NCCN

Brentuximab vedotin (ADCETRIS®) + AVD recommended by NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Category 2A for frontline Stage III/IV cHL patients with no known neuropathy[1]

ECHELON-1: 4-YEAR PFS UPDATE

Improvement consistent with PFS benefit at 2 years*[2]

ECHELON-1 trial design

A randomized, open-label, multicenter trial assessing the efficacy and safety of A+AVD vs ABVD in 1334 adult patients with newly diagnosed Stage III/IV cHL. Patients were randomized 1:1 to A+AVD (n = 664) or ABVD (n = 670), and received treatment on Days 1 and 15 of each 28-day cycle for up to 6 cycles. The primary endpoint was modified PFS per IRF. The key secondary endpoint was overall survival.[3,4]

Review of:

Modified PFS per IRF for A+AVD vs ABVD, primary endpoint†[3]

PFS per INV at 4-year follow-up, exploratory post hoc analysis†[2]

*2-year PFS per INV was a prespecified exploratory analysis; 4-year PFS per INV was an exploratory post hoc analysis.

†Modified PFS event = a PFS event or receipt of additional anticancer treatment for patients not in complete response after frontline therapy. PFS event = progression or death from any cause.

A+AVD = ADCETRIS+AVD; ABVD = doxorubicin, bleomycin, vinblastine, dacarbazine; CI = confidence interval; HR = hazard ratio; INV = investigator; IRF = independent review facility; PFS = progression-free survival.

Indication

ADCETRIS is indicated for the treatment of adult patients with previously untreated Stage III/IV classical Hodgkin lymphoma (cHL) in combination with doxorubicin, vinblastine, and dacarbazine (AVD).

Important Safety Information

BOXED WARNING

PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY (PML): JC virus infection resulting in PML and death can occur in ADCETRIS-treated patients.

Contraindication

ADCETRIS concomitant with bleomycin due to pulmonary toxicity (e.g., interstitial infiltration and/or inflammation).

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A+AVD: Superior modified PFS at 2 years (per independent review facility)

Consistent PFS benefit at 4 years (per investigator)

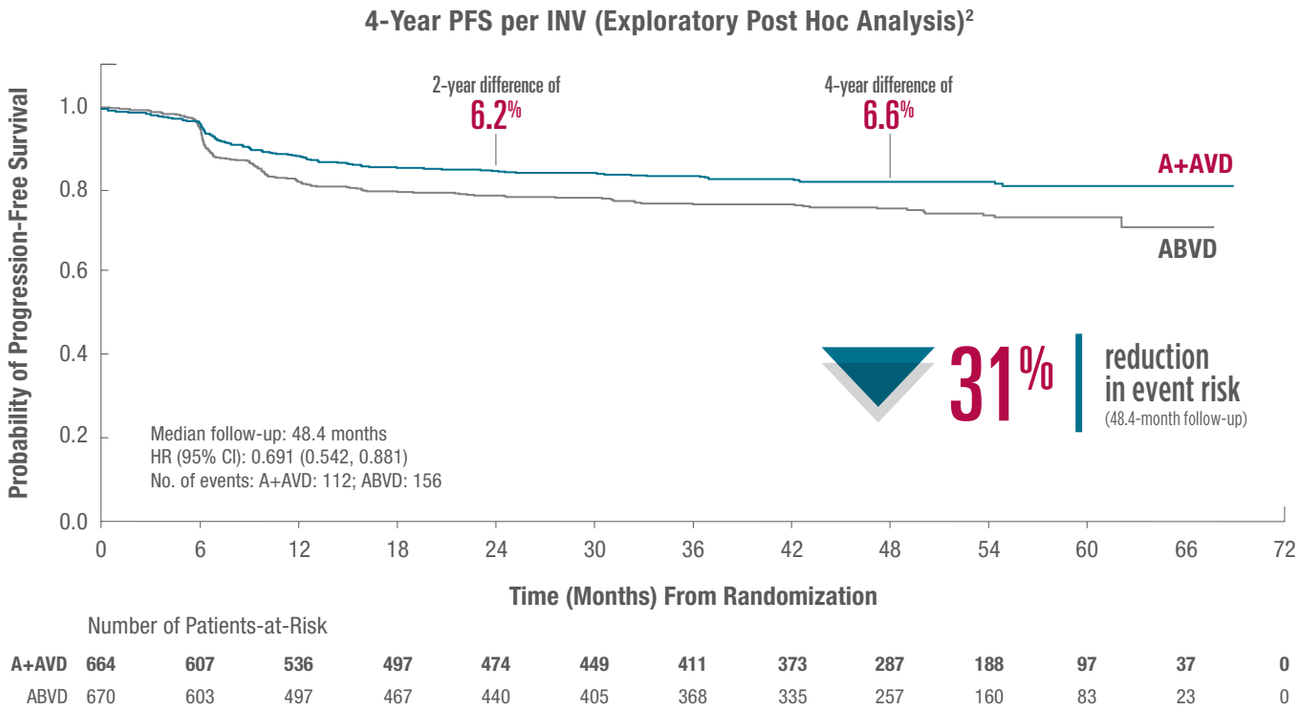
Superior efficacy vs ABVD
(modified PFS per IRF, primary endpoint, median follow-up of 24.6 months)[3]

23% reduction in event risk

HR (95% CI): 0.77 (0.60, 0.98); $P = 0.035$; overall survival (OS) data are still premature; an interim OS analysis did not demonstrate a significant difference between treatment arms[3,4]

The information below is not contained in the approved product labeling and is provided as supportive clinical information. Demonstration of PFS at 4 years was not a study objective, and thus not statistically powered to determine differences between groups.

PFS benefit over ABVD consistent at 4 years[2]



Number of Patients-at-Risk

A+AVD	**664**	**607**	**536**	**497**	**474**	**449**	**411**	**373**	**287**	**188**	**97**	**37**	**0**
ABVD	670	603	497	467	440	405	368	335	257	160	83	23	0

PFS (95% CI): 2 years: A+AVD, 84.2% (81.1, 86.9) vs ABVD, 78.0% (74.4, 81.1); 4 years: A+AVD, 81.7% (78.3, 84.6) vs ABVD, 75.1% (71.4, 78.4).[2]

PFS benefit observed independent of PET2 status (post hoc analysis)*[2]

4-year PFS rates per INV (95% CI)	A+AVD	ABVD
PET2-negative	**84.5%** (81.1, 87.3); n = 588	**78.9%** (75.2, 82.2); n = 578
PET2-positive	**59.8%** (43.9, 72.4); n = 47	**44.5%** (30.8, 57.4); n = 58

*ECHELON-1 was a non-PET-adaptive trial. PET2 status was unknown or unavailable for 29 patients (4%) in the A+AVD arm and 35 patients (5%) in the ABVD arm.

PET = positron emission tomography; PET2 = PET scan after Cycle 2.

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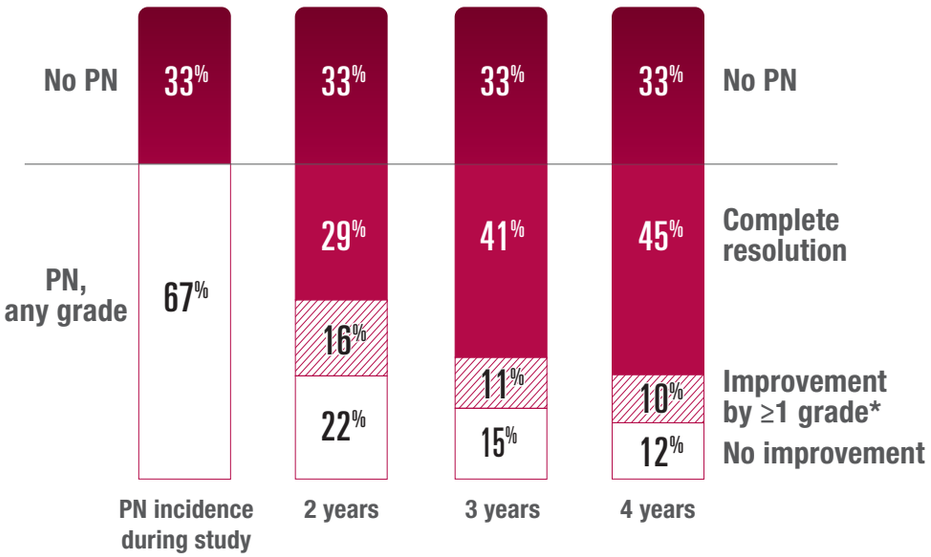
Adverse reactions and management

Peripheral neuropathy update

Most common and serious adverse reactions in ECHELON-1 with A+AVD

- Most common adverse reactions (≥20%, with ≥5% difference vs ABVD): anemia, neutropenia, peripheral sensory neuropathy, constipation, vomiting, diarrhea, pyrexia, decreased weight, stomatitis, and abdominal pain[3]
- Most common serious adverse reactions: febrile neutropenia (17%); pyrexia (7%); neutropenia and pneumonia (3% each)[3]
- 13% of A+AVD patients discontinued ≥1 drug due to adverse reactions[3]

Peripheral neuropathy (PN) with A+AVD continues to resolve or improve over time[2]



- 7% discontinued due to PN[3]
- 67% (442/662) experienced PN during the study[3]

*Improvement defined as improvement by ≥1 grade from worst grade as of the latest assessment.

Monitoring recommendations for PN and neutropenia

- **PN:** Cases were predominantly sensory (65% sensory, 11% motor); ADCETRIS-induced PN is cumulative[3]
  - Monitor for hypoesthesia, hyperesthesia, paresthesia, discomfort, a burning sensation, neuropathic pain, or weakness[3]
- **Neutropenia:** Monitor complete blood counts prior to each dose; monitor for fever; monitor more frequently for those with Grade 3 or 4 neutropenia[3]
  - Neutropenia led to dose delays of ≥1 drug in 21% of patients; febrile neutropenia led to dose delays in 8% of patients[3]

Recommended dose and modifications[3]

<table>
<tr><th>RECOMMENDED DOSE</th><th>MODIFICATIONS</th><th>GRADE 2</th><th>GRADE 3</th><th>GRADE 4</th></tr>
<tr><td rowspan="2">ADCETRIS 1.2 mg/kg up to a maximum of 120 mg‡ in combination with AVD, every 2 weeks until a maximum of 12 doses, disease progression, or unacceptable toxicity
Mild hepatic impairment: Reduce dose to 0.9 mg/kg up to a maximum of 90 mg†</td><td>PN</td><td>Reduce dose to 0.9 mg/kg up to a maximum of 90 mg†</td><td>Hold ADCETRIS dosing until improvement to ≤Grade 2; restart at 0.9 mg/kg up to a maximum of 90 mg†; consider modifying the dose of other neurotoxic chemotherapy agents</td><td>Discontinue</td></tr>
<tr><td colspan="2">Neutropenia</td><td colspan="2">G-CSF prophylaxis in subsequent cycles for those not receiving primary G-CSF</td></tr>
</table>

- Administer G-CSF primary prophylaxis beginning with Cycle 1 of A+AVD[3]

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

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Important Safety Information, cont'd

Warnings and Precautions

- Peripheral neuropathy (PN): ADCETRIS® (brentuximab vedotin) causes PN that is predominantly sensory. Cases of motor PN have also been reported. ADCETRIS-induced PN is cumulative. Monitor for symptoms such as hypoesthesia, hyperesthesia, paresthesia, discomfort, a burning sensation, neuropathic pain, or weakness. Institute dose modifications accordingly.
- Anaphylaxis and infusion reactions: Infusion-related reactions (IRR), including anaphylaxis, have occurred with ADCETRIS. Monitor patients during infusion. If an IRR occurs, interrupt the infusion and institute appropriate medical management. If anaphylaxis occurs, immediately and permanently discontinue the infusion and administer appropriate medical therapy. Premedicate patients with a prior IRR before subsequent infusions. Premedication may include acetaminophen, an antihistamine, and a corticosteroid.
- Hematologic toxicities: Fatal and serious cases of febrile neutropenia have been reported with ADCETRIS. Prolonged (≥1 week) severe neutropenia and Grade 3 or 4 thrombocytopenia or anemia can occur with ADCETRIS.

  Administer G-CSF primary prophylaxis beginning with Cycle 1 for patients who receive ADCETRIS in combination with chemotherapy for previously untreated Stage III/IV cHL or previously untreated PTCL.

  Monitor complete blood counts prior to each ADCETRIS dose. 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 doses.
- Serious infections and opportunistic infections: Infections such as pneumonia, bacteremia, and sepsis or septic shock (including fatal outcomes) have been reported in ADCETRIS-treated patients. Closely monitor patients during treatment for bacterial, fungal, or viral infections.
- Tumor lysis syndrome: Closely monitor patients with rapidly proliferating tumor and high tumor burden.
- 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. Avoid use in patients with severe renal impairment.
- 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 or severe hepatic impairment compared to patients with normal hepatic function. Avoid use in patients with moderate or severe hepatic impairment.
- Hepatotoxicity: Fatal and serious cases have occurred in ADCETRIS-treated patients. Cases were consistent with hepatocellular injury, including elevations of transaminases and/or bilirubin, and occurred after the first ADCETRIS dose or rechallenge. Preexisting liver disease, elevated baseline liver enzymes, and concomitant medications may increase the risk. Monitor liver enzymes and bilirubin. Patients with new, worsening, or recurrent hepatotoxicity may require a delay, change in dose, or discontinuation of ADCETRIS.
- PML: Fatal cases of JC virus infection resulting in PML have been reported in ADCETRIS-treated patients. First onset of symptoms occurred at various times from initiation of ADCETRIS, 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 PML diagnosis in patients with new-onset signs and symptoms of central nervous system abnormalities. Hold ADCETRIS if PML is suspected and discontinue ADCETRIS if PML is confirmed.
- Pulmonary toxicity: Fatal and serious events of noninfectious pulmonary toxicity, including pneumonitis, interstitial lung disease, and acute respiratory distress syndrome, have been reported. Monitor patients for signs and symptoms, including cough and dyspnea. In the event of new or worsening pulmonary symptoms, hold ADCETRIS dosing during evaluation and until symptomatic improvement.
- Serious dermatologic reactions: Fatal and serious cases of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported with ADCETRIS. If SJS or TEN occurs, discontinue ADCETRIS and administer appropriate medical therapy.
- Gastrointestinal (GI) complications: Fatal and serious cases of acute pancreatitis have been reported. Other fatal and serious 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.
- Hyperglycemia: Serious cases, such as new-onset hyperglycemia, exacerbation of preexisting diabetes mellitus, and ketoacidosis (including fatal outcomes) have been reported with ADCETRIS. Hyperglycemia occurred more frequently in patients with high body mass index or diabetes. Monitor serum glucose and if hyperglycemia develops, administer anti-hyperglycemic medications as clinically indicated.
- Embryo-fetal toxicity: Based on the mechanism of action and animal studies, ADCETRIS can cause fetal harm. Advise females of reproductive potential of the potential risk to the fetus, and to avoid pregnancy during ADCETRIS treatment and for at least 6 months after the final dose of ADCETRIS.

Most Common (≥20% in any study) Adverse Reactions

Peripheral neuropathy, fatigue, nausea, diarrhea, neutropenia, upper respiratory tract infection, pyrexia, constipation, vomiting, alopecia, decreased weight, abdominal pain, anemia, stomatitis, lymphopenia, and mucositis.

Drug Interactions

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

Use in Specific Populations

Moderate or severe hepatic impairment or severe renal impairment: MMAE exposure and adverse reactions are increased. Avoid use.

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.

Advise patients to report pregnancy immediately and avoid breastfeeding while receiving ADCETRIS.

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References: 1. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Hodgkin lymphoma (v.2.2019). © National Comprehensive Cancer Network, Inc. 2019. All rights reserved. Accessed November 18, 2019. To view the most recent and complete version of the guideline, go online to NCCN.org. **2.** Bartlett NL, Straus DJ, Długosz-Danecka M, et al. Brentuximab vedotin with chemotherapy for Stage III/IV classical Hodgkin lymphoma (cHL): 4-year update of the ECHELON-1 Study. Poster presented at the 61st Annual Meeting of the American Society of Hematology (ASH); December 7-10, 2019; Orlando, FL. **3.** ADCETRIS [Prescribing Information]. Bothell, WA: Seattle Genetics, Inc. October 2019. **4.** Connors JM, Jurczak W, Straus DJ, et al. Brentuximab vedotin with chemotherapy for stage III or IV Hodgkin's lymphoma. *N Engl J Med.* 2018;378:331-344.

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