

ECHELON-1 TRIAL

5-YEAR DATA UPDATE

STAGE III/IV cHL

LASTING REMISSION THE FIRST TIME AROUND

Consistent PFS benefit at 5 years*[1]

ECHELON-1: A randomized, open-label trial assessing the efficacy and safety of A+AVD vs ABVD in 1334 adult patients with newly diagnosed Stage III/IV cHL. Primary endpoint was modified PFS per IRF, with an event defined as progression, death due to any cause, or receipt of additional anticancer therapy for patients not in complete remission after frontline therapy. Key secondary endpoint was OS. Modified PFS per IRF: HR: 0.77 (95% CI: 0.60, 0.98); *P* = 0.035; median follow-up: 24.6 months.[2,3]

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).

Select Important Safety Information

BOXED WARNING

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

Please see additional Important Safety Information on page 7, and full Prescribing Information, including BOXED WARNING, at adcetrispro.com

*5-year PFS per INV was a prespecified exploratory analysis. A PFS event was defined as progression or death. HR: 0.68 (95% CI: 0.53, 0.87).

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

See how patients with Stage III/IV cHL may benefit from ADCETRIS+AVD

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ECHELON-1 PRIMARY ENDPOINT

A+AVD showed superior efficacy over ABVD at 2 years[2]



23% REDUCTION IN EVENT RISK

- Modified PFS per IRF (intent-to-treat population)*
- HR (95% CI): 0.77 (0.60, 0.98); *P* = 0.035; median follow-up: 24.6 months

Select Important Safety Information

Contraindication

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

Warnings and Precautions

- Peripheral neuropathy (PN): ADCETRIS 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.

*Patients were randomized 1:1 to A+AVD (n = 664) or ABVD (n = 670) then received treatment on Days 1 and 15 of each 28-day cycle for up to 6 cycles.[2]

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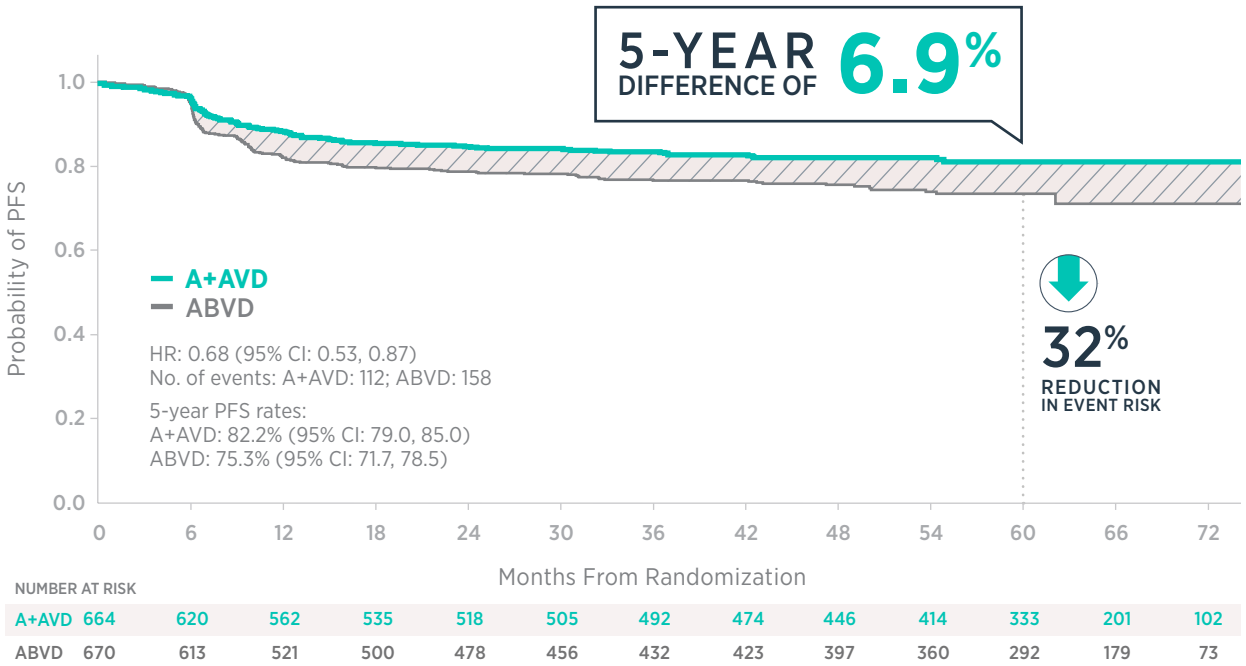
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ECHELON-1 **5-YEAR** DATA UPDATE

A+AVD: a better chance at living relapse-free[1]

The 5-year data provided are not contained in the approved product labeling. 5-year PFS per INV was a prespecified exploratory analysis. Data are provided as supportive clinical information.

A+AVD showed an ~7% PFS per INV benefit over ABVD at 5 years



NUMBER AT RISK													
A+AVD	664	620	562	535	518	505	492	474	446	414	333	201	102
ABVD	670	613	521	500	478	456	432	423	397	360	292	179	73

- OS, a key secondary endpoint, not reached at 5 years*[1]

*At the time of the modified PFS analysis, an interim OS analysis did not demonstrate a significant difference.[2,3]

Select Important Safety Information

Warnings and Precautions

- 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.

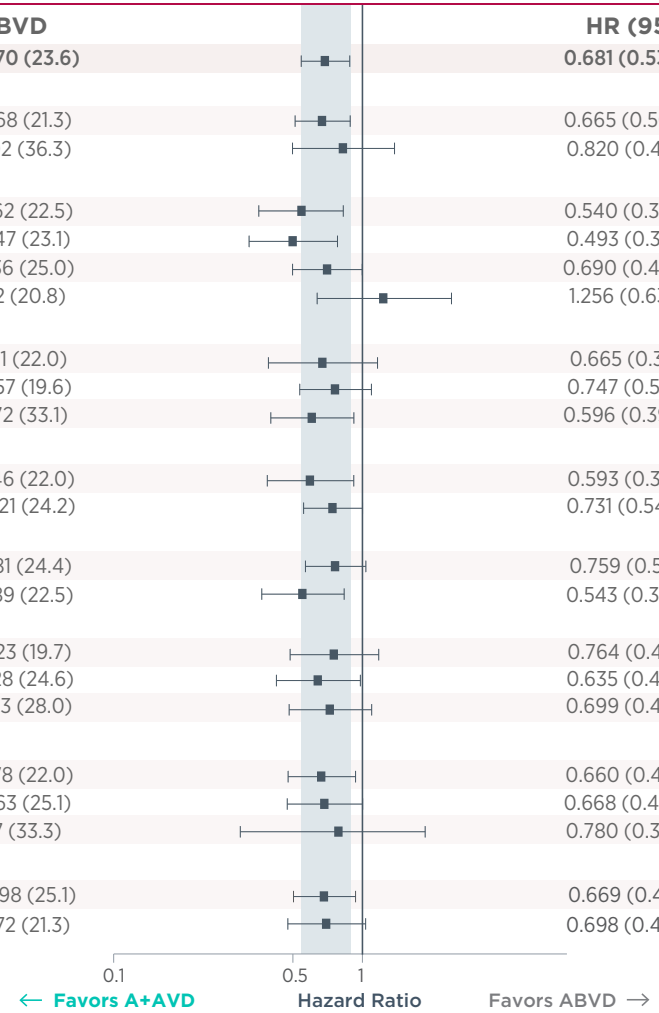
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Consistent 5-year benefit in PFS per INV across subgroups[1]

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Subgroup	A+AVD Events, n/N (%)	ABVD Events, n/N (%)	HR (95% CI)
Overall	**112/664 (16.9)**	**158/670 (23.6)**	**0.681 (0.534, 0.867)**
Age			
<60 years	87/580 (15.0)	121/568 (21.3)	0.665 (0.505, 0.876)
≥60 years	25/84 (29.8)	37/102 (36.3)	0.820 (0.494, 1.362)
Region			
Americas	34/261 (13.0)	59/262 (22.5)	0.540 (0.354, 0.823)
North America	31/250 (12.4)	57/247 (23.1)	0.493 (0.318, 0.764)
Europe	59/333 (17.7)	84/336 (25.0)	0.690 (0.487, 0.948)
Asia	19/70 (27.1)	15/72 (20.8)	1.256 (0.638, 2.472)
International Prognostic Score			
0–1	22/142 (15.5)	31/141 (22.0)	0.665 (0.385, 1.148)
2–3	54/355 (15.2)	70/357 (19.6)	0.747 (0.524, 1.065)
4–7	36/167 (21.6)	57/172 (33.1)	0.596 (0.392, 0.904)
Baseline cancer stage			
Stage III	33/237 (13.9)	54/246 (22.0)	0.593 (0.385, 0.915)
Stage IV	79/425 (18.6)	102/421 (24.2)	0.731 (0.545, 0.980)
Baseline B symptoms			
Present	77/400 (19.3)	93/381 (24.4)	0.759 (0.561, 1.026)
Absent	35/264 (13.3)	65/289 (22.5)	0.543 (0.360, 0.819)
Baseline extranodal sites			
0	35/217 (16.1)	44/223 (19.7)	0.764 (0.490, 1.190)
1	36/217 (16.6)	56/228 (24.6)	0.635 (0.418, 0.965)
>1	39/194 (20.1)	54/193 (28.0)	0.699 (0.463, 1.056)
Baseline ECOG status			
0	57/376 (15.2)	83/378 (22.0)	0.660 (0.471, 0.924)
1	46/260 (17.7)	66/263 (25.1)	0.668 (0.458, 0.974)
2	9/28 (32.1)	9/27 (33.3)	0.780 (0.309, 1.969)
Gender			
Male	67/378 (17.7)	100/398 (25.1)	0.669 (0.491, 0.912)
Female	45/286 (15.7)	58/272 (21.3)	0.698 (0.473, 1.030)



ECOG = Eastern Cooperative Oncology Group.

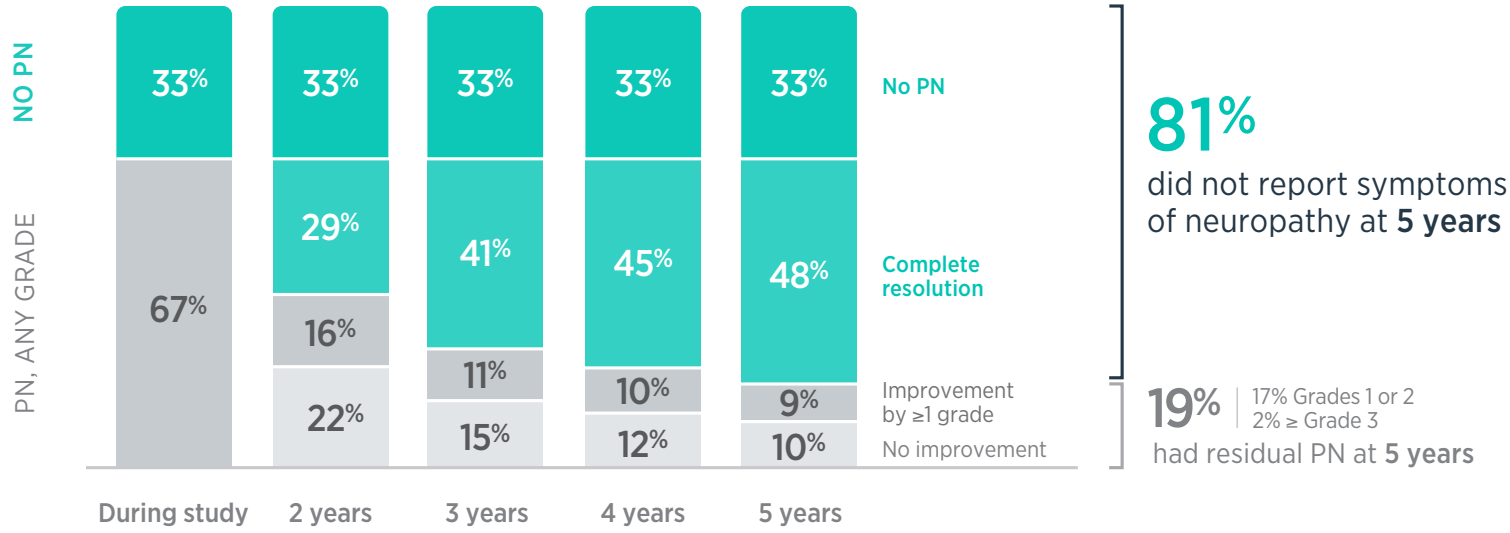
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Most peripheral neuropathy (PN) with A+AVD completely resolved or improved at 5 years[1-4]

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PN incidence and resolution over 5 years



81% did not report symptoms of neuropathy at **5 years**

19% had residual PN at **5 years** | 17% Grades 1 or 2; 2% ≥ Grade 3

67% (442/662) experienced PN during the study; most had Grade 1 or 2 PN (56%; 372/662), 11% had ≥Grade 3 (70/662); 7% discontinued due to PN.

Please refer to page 6 for recommended dose modifications to manage PN.

Use dose modifications to manage PN and neutropenia[2]

Normal recommended dose: 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.

Dose modifications for PN and neutropenia

	Severity	Dose Modification
PN	Grade 2	• **Reduce** dose to 0.9 mg/kg up to a maximum of 90 mg* every 2 weeks
	Grade 3	• **Hold** ADCETRIS dosing until improvement to Grade 2 or lower • **Restart** at 0.9 mg/kg up to a maximum of 90 mg* every 2 weeks • **Consider** modifying the dose of other neurotoxic chemotherapy agents
	Grade 4	• **Discontinue** dosing
Neutropenia	Grade 3 and 4	• **Administer G-CSF prophylaxis** for subsequent cycles for patients not receiving primary G-CSF prophylaxis

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

G-CSF = granulocyte colony-stimulating factor.

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  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.

Please see full Prescribing Information, including BOXED WARNING, at adcetrispro.com

References: 1. Straus DJ, Długosz-Danecka M, Connors JM, et al. Brentuximab vedotin with chemotherapy for patients with previously untreated, stage III/IV classical Hodgkin lymphoma: 5-year update of the ECHELON-1 study. Poster presented at: 62nd Annual Meeting of the American Society of Hematology; December 5-8, 2020. **2.** ADCETRIS [Prescribing Information]. Bothell, WA: Seattle Genetics, Inc. October 2019. **3.** 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. **4.** 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: 61st Annual Meeting of the American Society of Hematology; December 7-10, 2019; Orlando, FL.

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