HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ADCETRIS safely and effectively. See full prescribing information for ADCETRIS.

ADCETRIS® (brentuximab vedotin) for injection, for intravenous use
Initial U.S. approval: 2011

WARNING: PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY (PML)
See full prescribing information for complete boxed warning.

JC virus infection resulting in PML and death can occur in patients receiving ADCETRIS (5.9, 6.1).

RECENT MAJOR CHANGES

Indications and Usage, primary cutaneous anaplastic large cell lymphoma and CD30-expressing mycosis fungoides (1)	11/2017
Dosage and Administration, Dosage (2.1)	11/2017
Warnings and Precautions, Gastrointestinal Complications (5.12)	11/2017

INDICATIONS AND USAGE

ADCETRIS is a CD30-directed antibody-drug conjugate indicated for treatment of adult patients with:

- Classical Hodgkin lymphoma (cHL) at high risk of relapse or progression as post autologous hematopoietic stem cell transplantation (auto-HSCT) consolidation (1.1).
- Classical Hodgkin lymphoma after failure of auto-HSCT or after failure of at least two prior multi-agent chemotherapy regimens in patients who are not auto-HSCT candidates (1.2).
- Systemic anaplastic large cell lymphoma (sALCL) after failure of at least one prior multi-agent chemotherapy regimen (1.3).

  Accelerated approval was granted for the sALCL indication based on overall response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.
- Primary cutaneous anaplastic large cell lymphoma (pcALCL) or CD30-expressing mycosis fungoides (MF) who have received prior systemic therapy (1.4).

DOSAGE AND ADMINISTRATION

- Administer only as an intravenous infusion over 30 minutes every 3 weeks (2.1).
- The recommended dose is 1.8 mg/kg up to a maximum of 180 mg (2.1).
- Reduce dose in patients with mild hepatic impairment (2.2).

DOSAGE FORMS AND STRENGTHS

For injection: 50 mg lyophilized powder in a single-dose vial (3).

CONTRAINDICATIONS

Concomitant use with bleomycin due to pulmonary toxicity (4).

WARNINGS AND PRECAUTIONS

- Peripheral neuropathy: Monitor patients for neuropathy and institute dose modifications accordingly (5.1).
- Anaphylaxis and infusion reactions: If an infusion reaction occurs, interrupt the infusion. If anaphylaxis occurs, immediately discontinue the infusion (5.2).
- Hematologic toxicities: Monitor complete blood counts prior to each dose of ADCETRIS. Closely monitor patients for fever. If Grade 3 or 4 neutropenia develops, consider dose delays, reductions, discontinuation, or G-CSF prophylaxis with subsequent doses (5.3).
- Serious infections and opportunistic infections: Closely monitor patients for the emergence of bacterial, fungal or viral infections (5.4).
- Tumor lysis syndrome: Closely monitor patients with rapidly proliferating tumor or high tumor burden (5.5).
- Hepatotoxicity: Monitor liver enzymes and bilirubin (5.8).
- Pulmonary toxicity: Monitor patients for new or worsening symptoms (5.10).
- Serious dermatologic reactions: Discontinue if Stevens-Johnson syndrome or toxic epidermal necrolysis occurs (5.11).
- Gastrointestinal complications: Monitor patients for new or worsening symptoms (5.12).
- Embryo-Fetal toxicity: Can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and to avoid pregnancy (5.13).

ADVERSE REACTIONS

The most common adverse reactions (≥20%) were peripheral sensory neuropathy, fatigue, nausea, diarrhea, neutropenia, upper respiratory tract infection, and pyrexia.

To report SUSPECTED ADVERSE REACTIONS, contact Seattle Genetics, Inc. at 1-855-473-2436 or FDA at 1-800-FDA-1088 or www.fda.gov/Safety/MedWatch.

DRUG INTERACTIONS

Concomitant use of strong CYP3A4 inhibitors or inducers, or P-gp inhibitors, has the potential to affect the exposure to monomethyl auristatin E (MMAE) (7.1).

USE IN SPECIFIC POPULATIONS

Moderate or severe hepatic impairment or severe renal impairment: MMAE exposure and adverse reactions are increased. Avoid use (5.6, 5.7, 8.6, 8.7).

Lactation: Advise women not to breastfeed (8.2).

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 11/2017

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY (PML)

JC virus infection resulting in PML and death can occur in patients receiving ADCETRIS *[see Warnings and Precautions (5.9), Adverse Reactions (6.1)]*.

1 INDICATIONS AND USAGE

ADCETRIS is indicated for the treatment of:

1.1 Classical Hodgkin lymphoma (cHL) Consolidation

Adult patients with cHL at high risk of relapse or progression as post-autologous hematopoietic stem cell transplantation (auto-HSCT) consolidation *[see Clinical Studies (14.1)]*.

1.2 Relapsed cHL

Adult patients with cHL after failure of auto-HSCT or after failure of at least two prior multi-agent chemotherapy regimens in patients who are not auto-HSCT candidates *[see Clinical Studies (14.1)]*.

ADCETRIS is also indicated for the treatment of:

1.3 Relapsed sALCL

Adult patients with systemic anaplastic large cell lymphoma (sALCL) after failure of at least one prior multi-agent chemotherapy regimen *[see Clinical Studies (14.2)]*.

The sALCL indication is approved under accelerated approval based on overall response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

1.4 Relapsed pcALCL or CD30-expressing MF

Adult patients with pcALCL or CD30-expressing MF who have received prior systemic therapy *[see Clinical Studies (14.2)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The recommended ADCETRIS dosage is provided in Table 1.

The recommended dose for patients with renal or hepatic impairment is provided in Table 2.

Table 1: Recommended ADCETRIS Dosage

Indication	Recommended Dose*	Administration	Frequency and Duration
Classical 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-auto-HSCT or upon recovery from auto-HSCT. Administer every 3 weeks until a maximum of 16 cycles, disease progression, or unacceptable toxicity
Relapsed Classical 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
Relapsed 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 until a maximum of 16 cycles, disease progression, or unacceptable toxicity
Relapsed 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

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

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

Impairment	Degree of Impairment	Recommended Dose
Renal	Normal Mild (CrCL greater than 50–80 mL/min) Moderate (CrCL 30–50 mL/min)	1.8 mg/kg up to a maximum of 180 mg*
	Severe (CrCL less than 30 mL/min)	Avoid use [see Warnings and Precautions (5.6)]
Hepatic	Normal	1.8 mg/kg up to a maximum of 180 mg*
	Mild (Child-Pugh A)	1.2 mg/kg up to a maximum of 120 mg*
	Moderate (Child-Pugh B) Severe (Child-Pugh C)	Avoid use [see Warnings and Precautions (5.7)]

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

CrCL: creatinine clearance

2.2 Dose Modification

Table 3: Dose Modifications for Peripheral Neuropathy or Neutropenia

Toxicity	Severity	Dose Modification
Peripheral Neuropathy	New or worsening Grade 2 or 3	Hold dosing until improvement to baseline or Grade 1 Restart at 1.2 mg/kg up to a maximum of 120 mg*
	Grade 4	Dosing should be discontinued
Neutropenia	Grade 3 or 4	Hold dosing until improvement to baseline or Grade 2 or lower Consider G-CSF prophylaxis for subsequent cycles
	Recurrent Grade 4 despite G-CSF prophylaxis	Consider discontinuation or dose reduction to 1.2 mg/kg up to a maximum of 120 mg*

Events were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 3.0

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

2.3 Instructions for Preparation and Administration

Administration

- Administer ADCETRIS as an intravenous infusion only.
- **Do not mix ADCETRIS with, or administer as an infusion with, other medicinal products.**

Reconstitution

- Follow procedures for proper handling and disposal of anticancer drugs *[see References (15)]*.
- Use appropriate aseptic technique for reconstitution and preparation of dosing solutions.
- Determine the number of 50 mg vials needed based on the patient's weight and the prescribed dose *[see Dosage and Administration (2.1)]*.
- 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 the 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.
- Following reconstitution, dilute immediately into an infusion bag. If not diluted immediately, store the solution at 2–8°C (36–46°F) and use within 24 hours of reconstitution. **DO NOT FREEZE.**
- Discard any unused portion left in the vial.

Dilution

- Calculate the required volume of 5 mg/mL reconstituted ADCETRIS solution needed.
- Withdraw this amount from the vial and immediately add it to an infusion bag containing a minimum volume of 100 mL of 0.9% Sodium Chloride Injection, 5% Dextrose Injection or Lactated Ringer's Injection to achieve a final concentration of 0.4 mg/mL to 1.8 mg/mL brentuximab vedotin.
- Gently invert the bag to mix the solution.
- Following dilution, infuse the ADCETRIS solution immediately. If not used immediately, store the solution at 2–8°C (36–46°F) and use within 24 hours of reconstitution. **DO NOT FREEZE.**

3 DOSAGE FORMS AND STRENGTHS

For injection: 50 mg of brentuximab vedotin as a sterile, white to off-white lyophilized, preservative-free cake or powder in a single-use vial for reconstitution.

4 CONTRAINDICATIONS

ADCETRIS is contraindicated with concomitant bleomycin due to pulmonary toxicity (e.g., interstitial infiltration and/or inflammation) *[see Adverse Reactions (6.1)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Peripheral Neuropathy

ADCETRIS treatment causes a peripheral neuropathy that is predominantly sensory. Cases of peripheral motor neuropathy have also been reported. ADCETRIS-induced peripheral neuropathy is cumulative.

In studies of ADCETRIS as monotherapy, 62% of patients experienced any grade of neuropathy. The median time to onset of any grade was 13 weeks (range, 0–52). Of the patients who experienced neuropathy, 62% had complete resolution, 24% had partial improvement, and 14% had no improvement at the time of their last evaluation. The median time from onset to resolution or improvement of any grade was 21 weeks (range, 0–195). Of the patients who reported neuropathy, 38% had residual neuropathy at the time of their last evaluation [Grade 1 (27%), Grade 2 (9%), Grade 3 (2%)].

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 Dosage and Administration (2.2) and Adverse Reactions (6.1)]*.

5.2 Anaphylaxis and Infusion Reactions

Infusion-related reactions, including anaphylaxis, have occurred with ADCETRIS. Monitor patients during infusion. If anaphylaxis occurs, immediately and permanently discontinue administration of ADCETRIS and administer appropriate medical therapy. If an infusion-related reaction occurs, interrupt the infusion and institute appropriate medical management. Patients who have experienced a prior infusion-related reaction should be premedicated for subsequent infusions. Premedication may include acetaminophen, an antihistamine, and a corticosteroid.

5.3 Hematologic Toxicities

Prolonged (≥1 week) severe neutropenia and Grade 3 or Grade 4 thrombocytopenia or anemia can occur with ADCETRIS. Febrile neutropenia has been reported with treatment with ADCETRIS. Monitor complete blood counts prior to each dose of ADCETRIS. Monitor more frequently for patients with Grade 3 or 4 neutropenia. Monitor patients for fever. If Grade 3 or 4 neutropenia develops, consider dose delays, reductions, discontinuation, or G-CSF prophylaxis with subsequent ADCETRIS doses *[see Dosage and Administration (2.2)]*.

5.4 Serious Infections and Opportunistic Infections

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

5.5 Tumor Lysis Syndrome

Patients with rapidly proliferating tumor and high tumor burden may be at increased risk of tumor lysis syndrome. Monitor closely and take appropriate measures.

5.6 Increased Toxicity in the Presence of Severe Renal Impairment

The frequency of ≥Grade 3 adverse reactions and deaths was greater in patients with severe renal impairment compared to patients with normal renal function. 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. Avoid the use of ADCETRIS in patients with severe renal impairment [creatinine clearance (CrCL) <30 mL/min] *[see Use in Specific Populations (8.6)]*.

5.7 Increased Toxicity in the Presence of Moderate or Severe Hepatic Impairment

The frequency of ≥Grade 3 adverse reactions and deaths was greater in patients with moderate and severe hepatic impairment compared to patients with normal hepatic function. Avoid the use of ADCETRIS in patients with moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment *[see Use in Specific Populations (8.7)]*.

5.8 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.

5.9 Progressive Multifocal Leukoencephalopathy

JC virus infection resulting in PML and death has been reported in ADCETRIS-treated patients. First onset of symptoms occurred at various times from initiation of ADCETRIS therapy, with some cases occurring within 3 months of initial exposure. In addition to ADCETRIS therapy, other possible contributory factors include prior therapies and underlying disease that may cause immunosuppression. Consider the diagnosis of PML in any patient presenting with new-onset signs and symptoms of central nervous system abnormalities. Hold ADCETRIS dosing for any suspected case of PML and discontinue ADCETRIS dosing if a diagnosis of PML is confirmed.

5.10 Pulmonary Toxicity

Events of noninfectious pulmonary toxicity including pneumonitis, interstitial lung disease, and acute respiratory distress syndrome (ARDS), some with fatal outcomes, have been reported. Monitor patients for signs and symptoms of pulmonary toxicity, including cough and dyspnea. In the event of new or worsening pulmonary symptoms, hold ADCETRIS dosing during evaluation and until symptomatic improvement.

5.11 Serious Dermatologic Reactions

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), including fatal outcomes, have been reported with ADCETRIS. If SJS or TEN occurs, discontinue ADCETRIS and administer appropriate medical therapy.

5.12 Gastrointestinal Complications

Acute pancreatitis, including fatal outcomes,has been reported. Other fatal and serious gastrointestinal (GI) complications include perforation, hemorrhage, erosion, ulcer, intestinal obstruction, enterocolitis, neutropenic colitis, and ileus. 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.

5.13 Embryo-Fetal Toxicity

Based on the mechanism of action and findings in animals, ADCETRIS can cause fetal harm when administered to a pregnant woman. There are no adequate and well-controlled studies of ADCETRIS in pregnant women. Brentuximab vedotin caused embryo-fetal toxicities, including significantly decreased embryo viability and fetal malformations, in animals at maternal exposures that were similar to the clinical dose of 1.8 mg/kg every three weeks.

Advise females of reproductive potential to avoid pregnancy during ADCETRIS treatment and for at least 6 months after the final dose of ADCETRIS. If ADCETRIS is used during pregnancy or if the patient becomes pregnant during ADCETRIS treatment, the patient should be apprised of the potential risk to the fetus *[see Use in Specific Populations (8.1, 8.3]*.

6 ADVERSE REACTIONS

The following serious adverse reactions are described elsewhere in the labeling:

- Peripheral Neuropathy *[see Warnings and Precautions (5.1)]*
- Anaphylaxis and Infusion Reactions *[see Warnings and Precautions (5.2)]*
- Hematologic Toxicities *[see Warnings and Precautions (5.3)]*
- Serious Infections and Opportunistic Infections *[see Warnings and Precautions (5.4)]*
- Tumor Lysis Syndrome *[see Warnings and Precautions (5.5)]*
- Increased Toxicity in the Presence of Severe Renal Impairment *[see Warnings and Precautions (5.6)]*
- Increased Toxicity in the Presence of Moderate or Severe Hepatic Impairment *[see Warnings and Precautions (5.7)]*
- Hepatotoxicity *[see Warnings and Precautions (5.8)]*
- Progressive Multifocal Leukoencephalopathy *[see Warnings and Precautions (5.9)]*
- Pulmonary Toxicity *[see Warnings and Precautions (5.10)]*
- Serious Dermatologic Reactions *[see Warnings and Precautions (5.11)]*
- Gastrointestinal Complications *[see Warnings and Precautions (5.12)]*

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data below reflect exposure to ADCETRIS as monotherapy in 393 patients, including 160 patients in two uncontrolled single-arm trials in cHL and systemic ALCL (Studies 1 and 2) and 233 patients in two controlled randomized trials in cHL, and pcALCL and CD30-expressing MF (Study 3: AETHERA and Study 4: ALCANZA). In these trials, ADCETRIS was administered at 1.8 mg/kg every 3 weeks.

Across the clinical trials of ADCETRIS as monotherapy (Studies 1-4), the most common adverse reactions (≥20%) in ADCETRIS-treated patients were peripheral sensory neuropathy, fatigue, nausea, diarrhea, neutropenia, upper respiratory tract infection, and pyrexia.

Classical Hodgkin Lymphoma Post-auto-HSCT Consolidation (Study 3: AETHERA)

ADCETRIS was studied in 329 patients with cHL at high risk of relapse or progression post-auto-HSCT in a 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. 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 Clinical Studies (14.1)]*.

Standard international guidelines were followed for infection prophylaxis for herpes simplex virus (HSV), varicella-zoster virus (VZV), and *Pneumocystis jiroveci* pneumonia (PJP) post-auto-HSCT. Overall, 312 patients (95%) received HSV and VZV prophylaxis with a median duration of 11.1 months (range, 0–20) and 319 patients (98%) received PJP prophylaxis with a median duration of 6.5 months (range, 0–20).

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%) *[see Dosage and Administration (2.2)]*. 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%), paraesthesia (1%), and vomiting (1%). Serious adverse reactions, 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%).

Table 4: Adverse Reactions Reported in ≥10% in ADCETRIS-treated Patients with Classical Hodgkin Lymphoma Post-auto-HSCT Consolidation (Study 3: AETHERA)

	ADCETRIS Total N = 167 % of patients			Placebo Total N = 160 % of patients		
Adverse Reaction	**Any Grade**	**Grade 3**	**Grade 4**	**Any Grade**	**Grade 3**	**Grade 4**
Blood and lymphatic system disorders						
Neutropenia*	78	30	9	34	6	4
Thrombocytopenia*	41	2	4	20	3	2
Anemia*	27	4	-	19	2	-
Nervous system disorders						
Peripheral sensory neuropathy	56	10	-	16	1	-
Peripheral motor neuropathy	23	6	-	2	1	-
Headache	11	2	-	8	1	-
Infections and infestations						
Upper respiratory tract infection	26	-	-	23	1	-
General disorders and administration site conditions						
Fatigue	24	2	-	18	3	-
Pyrexia	19	2	-	16	-	-
Chills	10	-	-	5	-	-
Gastrointestinal disorders						
Nausea	22	3	-	8	-	-
Diarrhea	20	2	-	10	1	-
Vomiting	16	2	-	7	-	-
Abdominal pain	14	2	-	3	-	-
Constipation	13	2	-	3	-	-
Respiratory, thoracic and mediastinal disorders						
Cough	21	-	-	16	-	-
Dyspnea	13	-	-	6	-	1
Investigations						
Weight decreased	19	1	-	6	-	-
Musculoskeletal and connective tissue disorders						
Arthralgia	18	1	-	9	-	-
Muscle spasms	11	-	-	6	-	-
Myalgia	11	1	-	4	-	-
Skin and subcutaneous tissue disorders						
Pruritus	12	1	-	8	-	-
Metabolism and nutrition disorders						
Decreased appetite	12	1	-	6	-	-

*Derived from laboratory values and adverse reaction data
Events were graded using the NCI CTCAE Version 4

Relapsed Classical Hodgkin Lymphoma (Study 1)

ADCETRIS was studied in 102 patients with cHL in a single arm clinical trial in which the recommended starting dose and schedule was 1.8 mg/kg intravenously every 3 weeks. Median duration of treatment was 9 cycles (range, 1–16) *[see Clinical Studies (14.1)]*.

Adverse reactions that led to dose delays in more than 5% of ADCETRIS-treated patients were neutropenia (16%) and peripheral sensory neuropathy (13%) *[see Dosage and Administration (2.2)]*. Adverse reactions led to treatment discontinuation in 20% of ADCETRIS-treated patients. Adverse reactions that led to treatment discontinuation in 2 or more patients were peripheral sensory neuropathy (6%) and peripheral motor neuropathy (3%). Serious adverse reactions, were reported in 25% of ADCETRIS-treated patients. The most common serious adverse reactions were peripheral motor neuropathy (4%), abdominal pain (3%), pulmonary embolism (2%), pneumonitis (2%), pneumothorax (2%), pyelonephritis (2%), and pyrexia (2%).

Table 5: Adverse Reactions Reported in ≥10% of Patients with Relapsed Classical Hodgkin Lymphoma (Study 1)

	cHL Total N = 102 % of patients		
Adverse Reaction	**Any Grade**	**Grade 3**	**Grade 4**
Blood and lymphatic system disorders			
Neutropenia*	54	15	6
Anemia*	33	8	2
Thrombocytopenia*	28	7	2
Lymphadenopathy	11	-	-
Nervous system disorders			
Peripheral sensory neuropathy	52	8	-
Peripheral motor neuropathy	16	4	-
Headache	19	-	-
Dizziness	11	-	-
General disorders and administration site conditions			
Fatigue	49	3	-
Pyrexia	29	2	-
Chills	13	-	-
Infections and infestations			
Upper respiratory tract infection	47	-	-
Gastrointestinal disorders			
Nausea	42	-	-
Diarrhea	36	1	-
Abdominal pain	25	2	1
Vomiting	22	-	-
Constipation	16	-	-
Skin and subcutaneous tissue disorders			
Rash	27	-	-
Pruritus	17	-	-
Alopecia	13	-	-
Night sweats	12	-	-
Respiratory, thoracic and mediastinal disorders			
Cough	25	-	-
Dyspnea	13	1	-
Oropharyngeal pain	11	-	-
Musculoskeletal and connective tissue disorders			
Arthralgia	19	-	-
Myalgia	17	-	-
Back pain	14	-	-
Pain in extremity	10	-	-
Psychiatric disorders			
Insomnia	14	-	-
Anxiety	11	2	-
Metabolism and nutrition disorders			
Decreased appetite	11	-	-

*Derived from laboratory values and adverse reaction data
Events were graded using the NCI CTCAE Version 3.0

Relapsed Systemic Anaplastic Large Cell Lymphoma (Study 2)

ADCETRIS was studied in 58 patients with sALCL in a single arm clinical trial in which the recommended starting dose and schedule was 1.8 mg/kg intravenously every 3 weeks. Median duration of treatment was 7 cycles (range, 1–16) *[see Clinical Studies (14.2)]*.

Adverse reactions that led to dose delays in more than 5% of ADCETRIS-treated patients were neutropenia (12%) and peripheral sensory neuropathy (7%) *[see Dosage and Administration (2.2)]*. Adverse reactions led to treatment discontinuation in 19% of ADCETRIS-treated patients. The adverse reaction that led to treatment discontinuation in 2 or more patients was peripheral sensory neuropathy (5%). Serious adverse reactions were reported in 41% of ADCETRIS-treated patients. The most common serious adverse reactions were septic shock (3%), supraventricular arrhythmia (3%), pain in extremity (3%), and urinary tract infection (3%).

Table 6: Adverse Reactions Reported in ≥10% of Patients with Relapsed Systemic Anaplastic Large Cell Lymphoma (Study 2)

	sALCL Total N = 58 % of patients		
Adverse Reaction	**Any Grade**	**Grade 3**	**Grade 4**
Blood and lymphatic system disorders			
Neutropenia*	55	12	9
Anemia*	52	2	-
Thrombocytopenia*	16	5	5
Lymphadenopathy	10	-	-
Nervous system disorders			
Peripheral sensory neuropathy	53	10	-
Headache	16	2	-
Dizziness	16	-	-
General disorders and administration site conditions			
Fatigue	41	2	2
Pyrexia	38	2	-
Chills	12	-	-
Pain	28	-	5
Edema peripheral	16	-	-
Infections and infestations			
Upper respiratory tract infection	12	-	-
Gastrointestinal disorders			
Nausea	38	2	-
Diarrhea	29	3	-
Vomiting	17	3	-
Constipation	19	2	-
Skin and subcutaneous tissue disorders			
Rash	31	-	-
Pruritus	19	-	-
Alopecia	14	-	-
Dry skin	10	-	-
Respiratory, thoracic and mediastinal disorders			
Cough	17	-	-
Dyspnea	19	2	-
Musculoskeletal and connective tissue disorders			
Myalgia	16	2	-
Back pain	10	2	-
Pain in extremity	10	2	2
Muscle spasms	10	2	-
Psychiatric disorders			
Insomnia	16	-	-
Metabolism and nutrition disorders			
Decreased appetite	16	2	-
Investigations			
Weight decreased	12	3	-

*Derived from laboratory values and adverse reaction data
Events were graded using the NCI CTCAE Version 3.0

Primary Cutaneous Anaplastic Large Cell Lymphoma and CD30-expressing Mycosis Fungoides (Study 4: ALCANZA)

ADCETRIS was studied in 131 patients with pcALCL or CD30-expressing MF requiring systemic therapy in a randomized, open-label, multicenter clinical trial in which the recommended starting dose and schedule was 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 (66 brentuximab vedotin, 62 physician's choice) received at least one dose of study 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 Clinical Studies (14)]*.

Adverse reactions that led to dose delays in more than 5% of ADCETRIS-treated patients were peripheral sensory neuropathy (15%) and neutropenia (6%) *[see Dosage and Administration (2.2)]*. Adverse reactions led to treatment discontinuation in 24% of ADCETRIS-treated patients. The most common adverse reaction that led to treatment discontinuation was peripheral neuropathy (12%). Serious adverse reactions were reported in 29% of ADCETRIS-treated patients. The most common serious adverse reactions were cellulitis (3%) and pyrexia (3%).

Table 7: Adverse Reactions Reported in ≥10% ADCETRIS-treated Patients with pcALCL or CD30-expressing MF (Study 4: ALCANZA)

	ADCETRIS Total N = 66 % of patients			Physician's Choice[a] Total N = 62 % of patients		
Adverse Reaction	**Any Grade**	**Grade 3**	**Grade 4**	**Any Grade**	**Grade 3**	**Grade 4**
Blood and lymphatic system disorders						
Anemia*	62	-	-	65	5	-
Neutropenia*	21	3	2	24	5	-
Thrombocytopenia*	15	2	2	2	-	-
Nervous system disorders						
Peripheral sensory neuropathy	45	5	-	2	-	-
Gastrointestinal disorders						
Nausea	36	2	-	13	-	-
Diarrhea	29	3	-	6	-	-
Vomiting	17	2	-	5	-	-
General disorders and administration site conditions						
Fatigue	29	5	-	27	2	-
Pyrexia	17	-	-	18	2	-
Edema peripheral	11	-	-	10	-	-
Asthenia	11	2	-	8	-	2
Skin and subcutaneous tissue disorders						
Pruritus	17	2	-	13	3	-
Alopecia	15	-	-	3	-	-
Rash maculo-papular	11	2	-	5	-	-
Pruritus generalized	11	2	-	2	-	-
Metabolism and nutrition disorders						
Decreased appetite	15	-	-	5	-	-
Musculoskeletal and connective tissue disorders						
Arthralgia	12	-	-	6	-	-
Myalgia	12	-	-	3	-	-
Respiratory, thoracic and mediastinal disorders						
Dyspnea	11	-	-	-	-	-

*Derived from laboratory values and adverse reaction data
[a] Physician's choice of either methotrexate or bexarotene
Events were graded using the NCI CTCAE Version 4.03

Additional Important Adverse Reactions

Infusion reactions

In studies of ADCETRIS as monotherapy (Studies 1–4), 13% of ADCETRIS-treated patients experienced infusion-related reactions. The most common adverse reactions in Studies 1–4 (≥3% in any study) associated with infusion-related reactions were chills (4%), nausea (3–4%), dyspnea (2–3%), pruritus (2–5%), pyrexia (2%), and cough (2%). Grade 3 events were reported in 5 of the 51 ADCETRIS-treated patients who experienced infusion-related reactions.

Pulmonary toxicity
In a trial in patients with cHL that studied ADCETRIS with bleomycin as part of a combination regimen, the rate of non-infectious pulmonary toxicity was higher than the historical incidence reported with ABVD (adriamycin, bleomycin, vinblastine, dacarbazine). Patients typically reported cough and dyspnea. Interstitial infiltration and/or inflammation were observed on radiographs and computed tomographic imaging of the chest. Most patients responded to corticosteroids. The concomitant use of ADCETRIS with bleomycin is contraindicated *[see Contraindications (4)]*.

Cases of pulmonary toxicity have also been reported in patients receiving ADCETRIS. In Study 3 (AETHERA), pulmonary toxicity was reported in 8 patients (5%) in the ADCETRIS-treated arm and 5 patients (3%) in the placebo arm.

6.2 Post Marketing Experience
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.

Blood and lymphatic system disorders: febrile neutropenia *[see Warnings and Precautions (5.3)]*.

Gastrointestinal disorders: acute pancreatitis and gastrointestinal complications (including fatal outcomes) *[see Warnings and Precautions (5.12)]*.

Hepatobiliary disorders: hepatotoxicity *[see Warnings and Precautions (5.8)]*.

Infections: PML *[see Boxed Warning, Warnings and Precautions (5.9)]*, serious infections and opportunistic infections *[see Warnings and Precautions (5.4)]*.

Metabolism and nutrition disorders: hyperglycemia.

Respiratory, thoracic and mediastinal disorders: noninfectious pulmonary toxicity including pneumonitis, interstitial lung disease, and ARDS (some with fatal outcomes) *[see Warnings and Precautions (5.10) and Adverse Reactions (6.1)]*.

Skin and subcutaneous tissue disorders: Toxic epidermal necrolysis, including fatal outcomes *[see Warnings and Precautions (5.11)]*.

6.3 Immunogenicity
As with all therapeutic proteins, there is 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 the incidence of antibodies to ADCETRIS in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.

Patients with cHL and sALCL in Studies 1 and 2 *[see Clinical Studies (14)]* were tested for antibodies to brentuximab vedotin every 3 weeks using a sensitive electrochemiluminescent immunoassay. Approximately 7% of patients in these trials developed persistently positive antibodies (positive test at more than 2 timepoints) and 30% developed transiently positive antibodies (positive in 1 or 2 post-baseline timepoints). The anti-brentuximab antibodies were directed against the antibody component of brentuximab vedotin in all patients with transiently or persistently positive antibodies. Two of the patients (1%) with persistently positive antibodies experienced adverse reactions consistent with infusion reactions that led to discontinuation of treatment. Overall, a higher incidence of infusion related reactions was observed in patients who developed persistently positive antibodies.

A total of 58 patient samples that were either transiently or persistently positive for anti-brentuximab vedotin antibodies were tested for the presence of neutralizing antibodies. Sixty-two percent (62%) of these patients had at least one sample that was positive for the presence of neutralizing antibodies. The effect of anti-brentuximab vedotin antibodies on safety and efficacy is not known.

7 DRUG INTERACTIONS
7.1 Effect of Other Drugs on ADCETRIS
CYP3A4 Inhibitors: Co-administration of ADCETRIS with ketoconazole, a potent CYP3A4 inhibitor, increased exposure to MMAE *[see Clinical Pharmacology (12.3)]* which may increase the risk of adverse reaction. Closely monitor adverse reactions when ADCETRIS is given concomitantly with strong CYP3A4 inhibitors.

P-gp Inhibitors: Co-administration of ADCETRIS with P-gp inhibitors may increase exposure to MMAE. Closely monitor adverse reactions when ADCETRIS is given concomitantly with P-gp inhibitors.

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Risk Summary
ADCETRIS can cause fetal harm based on the findings from animal studies and the drug's mechanism of action *[see Clinical Pharmacology (12.1)]*. In animal reproduction studies, administration of brentuximab vedotin to pregnant rats during organogenesis at doses similar to the clinical dose of 1.8 mg/kg every three weeks caused embryo-fetal toxicities, including congenital malformations *(see Data)*. Consider the benefits and risks of ADCETRIS and possible risks to the fetus when prescribing ADCETRIS to a pregnant woman.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2–4% and 15–20%, respectively.

Data
Animal Data
In an embryo-fetal developmental study, pregnant rats received 2 intravenous doses of 0.3, 1, 3, or 10 mg/kg brentuximab vedotin during the period of organogenesis (once each on Pregnancy Days 6 and 13). Drug-induced embryo-fetal toxicities were seen mainly in animals treated with 3 and 10 mg/kg of the drug and included increased early resorption (≥99%), post-implantation loss (≥99%), decreased numbers of live fetuses, and external malformations (i.e., umbilical hernias and malrotated hindlimbs). Systemic exposure in animals at the brentuximab vedotin dose of 3 mg/kg is approximately the same exposure in patients with cHL or sALCL who received the recommended dose of 1.8 mg/kg every three weeks.

8.2 Lactation
Risk Summary
There is no information regarding the presence of brentuximab vedotin in human milk, the effects on the breastfed child, or the effects on milk production. Because of the potential for serious adverse reactions in a breastfed child from ADCETRIS, including cytopenias and neurologic or gastrointestinal toxicities, advise patients that breastfeeding is not recommended during ADCETRIS treatment.

8.3 Females and Males of Reproductive Potential
ADCETRIS can cause fetal harm based on the findings from animal studies and the drug's mechanism of action *[see Use in Specific Populations (8.1), Clinical Pharmacology (12.1)]*.

Pregnancy Testing
Verify the pregnancy status of females of reproductive potential prior to initiating ADCETRIS therapy.

Contraception
Females
Advise females of reproductive potential to avoid pregnancy during ADCETRIS treatment and for at least 6 months after the final dose of ADCETRIS. Advise females to immediately report pregnancy *[see Use in Specific Populations (8.1)]*.

Males
ADCETRIS may damage spermatozoa and testicular tissue, resulting in possible genetic abnormalities. Males with female sexual partners of reproductive potential should use effective contraception during ADCETRIS treatment and for at least 6 months after the final dose of ADCETRIS *[see Nonclinical Toxicology (13.1)]*.

Infertility
Males
Based on findings in rats, male fertility may be compromised by treatment with ADCETRIS *[see Nonclinical Toxicology (13.1)]*.

8.4 Pediatric Use
Safety and effectiveness of ADCETRIS have not been established in pediatric patients.

8.5 Geriatric Use
Clinical trials of ADCETRIS in cHL (Studies 1 and 3: AETHERA) and sALCL (Study 2) did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients.

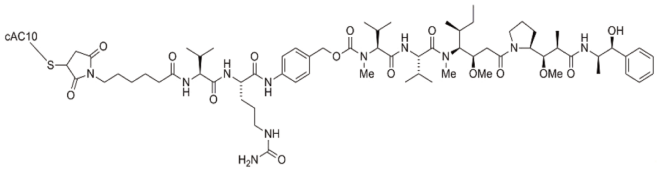
In the clinical trial of ADCETRIS in pcALCL or CD30-expressingMF (Study 4: ALCANZA), 42% of ADCETRIS-treated patients were aged 65 or older. No meaningful differences in safety or efficacy were observed between these patients and younger patients.

8.6 Renal Impairment
Avoid the use of ADCETRIS in patients with severe renal impairment (CrCL <30 mL/min) *[See Warnings and Precautions (5.6) and Clinical Pharmacology (12.3)]*. No dosage adjustment is required for mild (CLcr >50–80 mL/min) or moderate (CrCL 30–50 mL/min) renal impairment.

8.7 Hepatic Impairment
Avoid the use of ADCETRIS in patients with moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment *[See Warnings and Precautions (5.7) and Clinical Pharmacology (12.3)]*. Dosage reduction is required in patients with mild (Child-Pugh A) hepatic impairment *[See Dosage and Administration (2.1)]*.

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

11 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 microtubule disrupting agent MMAE, and 3) a protease-cleavable linker that covalently attaches MMAE to cAC10.



Brentuximab vedotin has an approximate molecular weight of 153 kDa. Approximately 4 molecules of MMAE are attached to each antibody molecule. Brentuximab vedotin is produced by chemical conjugation of the antibody and small molecule components.

The antibody is produced by mammalian (Chinese hamster ovary) cells, and the small molecule components are produced by chemical synthesis.

ADCETRIS (brentuximab vedotin) for Injection is supplied as a sterile, white to off-white, preservative-free lyophilized cake or powder in single-dose vials. Following reconstitution with 10.5 mL Sterile Water for Injection, USP, a solution containing 5 mg/mL brentuximab vedotin is produced. The reconstituted product contains 70 mg/mL trehalose dihydrate, 5.6 mg/mL sodium citrate dihydrate, 0.21 mg/mL citric acid monohydrate, and 0.20 mg/mL polysorbate 80 and water for injection. The pH is approximately 6.6.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

CD30 is a member of the tumor necrosis factor receptor family. CD30 is expressed on the surface of sALCL cells and on Hodgkin Reed-Sternberg (HRS) cells in cHL, and has limited expression on healthy tissue and cells. In vitro data suggest that signaling through CD30-CD30L binding may affect cell survival and proliferation.

Brentuximab vedotin is an ADC. The antibody is a chimeric IgG1 directed against CD30. The small molecule, MMAE, is a 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 for antibody-dependent cellular phagocytosis (ADCP).

12.2 Pharmacodynamics

Cardiac Electrophysiology

The effect of brentuximab vedotin (1.8 mg/kg) on the QTc interval was evaluated in an open-label, single-arm study in 46 evaluable patients with CD30-expressing hematologic malignancies. Administration of brentuximab vedotin did not prolong the mean QTc interval >10 ms from baseline. Small increases in the mean QTc interval (<10 ms) cannot be excluded because this study did not include a placebo arm and a positive control arm.

12.3 Pharmacokinetics

The pharmacokinetics of brentuximab vedotin were evaluated in early development trials, including dose-finding trials, and in a population pharmacokinetic analysis of data from 314 patients. The pharmacokinetics of three analytes were determined: the ADC, MMAE, and total antibody. Total antibody had the greatest exposure and had a similar PK profile as the ADC. Hence, data on the PK of the ADC and MMAE have been summarized.

Maximum concentrations of ADC were typically observed close to the end of infusion. 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 humans, the mean steady state volume of distribution was approximately 6–10 L for ADC.

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.

Elimination

MMAE appeared to follow metabolite kinetics, with the elimination of MMAE appearing to be limited by its rate of release from ADC.

In pharmacokinetic analyses, a multiexponential decline in ADC serum concentrations was observed with a terminal half-life of approximately 4 to 6 days.

Metabolism

In vivo data in animals and 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.

Excretion

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.

Specific Populations

Renal Impairment: The pharmacokinetics and safety of brentuximab vedotin and MMAE were evaluated after the administration of 1.2 mg/kg of ADCETRIS to patients with mild (CrCL >50–80 mL/min; n=4), moderate (CrCL 30–50 mL/min; n=3) and severe (CrCL <30 mL/min; n=3) renal impairment. In patients with severe renal impairment, the rate of ≥Grade 3 adverse reactions was 3/3 (100%) compared to 3/8 (38%) in patients with normal renal function. Additionally, the AUC of MMAE (component of ADCETRIS) was approximately 2-fold higher in patients with severe renal impairment compared to patients with normal renal function.

Hepatic Impairment: The pharmacokinetics and safety of brentuximab vedotin and MMAE were evaluated 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. In patients with moderate and severe hepatic impairment, the rate of ≥Grade 3 adverse reactions was 6/6 (100%) compared to 3/8 (38%) in patients with normal hepatic function. Additionally, the AUC of MMAE was approximately 2.2-fold higher in patients with hepatic impairment compared to patients with normal hepatic function.

Effects of Gender, Age, and Race: Based on the population pharmacokinetic analysis, gender, age, and race do not have a meaningful effect on the pharmacokinetics of brentuximab vedotin.

Drug Interaction Studies

CYP3A4 Inhibitors/Inducers**:** In vitro data indicate that monomethyl auristatin E (MMAE) is a substrate of CYP3A4/5. MMAE is primarily metabolized by CYP3A. Co-administration of ADCETRIS with ketoconazole, a potent CYP3A4 inhibitor, increased exposure to MMAE by approximately 34%.

Co-administration of ADCETRIS with rifampin, a potent CYP3A4 inducer, reduced exposure to MMAE by approximately 46%.

P-gp Inhibitors**:** In vitro data indicate that MMAE is a substrate of the efflux transporter P-glycoprotein (P-gp). Co-administration of ADCETRIS with P-gp inhibitors may increase exposure to MMAE.

Effects of ADCETRIS on Other Drugs

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies with brentuximab vedotin or the small molecule (MMAE) have not been conducted.

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.

Fertility studies with brentuximab vedotin or MMAE have not been conducted. However, results of repeat-dose toxicity studies in rats indicate the potential for brentuximab vedotin to impair male reproductive function and fertility. In a 4-week repeat-dose toxicity study in rats with weekly dosing at 0.5, 5, or 10 mg/kg brentuximab vedotin, seminiferous tubule degeneration, Sertoli cell vacuolation, reduced spermatogenesis, and aspermia were observed. Effects in animals were seen mainly at 5 and 10 mg/kg of brentuximab vedotin. These doses are approximately 3 and 6-fold the human recommended dose of 1.8 mg/kg, respectively, based on body weight.

14 CLINICAL STUDIES

14.1 Classical Hodgkin Lymphoma

Randomized Placebo-controlled Clinical Trial in Classical Hodgkin Lymphoma Post-auto-HSCT Consolidation (Study 3: AETHERA)

The efficacy of ADCETRIS in patients with cHL at high risk of relapse or disease progression post-auto-HSCT was studied in a 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-auto-HSCT. Patients in the placebo arm with progressive disease per investigator could receive ADCETRIS as part of a separate trial. The primary endpoint was progression-free survival (PFS) determined by independent review facility (IRF). Standard international guidelines were followed for infection prophylaxis for HSV, VZV, and PJP post-auto-HSCT *[see Clinical Trial Experience (6.1)]*.

High risk of post-auto-HSCT relapse or progression was defined according to status following frontline therapy: refractory, relapse within 12 months, or relapse ≥12 months with extranodal disease. Patients were required to have obtained a complete response (CR), partial response (PR), or stable disease (SD) to most recent pre-auto-HSCT salvage therapy.

A total of 329 patients were enrolled and randomized (165 ADCETRIS, 164 placebo); 327 patients received study treatment. Patient demographics and baseline characteristics were generally balanced between treatment arms. The 329 patients ranged in age from 18–76 years (median, 32 years) and most were male (53%) and white (94%). Patients had received a median of 2 prior systemic therapies (range, 2–8) excluding autologous hematopoietic stem cell transplantation.

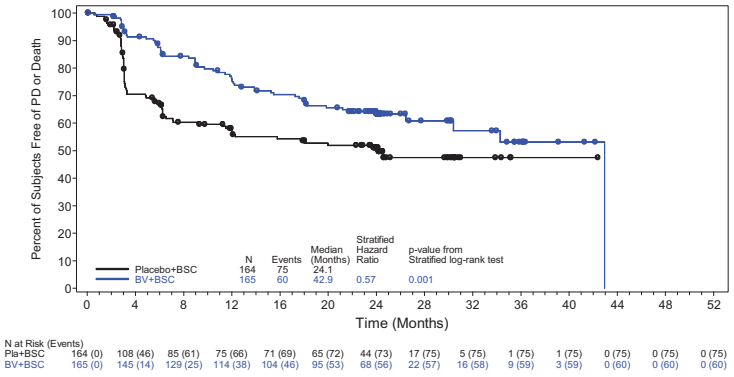
The efficacy results are summarized in Table 8. PFS is calculated from randomization to date of disease progression or death (due to any cause). The median PFS follow-up time from randomization was 22 months (range, 0–49). Study 3 (AETHERA) demonstrated a statistically significant improvement in IRF-assessed PFS and increase in median PFS in the ADCETRIS arm compared with the placebo arm. At the time of the PFS analysis, an interim overall survival analysis demonstrated no difference.

Table 8: Efficacy Results in Patients with Classical Hodgkin Lymphoma Post-auto-HSCT Consolidation (Study 3: AETHERA)

Progression-free Survival	ADCETRIS N = 165	Placebo N = 164
Independent Review Facility		
Number of events (%)	60 (36)	75 (46)
Median months (95% CI)	42.9+ (30.4, 42.9+)	24.1 (11.5, NE*)
Stratified Hazard Ratio (95% CI)	0.57 (0.40, 0.81)	
Stratified Log-Rank Test p-value	P=0.001	

* Not estimable
\+ Estimates are unreliable

Figure 1: Kaplan-Meier Curve of IRF-Assessed Progression-Free Survival (Study 3: AETHERA)



BV: Brentuximab Vedotin; BSC: Best Supportive Care

Clinical Trial in Relapsed Classical Hodgkin Lymphoma (Study 1)

The efficacy of ADCETRIS in patients with cHL who relapsed after autologous hematopoietic stem cell transplantation was evaluated in one open-label, single-arm, multicenter trial. One hundred two (102) patients were treated with 1.8 mg/kg of ADCETRIS intravenously over 30 minutes every 3 weeks. An independent review facility (IRF) performed efficacy evaluations which included overall response rate (ORR = complete remission [CR] + partial remission [PR]) and duration of response as defined by clinical and radiographic measures including computed tomography (CT) and positron-emission tomography (PET) as defined in the 2007 Revised Response Criteria for Malignant Lymphoma (modified).

The 102 patients ranged in age from 15–77 years (median, 31 years) and most were female (53%) and white (87%). Patients had received a median of 5 prior therapies including autologous hematopoietic stem cell transplantation.

The efficacy results are summarized in Table 9. Duration of response is calculated from date of first response to date of progression or data cutoff date.

Table 9: Efficacy Results in Patients with Classical Hodgkin Lymphoma (Study 1)

	N = 102		
		Duration of Response, in months	
	Percent (95% CI)	Median (95% CI)	Range
CR	32 (23, 42)	20.5 (12.0, NE*)	1.4 to 21.9+
PR	40 (32, 49)	3.5 (2.2, 4.1)	1.3 to 18.7
ORR	73 (65, 83)	6.7 (4.0, 14.8)	1.3 to 21.9+

*Not estimable
+Follow up was ongoing at the time of data submission

14.2 Systemic Anaplastic Large Cell Lymphoma

Clinical Trial in Relapsed sALCL (Study 2)

The efficacy of ADCETRIS in patients with relapsed sALCL was evaluated in one open-label, single-arm, multicenter trial. This trial included patients who had sALCL that was relapsed after prior therapy. Fifty-eight (58) patients were treated with 1.8 mg/kg of ADCETRIS administered intravenously over 30 minutes every 3 weeks. An IRF performed efficacy evaluations which included overall response rate (ORR = complete remission [CR] + partial remission [PR]) and duration of response as defined by clinical and radiographic measures including computed tomography (CT) and positron-emission tomography (PET) as defined in the 2007 Revised Response Criteria for Malignant Lymphoma (modified).

The 58 patients ranged in age from 14–76 years (median, 52 years) and most were male (57%) and white (83%). Patients had received a median of 2 prior therapies; 26% of patients had received prior autologous hematopoietic stem cell transplantation. Fifty percent (50%) of patients were relapsed and 50% of patients were refractory to their most recent prior therapy. Seventy-two percent (72%) were anaplastic lymphoma kinase (ALK)-negative.

The efficacy results are summarized in Table 10. Duration of response is calculated from date of first response to date of progression or data cutoff date.

Table 10: Efficacy Results in Patients with Systemic Anaplastic Large Cell Lymphoma (Study 2)

	N = 58		
		Duration of Response, in months	
	Percent (95% CI)	Median (95% CI)	Range
CR	57 (44, 70)	13.2 (10.8, NE*)	0.7 to 15.9+
PR	29 (18, 41)	2.1 (1.3, 5.7)	0.1 to 15.8+
ORR	86 (77, 95)	12.6 (5.7, NE*)	0.1 to 15.9+

*Not estimable
+ Follow up was ongoing at the time of data submission

14.3 Primary Cutaneous Anaplastic Large Cell Lymphoma and CD30-expressing Mycosis Fungoides

Randomized Clinical Trial in Primary Cutaneous Anaplastic Large Cell Lymphoma and CD30-expressing Mycosis Fungoides (Study 4: ALCANZA)

The efficacy of ADCETRIS in patients with primary cutaneous anaplastic large cell lymphoma (pcALCL) or mycosis fungoides (MF) requiring 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 1.8 mg/kg intravenously over 30 minutes every 3 weeks or physician's choice 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 at least 1 biopsy with CD30-expression of ≥10%. 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.

A total of 131 patients were randomized (66 ADCETRIS, 65 physician's choice). The efficacy results were based on 128 patients (64 patients in each arm with CD30-expression of ≥10% in at least one biopsy). Among 128 patients, the patients' age ranged from 22–83 years (median, 60 years) and 55% of them were male and 85% of them 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%).

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 independent review facility (IRF) using the global response score (GRS), consisting of skin evaluations per modified severity-weighted assessment tool (mSWAT), nodal and visceral radiographic assessment, and detection of circulating Sézary cells (MF patients only). Additional efficacy outcome measures included proportion of patients achieving a complete response (CR) per IRF, and progression-free survival (PFS) per IRF.

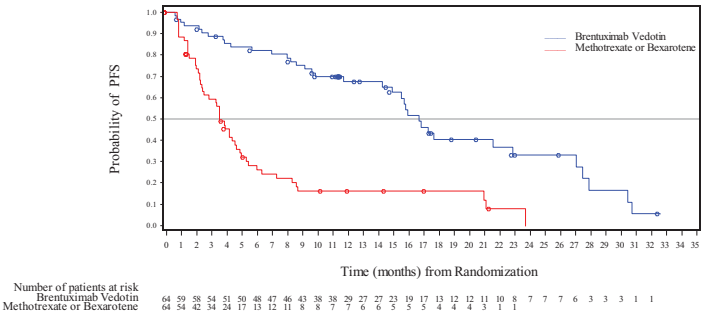
The efficacy results are summarized in Table 11 below and the Kaplan-Meier curves of IRF-Assessed Progression-free Survival are shown in Figure 2.

Table 11: Efficacy Results in Patients with Relapsed pcALCL or CD30-expressing MF (Study 4: ALCANZA)

	ADCETRIS N = 64	Physician's Choice[a] N = 64
ORR4[b]		
Percent (95% CI[c])	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[c])	15.6 (7.8, 26.9)	1.6 (0, 8.4)
P-value[d,e]	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[c])	16.7 (14.9, 22.8)	3.5 (2.4, 4.6)
Hazard Ratio[c] (95% CI[c])	0.27 (0.17, 0.43)	
Log-Rank Test p-value[d,e]	p<0.001	

[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] CI=Confidence Interval ;
[d] test of the treatment difference was stratified by baseline disease diagnosis (MF or pcALCL)
[e] adjusted for multiplicity

Figure 2: Kaplan-Meier Curve of Progression-free Survival (Study 4: ALCANZA)



Supportive trials include 2 single-arm trials which enrolled patients with MF and were treated with ADCETRIS 1.8 mg/kg intravenously over 30 minutes every 3 weeks. Out of 73 patients with MF from the 2 pooled supportive trials, 34% (25/73) achieved ORR4. Among these 73 patients, 35 had 1% to 9% CD30-expression and 31% (11/35) achieved ORR4.

15 REFERENCES

1. OSHA Hazardous Drugs. *OSHA*. [Accessed on 30 July 2013, from http://www.osha.gov/SLTC/hazardousdrugs/index.html]

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

ADCETRIS (brentuximab vedotin) for Injection is supplied as a sterile, white to off-white preservative-free lyophilized cake or powder in individually-boxed single-dose vials:

- NDC (51144-050-01), 50 mg brentuximab vedotin.

16.2 Storage

Store vial at 2–8°C (36–46°F) in the original carton to protect from light.

16.3 Special Handling

ADCETRIS is an antineoplastic product. Follow special handling and disposal procedures[1].

17 PATIENT COUNSELING INFORMATION

Peripheral Neuropathy

Advise patients that ADCETRIS can cause a peripheral neuropathy. They should be advised to report to their health care provider any numbness or tingling of the hands or feet or any muscle weakness *[see Warnings and Precautions (5.1)]*.

Fever/Neutropenia

Advise patients to contact their health care provider if a fever of 100.5°F or greater or other evidence of potential infection such as chills, cough, or pain on urination develops *[see Warnings and Precautions (5.3)]*.

Infusion Reactions

Advise patients to contact their health care provider if they experience signs and symptoms of infusion reactions including fever, chills, rash, or breathing problems within 24 hours of infusion *[see Warnings and Precautions (5.2)]*.

Hepatotoxicity

Advise patients to report symptoms that may indicate liver injury, including fatigue, anorexia, right upper abdominal discomfort, dark urine, or jaundice *[see Warnings and Precautions (5.8)]*.

Progressive Multifocal Leukoencephalopathy

Instruct patients receiving ADCETRIS to immediately report if they have any of the following neurological, cognitive, or behavioral signs and symptoms or if anyone close to them notices these signs and symptoms *[see Boxed Warning, Warnings and Precautions (5.9)]*:

- changes in mood or usual behavior
- confusion, thinking problems, loss of memory
- changes in vision, speech, or walking
- decreased strength or weakness on one side of the body

Pulmonary Toxicity

Instruct patients to report symptoms that may indicate pulmonary toxicity, including cough or shortness of breath *[see Warnings and Precautions (5.10)]*.

Acute Pancreatitis

Advise patients to contact their health care provider if they develop severe abdominal pain *[see Warnings and Precautions (5.12)]*.

Gastrointestinal Complications

Advise patients to contact their health care provider if they develop severe abdominal pain, chills, fever, nausea, vomiting, or diarrhea *[see Warnings and Precautions (5.12)]*.

Females and Males of Reproductive Potential

ADCETRIS can cause fetal harm. Advise women receiving ADCETRIS to avoid pregnancy during ADCETRIS treatment and for at least 6 months after the final dose of ADCETRIS.

Advise males with female sexual partners of reproductive potential to use effective contraception during ADCETRIS treatment and for at least 6 months after the final dose of ADCETRIS *[see Use in Specific Populations (8.3)]*.

Advise patients to report pregnancy immediately *[see Warnings and Precautions (5.13)]*.

Lactation

Advise patients to avoid breastfeeding while receiving ADCETRIS *[see Use in Specific Populations (8.2)]*.

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Manufactured by:
Seattle Genetics, Inc.
Bothell, WA 98021
1-855-473-2436
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