Seven-year overall survival analysis from the ECHELON-1 study of brentuximab vedotin plus chemotherapy in patients with previously untreated Stage III/IV classical Hodgkin lymphoma

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Stephen M. Ansell,[1] David J. Straus,[2] Joseph M. Connors,[3] Wojciech Jurczak,[4] Won-Seog Kim,[5] Andrea Gallamini,[6] Radhakrishnan Ramchandren,[7] Jonathan W. Friedberg,[8] Ranjana Advani,[9] Martin Hutchings,[10] Andrew M. Evens,[11] Kerry J. Savage,[3] Hyeon-Seok Eom,[12] Tatyana Feldman,[13] Jeremy S. Abramson,[14] Cassie Dong,[15] Bipin Savani,[15] Athanasios Zomas,[16] Keenan Fenton,[17] and John Radford[18]

[1]Division of Hematology, Mayo Clinic, Rochester, MN, USA; [2]Department of Medicine, Lymphoma Service, Memorial Sloan Kettering Cancer Center, New York, NY, USA; [3]BC Cancer, Centre for Lymphoid Cancer, Vancouver, Canada; [4]Maria Sklodowska-Curie National Research Institute of Oncology, Krakow, Poland; [5]Division of Hematology-Oncology, Department of Internal Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea; [6]Research and Innovation Department, Antoine-Lacassagne Cancer Center, Nice, France; [7]University of Tennessee Graduate School of Medicine, Knoxville, TN, USA; [8]Wilmot Cancer Institute, University of Rochester, Rochester, NY, USA; [9]Department of Medicine, Division of Oncology, Stanford University, Stanford, CA, USA; [10]Department of Hematology, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark; [11]Division of Blood Disorders, Rutgers Cancer Institute of New Jersey, New Brunswick, NJ, USA; [12]Department of Hematology-Oncology, Center for Hematologic Malignancy, National Cancer Center, Goyang, Republic of Korea; [13]John Theurer Cancer Center, Hackensack Meridian Health, Hackensack, NJ, USA; [14]Massachusetts General Hospital, Boston, MA, USA; [15]Takeda Development Center Americas, Inc. (TDCA), Lexington, MA, USA; [16]Takeda Pharmaceuticals International AG, Zurich, Switzerland; [17]Pfizer Inc., Bothell, WA, USA; [18]University of Manchester and the Christie NHS Foundation Trust, Manchester Academic Health Science Centre, Manchester, UK

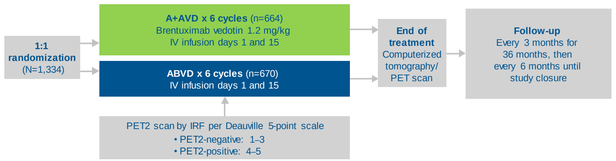
Background

- The standard-of-care for the treatment of advanced-stage classical Hodgkin lymphoma (cHL) has been first-line treatment with doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) for over 30 years[1]
  - However, a significant proportion of patients with Stage III/IV cHL either relapse or are refractory to ABVD[1,2]
- Although various approaches including positron emission tomography (PET)-adapted strategies and bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPP)-based regimens have succeeded in improving disease control or tolerability versus ABVD,[3] none show a meaningful overall survival (OS) advantage
- After a 6-year follow-up of the phase 3 ECHELON-1 study (NCT01712490), analyses demonstrated a long-term OS and progression-free survival (PFS) benefit with first-line brentuximab vedotin + doxorubicin, vinblastine, and dacarbazine (A+AVD) versus ABVD[4]
- Here we report an updated analysis of PFS, OS, and safety for patients in the ECHELON-1 study after a median follow-up of 7 years

Methods

- In the open-label, randomized, phase 3 ECHELON-1 study, patients with previously untreated Stage III/IV cHL were randomized 1:1 to receive 6 cycles of A+AVD or ABVD
- PET scan after cycle 2 (PET2) evaluation was mandatory
- Primary endpoint: Modified PFS per independent review facility (IRF; previously reported)
- Key secondary endpoint: Alpha-controlled, event-driven analysis of OS
- Safety outcomes include:
  - Second malignancies
  - Adverse events
  - Outcomes of pregnancy among patients and their partners
  - Peripheral neuropathy (PN) resolution and improvement rates
- P-values are descriptive only

Figure 3: Study design



Results

Patient demographics and disease characteristics

- In total, 1,334 patients were randomized to receive A+AVD (n=664) or ABVD (n=670)
- Median follow-up was 89.3 months (95% confidence interval [CI]: 87.0–90.2)
- Baseline demographics and disease characteristics were well balanced between the two treatment arms and have been described previously[4]

OS and PFS

- The clinical benefit of A+AVD was maintained compared to ABVD
  - 7-year OS rates: A+AVD 93.5% (95% confidence interval [CI]: 91.1–95.2); ABVD 88.8% (95% CI: 85.8–91.1); hazard ratio (HR) 0.617 (95% CI: 0.423–0.899); *P*=0.011 **(Figure 1)**
  - Median OS has not been reached in either treatment arm
- Consistent with previous PFS analysis in ECHELON-1, 7-year PFS rates with A+AVD versus ABVD were 82.3% (95% CI: 79.1–85.0) versus 74.5% (95% CI: 70.8–77.7); HR 0.677 (95% CI: 0.532–0.863); *P*=0.001 **(Figure 2)**
- OS benefit was generally consistent across subgroups, including in the age <40 years and Stage IV disease subgroups **(Figure 4)**

Question

Is the benefit seen with A+AVD versus ABVD in the ECHELON-1 study at 6 years' follow-up maintained after 7 years?

Study design

NCT01712490
open-label,
RCT, phase 3

A+AVD or ABVD
6 cycles, intravenous (IV) infusion
days 1 and 15

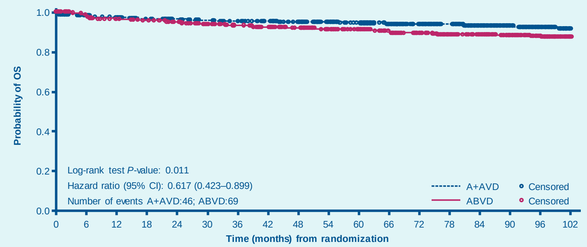
Endpoints
PFS and OS

Current analysis
Data cut-off
March 11, 2023

Key take aways

At 7-year median follow-up, patients with Stage III/IV cHL who received A+AVD continued to show a sustained PFS and OS benefit versus ABVD

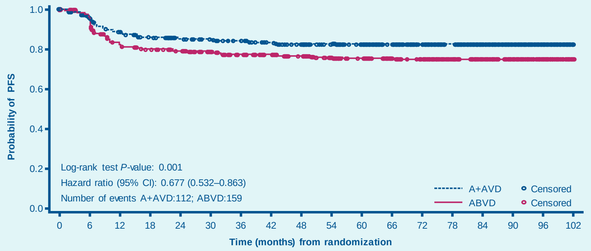
Figure 1: OS



Number of patients at risk

A+AVD	664	638	626	612	598	584	572	557	538	517	494	472	443	416	378	310	200	117
ABVD	670	634	614	604	587	567	545	527	505	479	455	426	398	372	340	268	178	97

Figure 2: PFS



Number of patients at risk

A+AVD	664	619	563	537	520	508	496	480	463	446	426	405	384	362	332	273	177	101
ABVD	670	612	519	500	484	464	441	430	412	389	369	348	321	301	278	220	146	78

Figure 4: OS benefit across subgroups

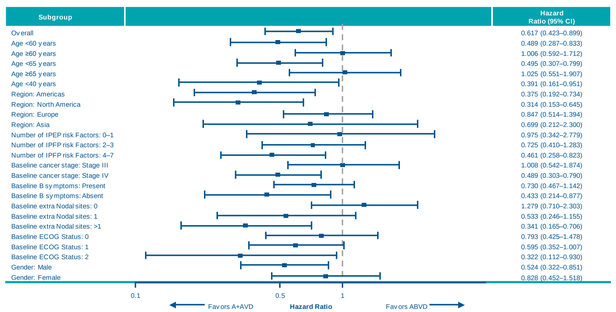
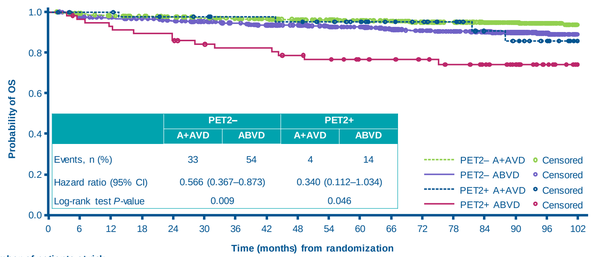


Figure 5: OS by PET2 status



	PET2–		PET2+	
	A+AVD	ABVD	A+AVD	ABVD
Events, n (%)	33	54	4	14
Hazard ratio (95% CI)	0.566 (0.367–0.873)		0.340 (0.112–1.034)	
Log-rank test *P*-value	0.009		0.046	

Number of patients at risk

A+AVD	588	580	569	557	545	533	524	510	493	474	456	439	412	388	358	293	187	110
ABVD	577	566	550	542	527	510	490	472	453	430	410	382	357	337	311	248	168	93
A+AVD	47	45	45	43	42	41	39	39	38	36	33	29	27	24	18	16	12	6
ABVD	58	55	53	51	49	46	44	44	41	39	35	34	32	28	25	20	10	4

OS by PET2 status

- Seven-year OS rates were improved with A+AVD compared to ABVD in patients with both PET2– (95.0% versus 90.2%; HR 0.57; 95% CI: 0.37–0.87; *P*=0.009) and PET2+ (90.7% versus 74.0%; HR 0.34; 95% CI: 0.11–1.03; *P*=0.046) status, respectively **(Figure 5)**

Causes of death

- In the A+AVD and ABVD treatment arms, 46 (22 disease-related) and 69 (30 disease-related) deaths were reported, respectively **(Table 1)**

Table 1: Summary of deaths

Cause of death	A+AVD (n=662)	ABVD (n=659)
All deaths, n (%)	46 (7)	69 (10)
Disease related, n (%)	22 (3)	30 (5)
Not disease related, n (%)	24 (4)	38 (6)
Unknown, n (%)	0	1 (<1)
Deaths >30 days after last dose of frontline therapy, n (%)	37 (6)	56 (8)
Disease related, n (%)	19 (3)	26 (4)
Not disease related*, n (%)	18 (3)	29 (4)
Unknown, n (%)	2 (<1)	7 (1)
Deceased, n (%)	3 (<1)	0
Cardiac arrest, n (%)	2 (<1)	0

*Causes of death in ≥2 patients in either arm

Second malignancies

- The rate of second malignancies was similar between arms; 33 (5%) in patients who received A+AVD and 39 (6%) in patients who received ABVD

Pregnancy

- A total of 92 patients reported pregnancies in the A+AVD arm (55 female patients and 37 males with pregnant partners); in the ABVD arm 73 patients reported pregnancies (31 female patients and 42 males with pregnant partners)
- Of these pregnancies, 1 or more live births were reported in 84/92 patients and their partners treated with A+AVD (91%) and 59/73 treated with ABVD (81%)
- No stillbirths were reported in either treatment arm

Peripheral neuropathy

- In patients with PN receiving A+AVD and ABVD:
  - Treatment-emergent PN resolved or improved in 86% (381/443) and 87% (249/286) of patients, respectively
  - Median (range) time to resolution was 16 (0–373) weeks with A+AVD and 10 (0–343) weeks with ABVD
  - Median (range) time to improvement was 42 (2–182) weeks with A+AVD and 19 (15–142) weeks with ABVD
- PN was ongoing in 28% of A+AVD (122/443; 12% grade ≥2) and 20% of ABVD (58/286; 7% grade ≥2) patients

Conclusions

- At 7-year median follow up, patients with Stage III and IV cHL who received A+AVD showed a sustained PFS and OS benefit vs ABVD, with fewer lymphoma-related deaths and PFS rates suggesting potential curability
- Based on these data, A+AVD should be considered a preferred first-line treatment option for patients with previously untreated Stage III or IV cHL

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