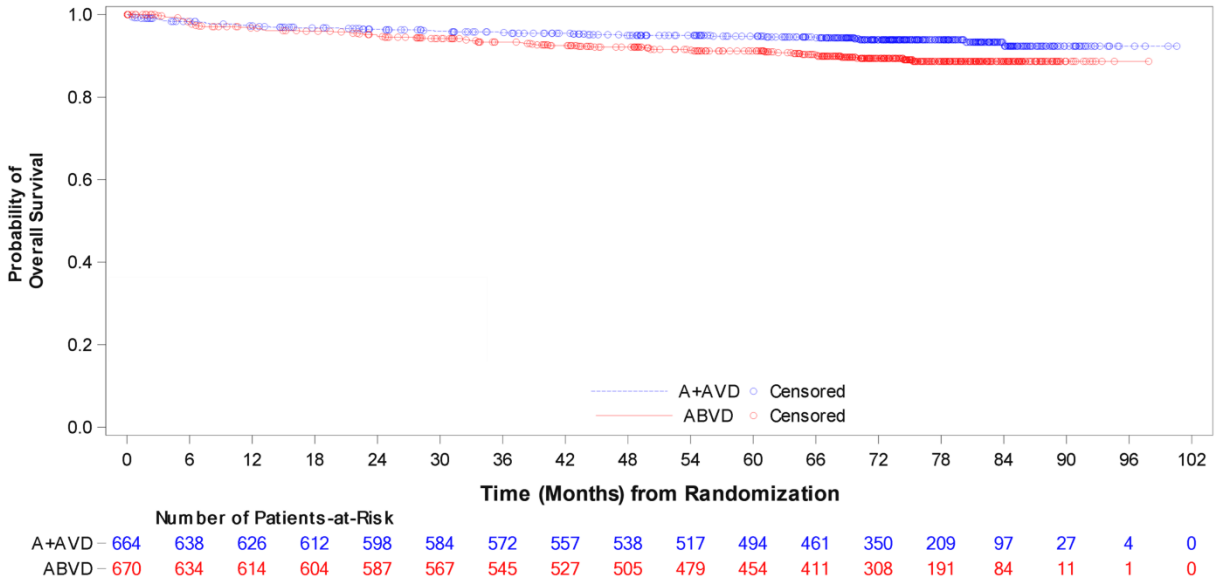


Figure 2: Kaplan-Meier Curve of IRF-Assessed mPFS (Study 5: ECHELON-1)



A pre-specified second interim OS analysis at 103 deaths (39 deaths ADCETRIS + AVD, 64 deaths for ABVD), demonstrated a statistically significant improvement in OS for ADCETRIS + AVD, with a 2-sided p-value of 0.009 based on a stratified log-rank test [threshold: P<0.0365]. The stratified hazard ratio was 0.59 (95% CI, 0.396; 0.879), indicating a 41% reduction in the risk of death for patients treated with ADCETRIS + AVD. Median OS was not reached for patients in either treatment arm. In patients with Stage III disease, the hazard ratio was 0.863 (95% CI, 0.452; 1.648). In patients with Stage IV disease, the hazard ratio was 0.478 (95% CI, 0.286; 0.799).

Figure 3: Kaplan-Meier Curve of OS (Study 5: ECHELON-1)



HL Consolidation

Table 22 – Summary of Patient Demographics for Clinical Trials in Hodgkin Lymphoma Consolidation

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Age[a] (range)	Sex
Study 3: AETHERA	Phase 3 randomized, double-blind, placebo-controlled clinical trial	1.8 mg/kg IV every 3 weeks for up to 16 cycles	Adcetris n=165	33 (18-71) years	46% M 54% F
			Placebo n=164	32 (18-76) years	59% M 41% F

[a] Median age; M=Male; F=Female

The efficacy of ADCETRIS in patients with HL at high risk of relapse or disease progression post-ASCT was studied in one phase 3 randomized, double-blind, placebo-controlled clinical trial. Three hundred twenty-nine (329) patients were randomized 1:1 to receive placebo or ADCETRIS 1.8 mg/kg intravenously over 30 minutes every 3 weeks for up to 16 cycles, beginning 30–45 days post-ASCT. Randomization was stratified by response status following frontline therapy and to most recent pre-ASCT salvage therapy. Patients in the placebo arm with progressive disease (PD) per investigator could receive ADCETRIS as part of a separate trial. The primary endpoint was progression-free survival (PFS) determined by IRF. Clinical lymphoma assessments were done at every cycle during treatment, every 3 months in follow up until 24 months, and then every 6 months until disease progression or study closure.

Subjects were enrolled based on meeting at least one of the three criteria used to define high risk of post-ASCT relapse or progression: refractory to frontline therapy, relapsed <12 months following frontline therapy, or relapsed >12 months with extranodal involvement. Patients were required to have obtained a complete response (CR), partial response (PR), or stable disease (SD) to most recent pre-ASCT salvage therapy.

The majority of the study population were refractory or relapsed <12 months to frontline therapy and had 1 or more other risk factors, including B symptoms following frontline therapy, extranodal disease, 2 or more prior salvage therapies, or response of PR or SD to most recent pre-ASCT salvage therapy.

Table 23: Summary of Baseline Patient and Disease Characteristics in Study 3 (AETHERA)

Patient characteristics	**ADCETRIS N = 165**	**Placebo N = 164**
Median age, (range)	33 years (18-71)	32 years (18-76)
Gender	76M (46%)/89F (54%)	97M (59%)/67F (41%)
ECOG status		
0	87 (53%)	97 (59%)
1	77 (47%)	67 (41%)
2[a]	1 (1%)	0 (0%)
Number of prior systemic salvage therapies		
1	94 (57%)	86 (52%)
≥2 (range, 2-7)	71 (43%)	79 (48%)
Disease characteristics		
HL status after frontline therapy[b]		
Refractory	99 (60%)	97 (59%)
Relapse < 12 months	53 (32%)	54 (33%)
Relapse ≥ 12 months with extranodal involvement	13 (8%)	13 (8%)
Best response to salvage therapy pre-ASCT[c]		
CR	61 (37%)	62 (38%)
PR	57 (35%)	56 (34%)
SD	47 (28%)	46 (28%)
Extranodal involvement at pre-ASCT relapse	54 (33%)	53 (32%)
B symptoms following frontline therapy	47 (28%)	40 (24%)

[a] Patient had an ECOG status of 1 at randomization, which worsened to a status of 2 prior to the first dose of study treatment

[b] Refractory/relapsed status at the end of frontline treatment with standard chemotherapy or a combined modality

[c] Per the Revised Response Criteria for Malignant Lymphoma (2007)

The efficacy results are summarized in Table 24. PFS is calculated from randomization to date of disease progression or death (due to any cause). The median PFS follow-up time from randomization was 22 months (range, 0–49). Study 3 demonstrated a statistically significant improvement in IRF-assessed PFS and increase in median PFS in the ADCETRIS arm compared with the placebo arm.

An interim OS analysis conducted after an observation of 30 months (range, 0–50) demonstrated 53 patients (16%) had died: 28/165 patients (17%) in the ADCETRIS arm versus 25/164 patients (15%) in

the placebo arm. Interpretation of the interim OS data is limited by the small number of events observed within a relatively short follow-up period and the high rate of crossover to ADCETRIS in the placebo arm (72/136 patients who received subsequent therapy).

Table 24: Efficacy Results in Patients with HL Consolidation (Study 3: AETHERA)

Progression-free Survival per IRF	**ADCETRIS N=165**	**Placebo N=164**
Number of events (%)	60 (36)	75 (46)
Median months (95% CI)	42.9[a] (30.4, 42.9[a])	24.1 (11.5, NE[b])
Stratified Hazard Ratio[c] (95% CI)	0.57 (0.40, 0.81)	
Stratified Log-Rank Test p-value[d]	0.001	

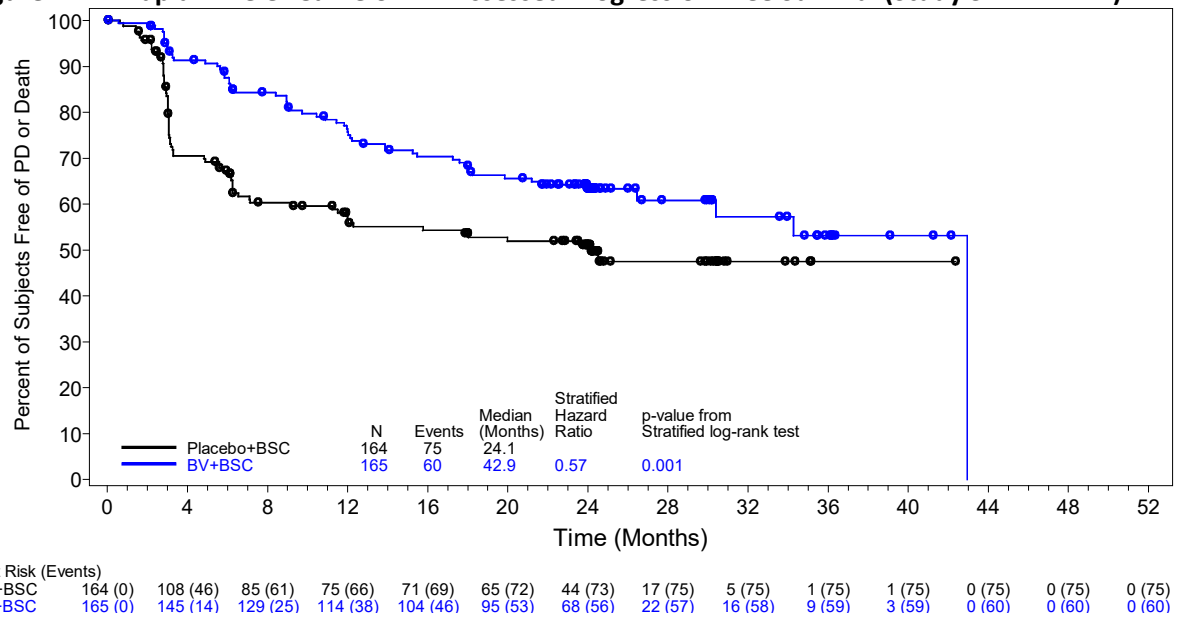
[a] Estimates are unreliable

[b] Not estimable

[c] Comparing ADCETRIS to placebo. HR <1.0 based on stratified Cox PH model adjusting for status following frontline therapy and best clinical response to most recent pre-ASCT salvage therapy

[d] Computed using stratification factors (see footnote c)

Figure 4: Kaplan-Meier Curve of IRF-Assessed Progression-Free Survival (Study 3: AETHERA)



BV: Brentuximab Vedotin; BSC: Best Supportive Care

Post-hoc exploratory analyses were performed to evaluate the potential association between the number of risk factors present at baseline and PFS. In the analyses of PFS per IRF stratified by number of risk factors present at baseline, the proportion of patients with ≥ 2 risk factors and disease progression or death was 36.1% (52/144) in the ADCETRIS arm and 50% (68/136) in the placebo arm. The corresponding proportions for patients with 1 risk factor were 42.9% (9/21) in the ADCETRIS arm and 28.6% (8/28) in the placebo arm. These results should be interpreted with caution given the inherent limitations associated with post-hoc exploratory sub-group analysis.

Relapsed/Refractory HL

Table 25 – Summary of Patient Demographics for Clinical Trials in Relapsed/Refractory HL

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Age[a] (range)	Sex
Study 1	Phase 2, open-label, single-arm, multicenter study	1.8 mg/kg of ADCETRIS IV every 3 weeks for up to 16 cycles	n=102	31 (15-77) years	47% M 53% F

[a] Median age; M=Male; F=Female

The efficacy of ADCETRIS in patients with relapsed or refractory HL was evaluated in one pivotal open-label, single-arm, multicenter study. One hundred two patients were treated with 1.8 mg/kg of ADCETRIS intravenously over 30 minutes every 3 weeks for up to 16 cycles. An IRF performed efficacy evaluations, including overall response rate (ORR = complete remission [CR] + partial remission [PR]) and duration of response, which were assessed using clinical and radiographic measures including computed tomography (CT) and positron-emission tomography (PET) as defined in the 2007 Revised Response Criteria for Malignant Lymphoma.

Table 26: Summary of Baseline Patient and Disease Characteristics in Study 1

	HL
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 ASCT	102 (100%)
Prior chemotherapy regimens (range)	3.5 (1-13)
Disease characteristics	
Relapsed	59 (58%)
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 disease is defined as a failure to achieve a complete remission to, or progressed within 3 months of completing frontline therapy.

The efficacy results for Study 1 are summarized in Table 27. Duration of response is calculated from date of first response to date of progression or data cutoff date.

Table 27: Efficacy Results in Patients with Hodgkin Lymphoma (Study 1)

	N=102		
	Percent (95% CI)	Duration of Response, in months	
		Median (95% CI)	Range
Overall response rate (ORR)	75 (65, 83)	6.7 (3.6, 14.8)	1.2+ to 26.1+
Complete remission (CR)	32 (23, 42)	Not reached (12.08, NE*)	1.4 to 26.1+
Partial remission (PR)	42 (32, 52)	3.5 (2.2, 4.1)	1.2+ to 21.9+

* Not estimable

\+ Follow up was ongoing at the time of data submission.

Retreatment with ADCETRIS

The efficacy of retreatment in patients who had previously responded to ADCETRIS was evaluated in one phase 2, open-label, multicenter trial. Retreatment with ADCETRIS was evaluated in 29 patients (21 with relapsed HL and 8 with relapsed sALCL). Twenty-seven patients received a starting dose of 1.8 mg/kg and two patients received a starting dose of 1.2 mg/kg (one patient each with HL and sALCL) administered intravenously over 30 minutes every 3 weeks.

Of the 20 evaluable patients with relapsed HL, 6 patients (30%) achieved a CR and 6 patients (30%) achieved a PR with ADCETRIS retreatment, for an ORR of 60%.

T-Cell Lymphoma

Previously Untreated Systemic Anaplastic Large Cell Lymphoma (sALCL), CD30-Expressing Peripheral T-Cell Lymphoma-Not Otherwise Specified (PTCL-NOS), or CD30-expressing Angioimmunoblastic T-cell lymphoma (AITL)

Table 28 – Summary of Patient Demographics for Clinical Trials in previously untreated CD30-expressing PTCL

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Age[a] (range)	Sex
Study 6, ECHELON-2	Randomized, Double-Blind, Phase 3 Trial in previously untreated Systemic Anaplastic Large Cell Lymphoma (sALCL), CD30-	ADCETRIS + CHP: ADCETRIS 1.8 mg/kg IV, cyclophosphamide 750 mg/m^2 IV, doxorubicin 50 mg/m^2 IV, and prednisone 100 mg PO	n=226	58 (18-85) years	59% M 41% F

	Expressing Peripheral T-Cell Lymphoma-Not Otherwise Specified (PTCL-NOS), or CD30-expressing Angioimmunoblastic T-cell lymphoma (AITL)	CHOP: cyclophosphamide 750 mg/m^2 IV, doxorubicin 50 mg/m^2 IV, vincristine 1.4 mg/m^2 IV, and prednisone 100 mg PO	n=226	58 (18-83) years	67% M 33% F

[a] Median age; M=Male; F=Female

The efficacy of ADCETRIS in combination with CHP for the treatment of patients with previously untreated CD30-expressing PTCL was evaluated in a multicenter, randomized, double-blind, double-dummy, active-controlled trial. The trial included patients who had CD30 expression in ≥10% neoplastic cells as determined by immunohistochemistry testing using antibody Ber-H2. Enrollment was based on the results from local assessment on the CD30 expression level by accredited laboratories using validated testing methods and was subsequently confirmed by central testing (Ventana anti-CD30 [Ber-H2]). For those with anaplastic lymphoma kinase [ALK]-positive sALCL an international prognostic index [IPI] ≥2 was required. Randomization was stratified by histologic type (ALK-positive sALCL versus all others) and IPI score (0-1 versus 2-3 versus 4-5).

Of 452 patients, 226 were randomized to ADCETRIS + CHP (cyclophosphamide [C], doxorubicin [D], and prednisone [P]); and 226 patients were randomized to CHOP (cyclophosphamide [C], doxorubicin [D], vincristine [O], and prednisone [P]). Patients were treated intravenously on Day 1 of each 21-day cycle for 6 or 8 cycles; prednisone was administered orally on Days 1-5. Dosing was administered according to the following:

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

Efficacy was established based on progression-free survival (PFS) per independent review facility (IRF). A PFS event is defined as progression, death due to any cause, or receipt of subsequent anticancer chemotherapy to treat residual or progressive disease.

Most patients were male (63%) and white (62%). The median age was 58 years (range, 18-85). Disease subtypes included sALCL (70%; 48% ALK negative and 22% ALK positive), PTCL-NOS (16%), AITL (12%), adult T-cell leukemia/lymphoma (2%), and enteropathy-associated T-cell lymphoma (<1%). Most patients had a baseline IPI of 2 (34%) or 3 (29%); Stage III (27%) or IV (53%) disease; and an ECOG performance status of 0 or 1 (78%).

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

The efficacy results for Study 6 are summarized in Table 29. Kaplan-Meier curves for PFS and overall survival (OS) are presented in Figure 5 and Figure 6, respectively.

Table 29: Efficacy Results in Patients with CD30-Expressing PTCL (Study 6: ECHELON-2)

Outcomes per IRF[a]	**ADCETRIS + CHP N=226**	**CHOP N=226**
PFS		
Number of events, n (%)	95 (42)	124 (55)
Median PFS, months (95% CI)	48.2 (35.2, NE)	20.8 (12.7, 47.6)
Hazard ratio (95% CI)[b]	0.71 (0.54, 0.93)	
P-value[c]	0.011	
OS[d]		
Number of deaths, n (%)	51 (23)	73 (32)
Median OS, months (95% CI)	NE (NE, NE)	NE (54.2, NE)
Hazard ratio (95% CI)[b]	0.66 (0.46, 0.95)	
P-value[c]	0.024	

ALK=anaplastic lymphoma kinase; CI=confidence interval; IPI=International Prognostic Index; NE=not estimable; PFS=progression-free survival; sALCL=systemic anaplastic large cell lymphoma.

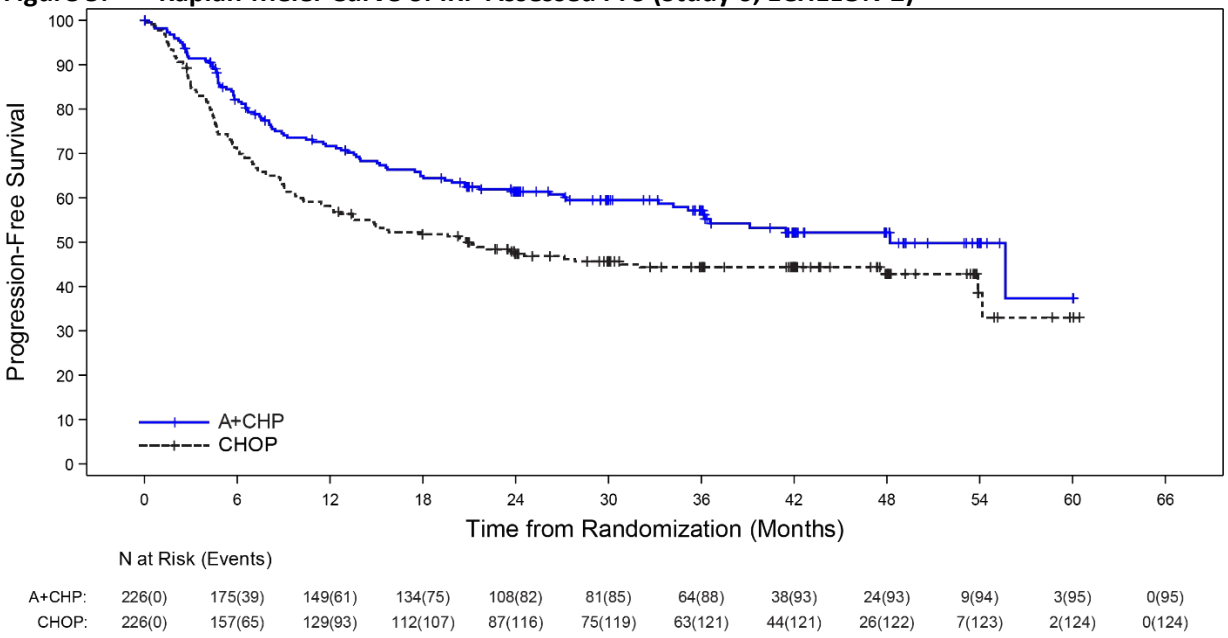
[a] Efficacy endpoints were tested at a two-sided alpha level 0.05 in a hierarchical order as the following: PFS in ITT, PFS in the sALCL subgroup, complete remission rate, overall survival, and objective response rate in ITT.

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

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

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

Figure 5: Kaplan-Meier Curve of IRF-Assessed PFS (Study 6; ECHELON-2)

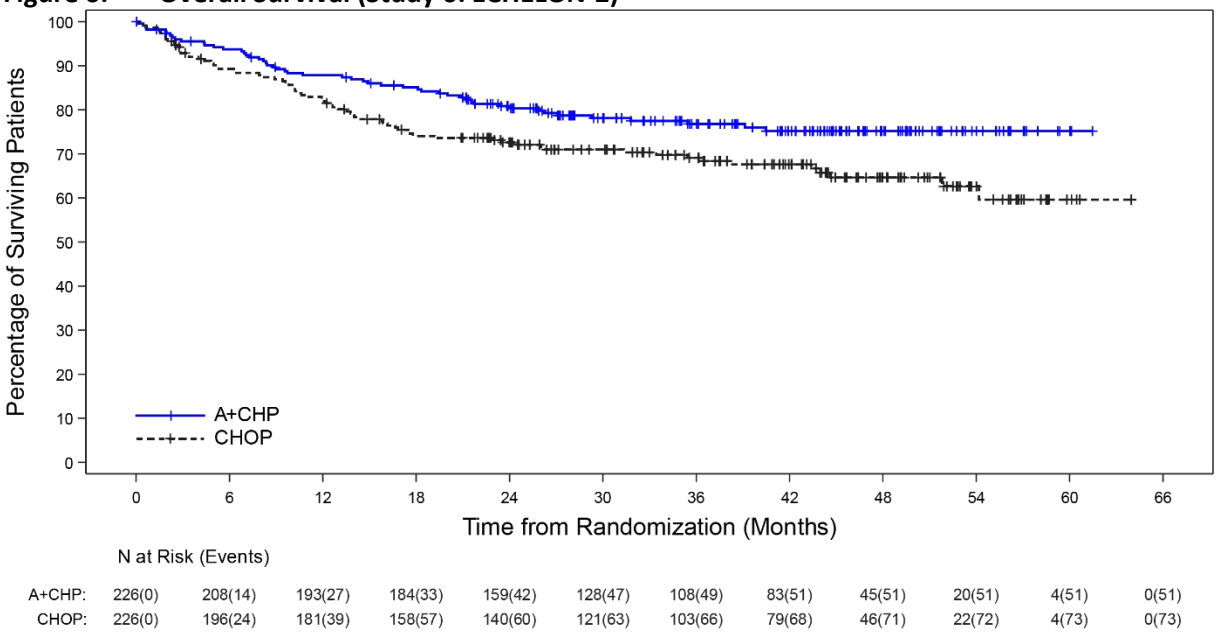


N at Risk (Events)

A+CHP:	226(0)	175(39)	149(61)	134(75)	108(82)	81(85)	64(88)	38(93)	24(93)	9(94)	3(95)	0(95)
CHOP:	226(0)	157(65)	129(93)	112(107)	87(116)	75(119)	63(121)	44(121)	26(122)	7(123)	2(124)	0(124)

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

Figure 6: Overall Survival (Study 6: ECHELON-2)



N at Risk (Events)

A+CHP:	226(0)	208(14)	193(27)	184(33)	159(42)	128(47)	108(49)	83(51)	45(51)	20(51)	4(51)	0(51)
CHOP:	226(0)	196(24)	181(39)	158(57)	140(60)	121(63)	103(66)	79(68)	46(71)	22(72)	4(73)	0(73)

Study 6 (ECHELON 2) demonstrated a statistically significant improvement in IRF-assessed PFS in patients with sALCL in the ADCETRIS + CHP arm compared to the CHOP arm (HR: 0.59 [95% CI: 0.42, 0.84]). The median PFS was 55.7 months (95% CI: 48.2, NE) in the ADCETRIS + CHP arm compared to 54.2 months (95% CI: 13.4, NE) in the CHOP arm. Complete remission was achieved in 68% (95% CI: 61,

74) of patients on the ADCETRIS + CHP arm compared to 56% (95% CI: 49, 62) of patients on the CHOP arm.

In exploratory subgroup analyses, the HR for PFS was 1.03 (95% CI: 0.55, 1.92) and the HR for OS was 1.15 (95% CI: 0.58, 2.31) in subjects with IPI score of 4-5 (A+CHP [n=33] versus CHOP [n=33]); the HR for PFS was 0.98 (95% CI: 0.51, 1.87) and the HR for OS was 1.48 (95% CI: 0.70, 3.11) in subjects with ECOG status of 2 (A+CHP [n=51] versus CHOP [n=47]). These findings should be interpreted with caution due to the limitations of exploratory subgroup analyses.

Relapsed/Refractory sALCL

Table 30 – Summary of Patient Demographics for Clinical Trials in Relapsed/Refractory sALCL

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Age[a] (range)	Sex
Study 2	Phase 2, open-label, single-arm, multicenter trial	1.8 mg/kg of ADCETRIS IV every 3 weeks for up to 16 cycles	n=58	52 (14-76) years	57% M 43% F

[a] Median age; M=Male; F=Female

The efficacy of ADCETRIS in patients with relapsed or refractory sALCL was evaluated in one open-label, single-arm, multicenter trial. This trial included patients who had sALCL that was relapsed or refractory after prior therapy. Fifty-eight patients were treated with 1.8 mg/kg of ADCETRIS administered intravenously over 30 minutes every 3 weeks for up to 16 cycles. An IRF performed efficacy evaluations, including overall response rate (ORR = complete remission [CR] + partial remission [PR]) and duration of response, which were assessed using clinical and radiographic measures including computed tomography (CT) and positron-emission tomography (PET) as defined in the 2007 Revised Response Criteria for Malignant Lymphoma.

Table 31: Summary of Baseline Patient and Disease Characteristics in Study 2

Patient characteristics	sALCL
	N = 58
Median age, yrs (range)	52 years (14-76)
Gender	33M (57%)/25F (43%)
ECOG status	
0	19 (33%)
1	38 (66%)
Prior ASCT	15 (26%)
Prior chemotherapy regimens (range)	2 (1-6)
Disease characteristics	
Relapsed	29 (50%)
Primary Refractory to frontline therapy[a]	36 (62%)
Refractory to most recent therapy	29 (50%)
ALK[b]-negative	42 (72%)
Baseline B symptoms	17 (29%)
Stage III at initial diagnosis	8 (14%)
Stage IV at initial diagnosis	21 (36%)

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

[b] Anaplastic lymphoma kinase

The efficacy results for Study 2 are summarized in Table 32. Duration of response is calculated from date of first response to date of progression or data cutoff date.

Table 32: Efficacy Results in Patients with Systemic Anaplastic Large Cell Lymphoma (Study 2)

	N=58		
	Percent (95% CI)	Duration of Response, in months	
		Median (95% CI)	Range
Overall response rate (ORR)	86 (75, 94)	13.2 (5.7, NE*)	0.1 to 21.7+
Complete remission (CR)	59 (45, 71)	Not reached (13.0, NE*)	0.7 to 21.7+
Partial remission (PR)	28 (17, 41)	2.0 (1.3, 3.0)	0.1 to 21+

* Not estimable

\+ Follow up was ongoing at the time of data submission

Retreatment with ADCETRIS

The efficacy of retreatment in patients who had previously responded to ADCETRIS was evaluated in one phase 2, open-label, multicenter trial. Retreatment with ADCETRIS was evaluated in 29 patients (21 with relapsed HL and 8 with relapsed sALCL). Twenty-seven patients received a starting dose of 1.8 mg/kg and two patients received a starting dose of 1.2 mg/kg (one patient each with HL and sALCL) administered intravenously over 30 minutes every 3 weeks.

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%.

Table 33 – Summary of Patient Demographics for Clinical Trials in Primary Cutaneous Anaplastic Large Cell Lymphoma (pcALCL) or CD30-Expressing Mycosis Fungoides (MF)

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Age[a] (range)	Sex
Study 4: ALCANZA	Phase 3, randomized trial in Primary Cutaneous Anaplastic Large Cell Lymphoma (pcALCL) or CD30-Expressing Mycosis Fungoides (MF)	Adcetris: 1.8 mg/kg IV every 3 weeks	n=64	62 (22-83) years	52% M 48% F
		Methotrexate: 5 to 50 mg orally weekly Or Bexarotene: 300 mg/m^2 orally daily	n=64	59 (22-83) years	58% M 42% F

[a] Median age; M=Male; F=Female

The efficacy of ADCETRIS in patients with mycosis fungoides (MF) or primary cutaneous anaplastic large cell lymphoma (pcALCL) who had received prior systemic therapy was studied in ALCANZA, a randomized, open-label, multicenter clinical trial. In ALCANZA, one hundred thirty-one (131) patients were randomized 1:1 to receive ADCETRIS (n = 66) 1.8 mg/kg intravenously over 30 minutes every 3 weeks or physician's choice (n = 65) of methotrexate (5 to 50 mg orally weekly) or bexarotene (300 mg/m^2 orally daily). The randomization was stratified by baseline disease diagnosis (MF or pcALCL). Patients could receive a maximum of 16 cycles (21-day cycle) of therapy every 3 weeks for those receiving brentuximab vedotin or 48 weeks of therapy for those in the control arm.

Patients with pcALCL must have received prior radiation or systemic therapy, and must have had at least 1 biopsy with CD30-expression of ≥10% as determined by immunohistochemistry (IHC). Patients with MF must have received prior systemic therapy and have had skin biopsies from at least 2 separate lesions, with CD30-expression of ≥10% in at least 1 biopsy as determined by IHC.

The efficacy results were based on 128 patients with at least one biopsy with CD30 expression (64 patients in each arm). Among these 128 patients, age ranged from 22–83 years (median, 60 years), 55% were male, and 85% were white. Patients had received a median of 4 prior systemic therapies (range, 0–15), including a median of 1 prior skin-directed therapy (range, 0–9) and 2 systemic therapies (range, 0–11). At study entry, patients were diagnosed as Stage 1 (25%), Stage 2 (38%), Stage 3 (5%), or Stage 4 (13%). The two arms were well balanced for demographics and baseline disease characteristics.

Table 34: Summary of Baseline Patient and Disease Characteristics in Study 4 (ALCANZA)

Patient characteristics	ADCETRIS N = 64	Physician's Choice[a] N = 64
Median age, (range)	62 years (22-83)	59 years (22-83)
Gender	33M (52%)/31F (48%)	37M (58%)/27F (42%)
ECOG status		
0	43 (67%)	46 (72%)
1	18 (28%)	16 (25%)
2[a]	3 (5%)	2 (3%)
Median number of prior therapies (range)		
Any therapy	4 (0-13)	3.5 (1-15)
Skin-directed therapy	1 (0-6)	1 (0-9)
Systemic therapy	2 (0-11)	2 (1-8)
Disease characteristics		
MF	N=48	N=49
Early (Stage 1A-IIA)	15 (31%)	18 (37%)
Advanced (Stage IIB-IVB)[b]	32 (67%)	30 (61%)
pcALCL	N=16	N=15
Skin only	9 (56%)	11 (73%)
Extracutaneous disease	7 (44%)	4 (27%)

[a] Physician's choice of either methotrexate or bexarotene

[b] Stage IVB MF, n=7 ADCETRIS vs. n=0 Physician's choice

Efficacy was established based on the proportion of patients achieving an objective response (CR +PR) that lasts at least 4 months (ORR4). ORR4 was determined by an IRF using the global response score (GRS), consisting of skin evaluations by non-blinded investigators using the modified severity-weighted assessment tool (mSWAT), nodal and visceral radiographic assessment by the IRF, and detection of circulating Sézary cells (MF patients only) by central laboratory testing. Additional efficacy outcome measures included proportion of patients achieving a complete response (CR) per IRF, and progression-free survival (PFS) per IRF.

The efficacy results are summarized in Table 35 below and the Kaplan-Meier curves of IRF-Assessed Progression-free Survival are shown in Figure 7.

Table 35: Efficacy Results in Patients with Previously Treated CD30-Expressing MF or pcALCL (Study 4: ALCANZA)

	ADCETRIS N = 64	Physician's Choice[a] N = 64
ORR4[b]		
Percent (95% CI)	56.3 (44.1, 68.4)	12.5 (4.4, 20.6)
P-value[d]	<0.001	
ORR	67.2 (55.7, 78.7)	20.3 (10.5, 30.2)
CR		
Percent (95% CI)	15.6 (7.8, 26.9)	1.6 (0, 8.4)
P-value[c,d]	0.0066	
PR	51.6 (39.3, 63.8)	18.8 (9.2, 28.3)
PFS		
Number of events (%)	36 (56.3)	50 (78.1)
Median months (95% CI)	16.7 (14.9, 22.8)	3.5 (2.4, 4.6)
Hazard Ratio (95% CI)	0.27 (0.17, 0.43)	
Log-Rank Test p-value[c,d]	p<0.001	

CI=confidence interval; CR=complete response; PR=partial response.

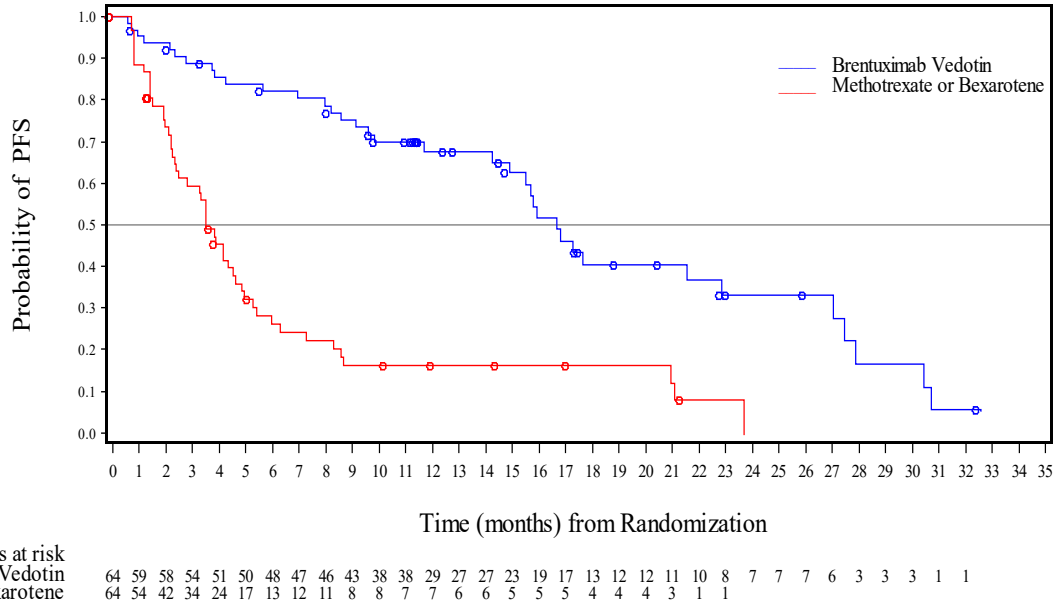
[a] Physician's choice of either methotrexate or bexarotene

[b] ORR4 is defined as proportion of patients achieving an objective response (CR +PR) that lasts at least 4 months

[c] Test of the treatment difference was stratified by baseline disease diagnosis (MF or pcALCL)

[d] Adjusted for multiplicity using the weighted Holm procedure

Figure 7: Kaplan-Meier Curve of Progression-free Survival (Study 4: ALCANZA)



16. Non-Clinical Toxicology

General toxicology:

Myelotoxicity

Myelotoxicity was the primary treatment-related toxicity associated with single-dose and repeat-dose IV administration of brentuximab vedotin and MMAE in both monkey and rat. Myelotoxicity was dose-dependent in both species. At the high dose-levels (up to 5 and 9-fold the human systemic exposure (AUC) in monkey and rat, respectively) myelotoxicity was characterized primarily as severe hypocellularity of hematopoietic cells. At exposures up to 3-fold that in human there was minimal hypocellularity, and at dose levels similar to or slightly less than that in humans no hypocellularity in the bone marrow was observed. At recovery, no bone marrow findings were noted at all dose levels, indicating complete reversibility.

Myelotoxicity-Related Hematologic Toxicity

Consistent with the primary target organ histopathology findings (bone marrow hypocellularity and lymphoid depletion) decreases in peripheral hematology parameters were observed in both monkey and rat. In monkeys, the predominant effect on hematology was a dose-dependent decrease in neutrophils with markedly decreased absolute neutrophil counts at 1 and 2 weeks following each dose with a nadir at 2 weeks post-dose, and reversibility by 3 weeks. In addition to the effects on neutrophils, other leukocyte, erythrocyte and reticulocyte counts were variably decreased. In rats, the hematology effects included evidence of significantly reduced erythropoiesis (lower reticulocyte count, red blood cell count, hemoglobin, and hematocrit) resulting in nonregenerative anemia. Within two weeks post-dose, complete recovery of all cell lineages was evident in the peripheral hematology endpoints as well as by bone marrow cytology and histopathology.

Neutropenia-Related Mortality

Mortality attributed to bacterial infections secondary to severe neutropenia was observed in 3 of 16 monkeys following administration of one dose of 6 mg/kg brentuximab vedotin. Thus, neutropenia was the most clinically significant toxicity observed in animals.

The primary treatment-related effects of repeat-dose brentuximab vedotin administration to rats and monkeys (bone marrow hypocellularity and lymphoid depletion) and the associated decreases in peripheral blood cells, most notably neutropenia are consistent with pharmacologic disruption of microtubules caused by MMAE.

Neurotoxicity

No histopathologic evidence of neurotoxicity was observed after 4 doses in monkeys or rats at systemic exposures (AUC) up to 6-fold that in humans. In the safety pharmacology study, there were no effects within 4 days following a single dose of 3 mg/kg brentuximab vedotin to monkeys on neurological endpoints. Additionally, in the 6-month chronic toxicity study in monkeys, after the administration of brentuximab vedotin at 3 mg/kg q3wk x 9, no histopathologic evidence of neurotoxicity was observed.

Hepatotoxicity

Brentuximab vedotin and MMAE treatment resulted in reversible, dose-dependent hepatic toxicity in rats. Focal hepatocellular coagulative necrosis and increases in serum hepatobiliary enzymes, was observed as early as four days post dose in rats administered >5 mg/kg brentuximab vedotin and at the MMAE doses of >0.1 mg/kg.

Other Toxicities

Brentuximab vedotin and MMAE treatment resulted in reversible, dose-dependent lymphoid depletion (thymus and spleen) and reduction in thymic weight in both rats and monkeys. In addition, brentuximab vedotin administered to rats resulted in sporadic, reversible, observations of cell necrosis in the intestine or pancreas and alveolar histiocytosis in the lung.

Clinical chemistry findings (other than those associated with hepatic toxicities described above) after brentuximab vedotin administration in either rats or monkeys were sporadic, minimal to mild and included; elevations in total protein, globulin and cholesterol, and slight decreases in albumin.

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.

Reproductive and developmental toxicology:

Embryotoxicity

Repeat-dose embryo-fetal development toxicity studies in rats revealed embryo-fetal lethality/teratogenicity. Embryo-fetal lethality and teratogenicity were observed in rats treated with brentuximab vedotin at 1.2 and 4 mg/kg (q3dx5 and 3 and 10 mg/kg (q7dx2), as well as in rats treated with MMAE at 0.2 mg/kg (q7dx2). Embryo-fetal toxicity was characterized by decrease in viable fetuses, increased early resorptions and post-implantation loss. The embryo-fetal toxicity was more severe following administration of 10 mg/kg brentuximab vedotin than MMAE at the molar equivalent dose level (0.2 mg/kg).

Placental transfer of brentuximab vedotin ADC, TAb, and MMAE in pregnant rats was investigated in repeated embryo-fetal development rat studies. Results from both studies were consistent; brentuximab vedotin ADC, TAb, and MMAE were transferred across the placenta of pregnant rats following administration of brentuximab vedotin. Brentuximab vedotin ADC, TAb, and MMAE were detectable in fetal serum, but at lower concentrations than those observed in maternal serum for the same timepoint and dose.

Impairment of Fertility

Fertility studies with brentuximab vedotin or MMAE have not been conducted. However, results of repeat-dose toxicity studies in rats and cynomolgus monkeys indicate the potential for brentuximab vedotin to impair male and female reproductive function and fertility.

Repeat-dose studies of brentuximab vedotin and MMAE treatment in rats resulted in partially reversible, dose-dependent testicular toxicity. Seminiferous tubule degeneration, Sertoli cell vacuolation, reduced spermatogenesis and aspermia were observed in rats treated with brentuximab vedotin at 5 and 10 mg/kg (q1wkx4) (approximately 3 times the exposure level of the clinical dose of 1.8 mg/kg) and MMAE at 0.194 and 0.29 mg/kg/dose (q1wkx4). In a repeat-dose study of brentuximab vedotin (q1wkx4) at 10 mg/kg/dose, partial reversibility of testicular toxicity was demonstrated following a 16-week recovery phase.

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.

Patient Medication Information

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

(Ad-SET-riss)

ADCETRIS®

brentuximab vedotin for injection

This patient medication information is written for the person who will be taking **ADCETRIS**. This may be you or a person you are caring for. Read this information carefully. Keep it as you may need to read it again.

This patient medication information is a summary. It will not tell you everything about this medication. If you have more questions about this medication or want more information about **ADCETRIS**, talk to a healthcare professional.

Serious warnings and precautions box

In patients treated with ADCETRIS, the following serious side effects have occurred and were fatal in some cases:

- Brain infection causing a serious and potentially fatal condition called progressive multifocal leukoencephalopathy (PML)
- Severe skin reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis
- Infections
- Pancreatitis (inflammation of the pancreas)
- Stomach or intestine (gastrointestinal) problems
- Lung problems

See below for signs and symptoms of these serious side effects. Immediately report to your doctor if you notice any of the described symptoms.

What ADCETRIS is used for:

ADCETRIS is used to treat patients with:

- Hodgkin lymphoma (HL) that is advanced stage and has not already been treated, when used in combination with a chemotherapy regimen of doxorubicin, vinblastine and dacarbazine.
- Hodgkin lymphoma (HL) at increased risk of continuing or returning, as additional treatment after an autologous stem cell transplant (ASCT).
- Hodgkin lymphoma (HL) that has come back after a stem cell transplant or after two types of chemotherapy if you cannot receive a stem cell transplant.
- Systemic Anaplastic Large Cell Lymphoma (sALCL), CD30-expressing Peripheral T-cell Lymphoma-not otherwise specified (PTCL-NOS), or CD30-expressing Angioimmunoblastic T-cell Lymphoma (AITL),

that has not already been treated, used in combination with cyclophosphamide, doxorubicin, and prednisone.

- Systemic anaplastic large cell lymphoma (sALCL) that comes back after treatment with chemotherapy.
- Primary cutaneous anaplastic large cell lymphoma (pcALCL) or CD30-expressing mycosis fungoides (MF) who have had prior systemic therapy.

How ADCETRIS works:

ADCETRIS contains brentuximab vedotin, which is made up of two types of medicine that are attached to each other. One part belongs to a group of medicines called monoclonal antibodies and the other belongs to a group of medicines called anti-mitotics. The monoclonal antibody part allows the drug to find the cancer cell in the body; the anti-mitotic part kills the cancer cell once it is found.

ADCETRIS attaches to a molecule called CD30 that is present on the surface of HL and sALCL cancer cells, but not usually on healthy cells. ADCETRIS then enters the cancer cells and kills them by releasing an anti-mitotic that is toxic to the cancer cells. Even though ADCETRIS usually attaches to cancer cells, and not healthy cells, it can still cause side effects. These should be discussed with your doctor.

The ingredients in ADCETRIS are:

Medicinal ingredients: brentuximab vedotin

Non-medicinal ingredients: polysorbate 80, sodium citrate, trehalose

ADCETRIS comes in the following dosage forms:

ADCETRIS comes in a single-use vial containing 50 mg of brentuximab vedotin for injection.

Do not use ADCETRIS if:

- You have a known allergy to the medicinal or non-medicinal ingredients.
- You are currently taking another drug called bleomycin. Bleomycin must be stopped before starting ADCETRIS.
- You have or have had progressive multifocal leukoencephalopathy (PML).

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take ADCETRIS. Talk about any health conditions or problems you may have, including if you:

- take a medicine to treat or prevent fungal infections;
- are taking antibiotics for tuberculosis;
- have or have had a liver or kidney disease;
- might be pregnant or are trying to become pregnant;
- are breast feeding;
- are allergic to the ingredients in ADCETRIS.

Other warnings you should know about:

- Women who may become pregnant should use at least 2 reliable methods of birth control during and for 6 months after treatment with ADCETRIS. Immediately report to your doctor if you become pregnant while receiving ADCETRIS.
- Do not breastfeed while you are receiving ADCETRIS. It is not known if the drug can get into breast milk, and therefore, into the baby.
- Men should use an appropriate method of barrier contraception during and for 6 months after treatment with ADCETRIS.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with ADCETRIS:

- Some medicines and foods (like grapefruit juice) may change the amount of the anti-mitotic in your body.

How to take ADCETRIS:

ADCETRIS is given as an intravenous infusion over 30 minutes**.**

Usual dose:

For patients with

- HL that is advanced stage and has not been previously treated, given in combination with a chemotherapy regimen of doxorubicin, vinblastine and dacarbazine.

The usual dose is 1.2 mg/kg given at 2-week intervals for up to 12 doses. If you have mild liver disease, the dose may be 0.9 mg/kg. If you have serious liver or serious kidney disease, ADCETRIS use should be avoided. If you weigh more than 100 kg, your dose will be calculated as if your weight was 100 kg. While taking ADCETRIS, you may also receive medicine that will help to reduce the chance of infection. Treatment with ADCETRIS will be stopped if your disease gets worse or if you experience unacceptable side effects.

For patients with

- HL at increased risk of continuing or returning, as additional treatment after an autologous stem cell transplant (ASCT).
- HL that has come back after a stem cell transplant or after two types of chemotherapy if you cannot receive a stem cell transplant.
- sALCL that has come back after treatment with chemotherapy.
- pcALCL or with certain types of MF after at least one systemic therapy

The usual dose is 1.8 mg/kg given at 3-week intervals. If you have mild liver disease, the dose may be 1.2 mg/kg. If you have more serious liver or serious kidney disease, ADCETRIS use should be avoided. If you weigh more than 100 kg, your dose will be calculated as if your weight is 100 kg. You will receive ADCETRIS at 3-week intervals. Treatment with ADCETRIS will be stopped if your disease gets worse, if you experience unacceptable side effects, or if you reach the recommended number of doses.

If you are receiving ADCETRIS after an ASCT, your treatment should begin within 4–6 weeks after ASCT or recovery from ASCT. Treatment with ADCETRIS will continue for up to 16 doses or until your disease gets worse or if you experience unacceptable side effects.

If you are a patient with certain types of PTCL that has not already been treated, you will receive ADCETRIS in combination with cyclophosphamide, doxorubicin, and prednisone.

Overdose:

It is unlikely that you will receive too much ADCETRIS as you will be closely monitored by healthcare professionals during your infusion.

If you think you, or a person you are caring for, have taken too much ADCETRIS, contact a healthcare professional, hospital emergency department, regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669) immediately, even if there are no signs or symptoms.

Missed Dose:

If you miss your appointment to receive ADCETRIS, you should make every effort to receive the missed dose as soon as possible. Doses should not be given less than 3 weeks apart.

Possible side effects from using ADCETRIS:

These are not all the possible side effects you may have when taking ADCETRIS. If you experience any side effects not listed here, tell your healthcare professional.

Very common (≥ 10%) side effects associated with the use of ADCETRIS include:

- Nausea
- Vomiting
- Fatigue
- Diarrhea
- Hair loss
- Rash
- Itching
- Fever
- Swelling in limbs
- Difficulty Sleeping
- Joint and muscle pain
- Shortness of breath
- Low red blood cell counts
- Low white blood cell counts.
- Low platelet counts
- Constipation
- Decreased appetite
- Headache
- Dizziness
- Cough
- Low blood potassium
- Decreased weight

These side effects may occur during and after treatment with ADCETRIS.

Serious side effects and what to do about them

Symptom / effect	Talk to your healthcare professional	
	Only if severe	In all cases
Very common (≥ 10%)		
Nerve damage: burning sensation, pain, numbness and tingling (feeling of pins and needles) of hands and/or feet, weakness, difficulty walking		X
Infection: fever of ≥38°C or greater, chills, cough, sore throat, or pain on urination		X
Infusion reaction: fever, wheezing or breathing problems, chills, nausea, cough, itching, rash, within 2 days after your dose	X	
Liver damage: yellow coloration to the skin or the whites of the eyes		X
Common (≥ 1% to <10%)		
Stomach/ intestine (gastrointestinal) problems: new or worsening severe abdominal pain, severe nausea, vomiting, or severe diarrhea		X
Lung problems: cough and shortness of breath	X	
High blood sugar: frequent need to urinate, increased thirst, blurred vision	X	
Uncommon (≥ 0.1% to <1%)		
Pancreatitis (inflammation of the pancreas): symptoms such as abdominal pain, fever, nausea, vomiting		X
Tumor lysis syndrome: nausea, vomiting, edema (swelling), shortness of breath, heart rhythm disturbance, and sudden kidney failure		X
Rare (<0.1%)		
Progressive multifocal leukoencephalopathy: changes in mood or usual behavior, confusion, difficulty with thinking, memory loss, changes in vision or speech, decreased control or sensation in one arm or leg, loss of balance, changes in way of walking. Inform anyone close to you about your treatment since they may notice symptoms of which you are not aware.		X
Severe skin reactions (Stevens-Johnson syndrome, toxic epidermal necrolysis): unexplained widespread skin pain, blisters on your skin and mucous membranes, hives, tongue swelling, a red or purple skin rash that spreads, or unexplained shedding of your skin		X

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects
You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (canada.ca/drug-device-reporting) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Store ADCETRIS at 2–8°C in the original carton. Protect from light.

Keep out of reach and sight of children.

If you want more information about ADCETRIS:

- Talk to your healthcare professional.
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada Drug Product Database website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website www.pfizer.ca, or by calling 1-800-463-6001.

This leaflet was prepared by Pfizer Canada ULC.

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