FIRST-LINE BRENTUXIMAB VEDOTIN PLUS CHEMOTHERAPY IMPROVES OVERALL SURVIVAL IN PATIENTS WITH STAGE III/IV CLASSICAL HODGKIN LYMPHOMA: AN UPDATED ANALYSIS OF ECHELON-1

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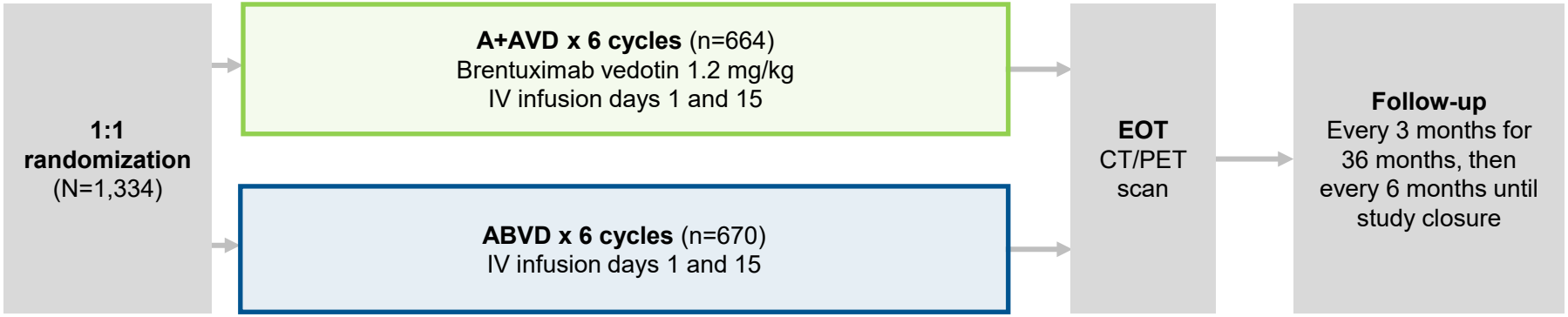
Background

- For the last decade, standard treatments (e.g., ABVD) have set a high bar for survival for patients with advanced cHL, in part due to the improved ability to salvage patients who relapse[1]
- Although various approaches including PET-adapted strategies and BEACOPP-based regimens have succeeded in improving tolerability or disease control versus ABVD, none have yet shown a meaningful OS advantage[2]
- In the phase 3 ECHELON-1 study (NCT01712490), analyses after a 5-year follow-up supported a long-term PFS benefit with first-line A+AVD vs ABVD[3]
- Here we report an alpha-controlled, prespecified OS analysis for patients in the ECHELON-1 study after approximately 6 years follow-up, as well as updates to long-term safety outcomes: second malignancies, pregnancies, and PN

A+AVD, brentuximab vedotin + doxorubicin, vinblastine, and dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; cHL, classical Hodgkin lymphoma; OS, overall survival; PET, positron emission tomography; PFS, progression-free survival; PN, peripheral neuropathy.

1. Canellos GP, et al. N Engl J Med 1992;327:1478-84.; 2. Kreissl S, et al. Lancet Haematol 2021;8:e398-e409.; 3. Straus DJ, et al. Lancet Haematol 2021;8(6):e410–e421.

Phase 3 ECHELON-1 study design



Primary endpoint: modified PFS per IRF (previously reported[1])

Key secondary endpoint: alpha-controlled, event-driven analysis of OS

Long-term follow-up assessments:

- Exploratory analysis of OS among patients who were PET2-positive and PET2-negative
- PFS per investigator
- Subsequent treatment use
- Safety outcomes including:
  - PN resolution and improvement rates
  - Second malignancies
  - Outcomes of pregnancy among patients and their partners

Data cut-off for current analysis, June 1, 2021.

CT, computerized tomography; EOT, end of treatment; IRF, independent review facility; ITT, intention to treat; IV, intravenous; PET2, PET status at the end of cycle 2.

1. Connors JM, et al. N Engl J Med 2018;378:331–44.

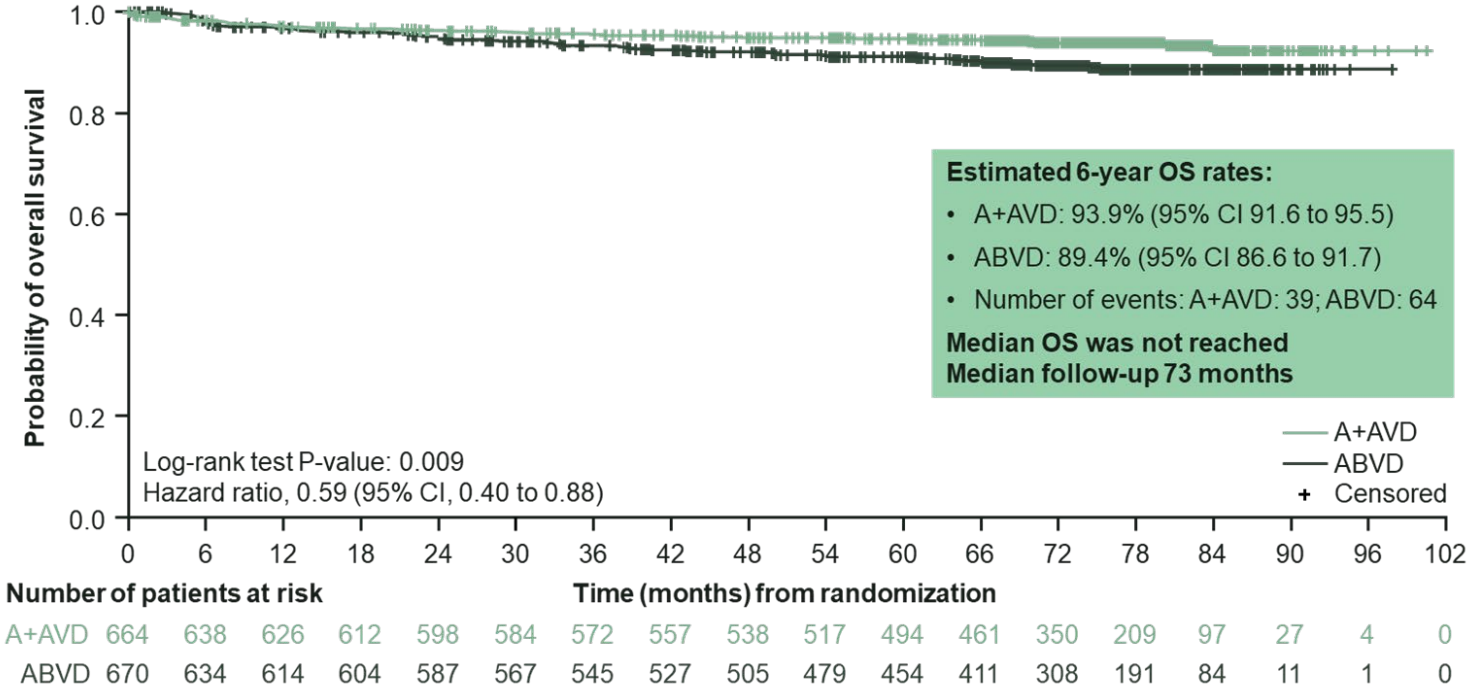
Key patient characteristics in ECHELON-1[1]

Characteristic	A+AVD (n=664)	ABVD (n=670)	Total (N=1,334)
Male sex, n (%)	378 (57)	398 (59)	776 (58)
Median age, years (interquartile range)	35 (26 to 51)	37 (27 to 53)	36 (26 to 52)
Aged <60 years, n (%)	580 (87)	568 (85)	1148 (86)
Aged ≥60 years, n (%)	84 (13)	102 (15)	186 (14)
Ann Arbor stage at initial diagnosis — n (%)*			
Stage II†	1 (<1)	0	1 (<1)
Stage III	237 (36)	246 (37)	483 (36)
Stage IV	425 (64)	421 (63)	846 (64)
Not applicable/unknown/missing	1 (<1)	3 (<1)	4 (<1)
IPS‡, n (%)			
0–1	142 (21)	141 (21)	283 (21)
2–3	355 (53)	357 (53)	712 (53)
4–7	167 (25)	172 (26)	339 (25)
PET2 status#, n (%)			
Positive	47 (7)	58 (9)	105 (8)
Negative	588 (89)	578 (86)	1166 (87)
Unknown/unavailable	29 (4)	34 (5)	63 (5)

*The Ann Arbor staging system ranges from I to IV, with higher stages indicating more widespread disease; †Patients in this category have major protocol violation; ‡The IPS ranges from 0 to 7, with higher scores indicating increased risk of treatment failure: low-risk, 0–1; intermediate-risk, 2–3; high-risk, 4–7; #PET status was assessed at post-index whereas other patient characteristics were assessed at baseline.
IPS, International Prognostic Score.

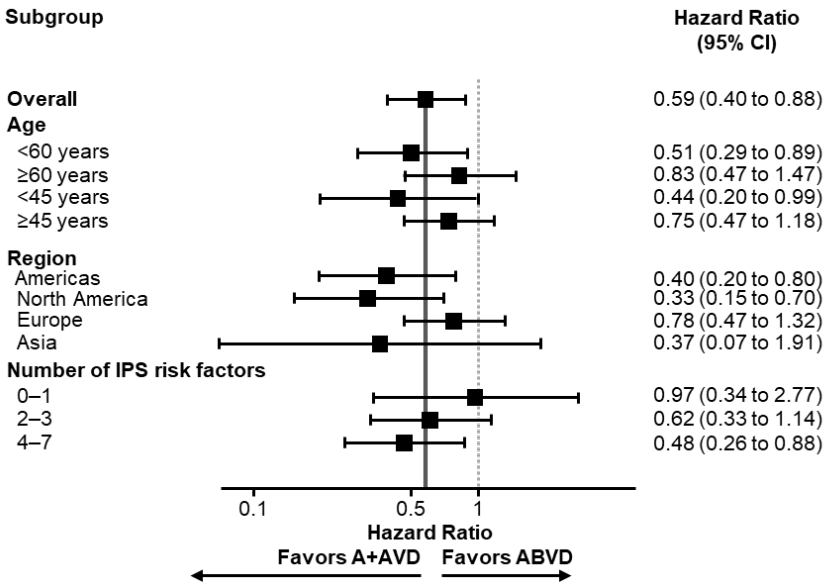
1. Straus DJ, et al. Lancet Haematol 2021;8(6):e410–e421.

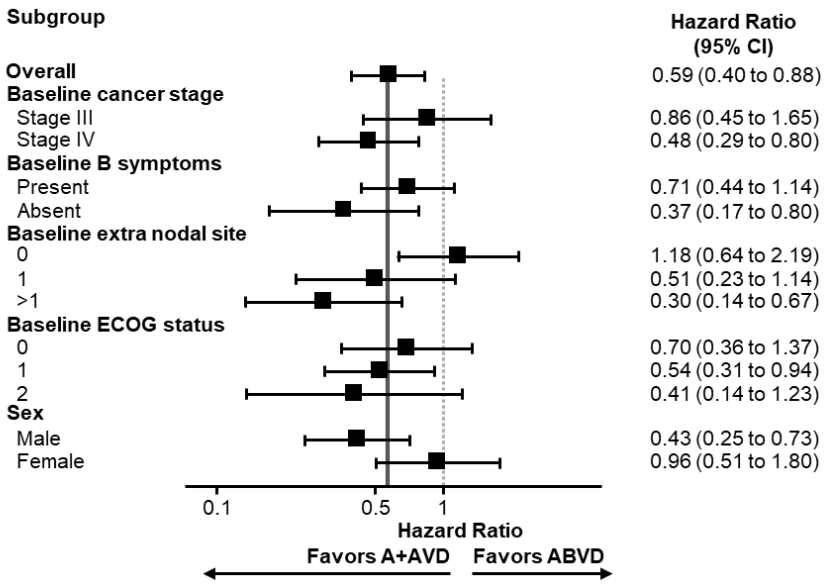
A+AVD significantly improved OS with a 41% reduction in risk of death compared with ABVD



CI, confidence interval.

OS benefit was generally consistent across subgroups

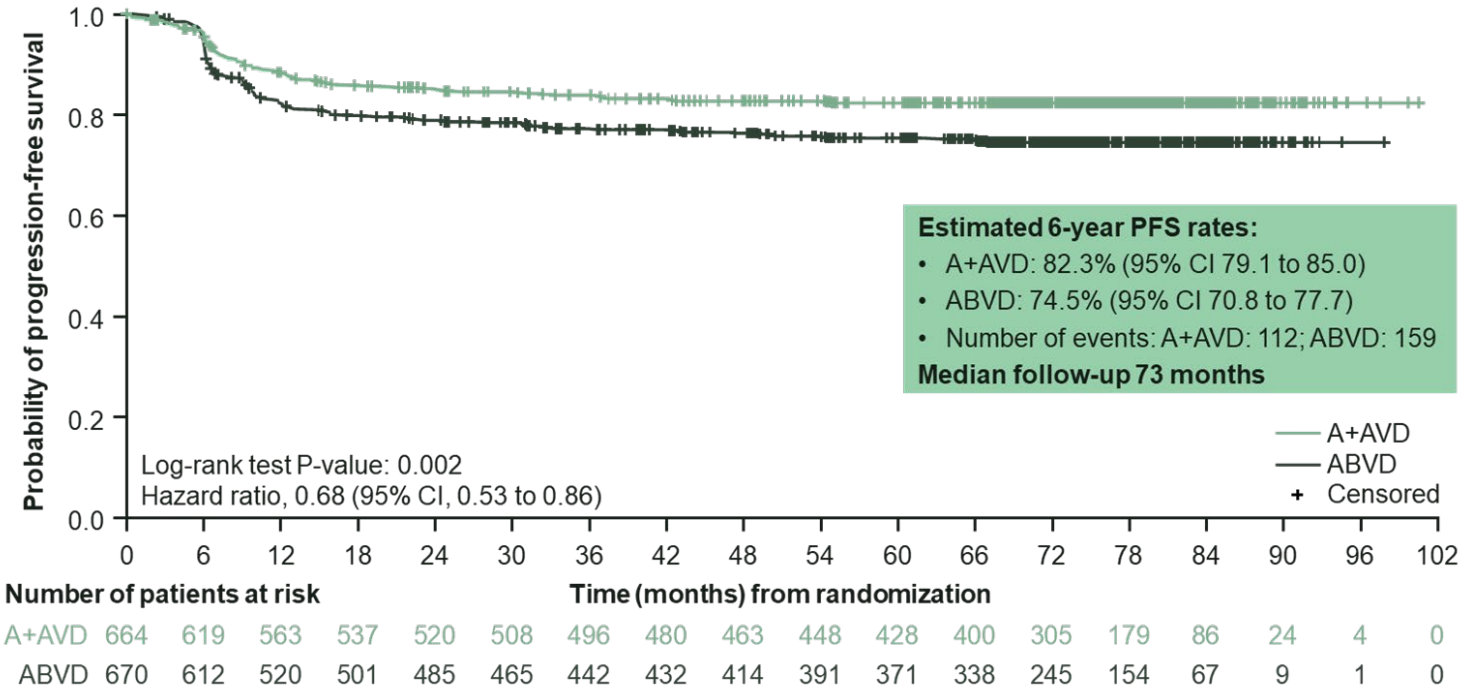




- The OS benefit with A+AVD was preserved in a multivariable analysis when simultaneously adjusting for baseline demographic and disease factors (HR 0.53; 95% CI, 0.34 to 0.83)
- Age, non-white race, ECOG performance status score, and PET2 status were identified as the covariates with greatest evidence of association with overall survival

ECOG, Eastern Cooperative Oncology Group; IPS, International Prognostic Score.

A+AVD reduced the risk of progression or death by 32% when compared with ABVD



Fewer patients died from HL and disease- or treatment-related complications with A+AVD vs ABVD

Cause of death per investigator	A+AVD (n=662)	ABVD (n=659)
Total Deaths	**39 (5.9%)**	**64 (9.7%)**
Hodgkin lymphoma or complications	32	45
Second malignancies	1	11
Other causes	**6**	**8**
Unknown cause	1	5*
Accident or suicide	3	0
COVID-19	0	1
Heart failure	1	1
Intracranial hemorrhage	1	0
Lower respiratory tract infection	0	1

*In 2 patients in the ABVD arm, death was reported to be of indeterminate cause, but the event occurred following investigator-documented disease progression.

Among those who died:

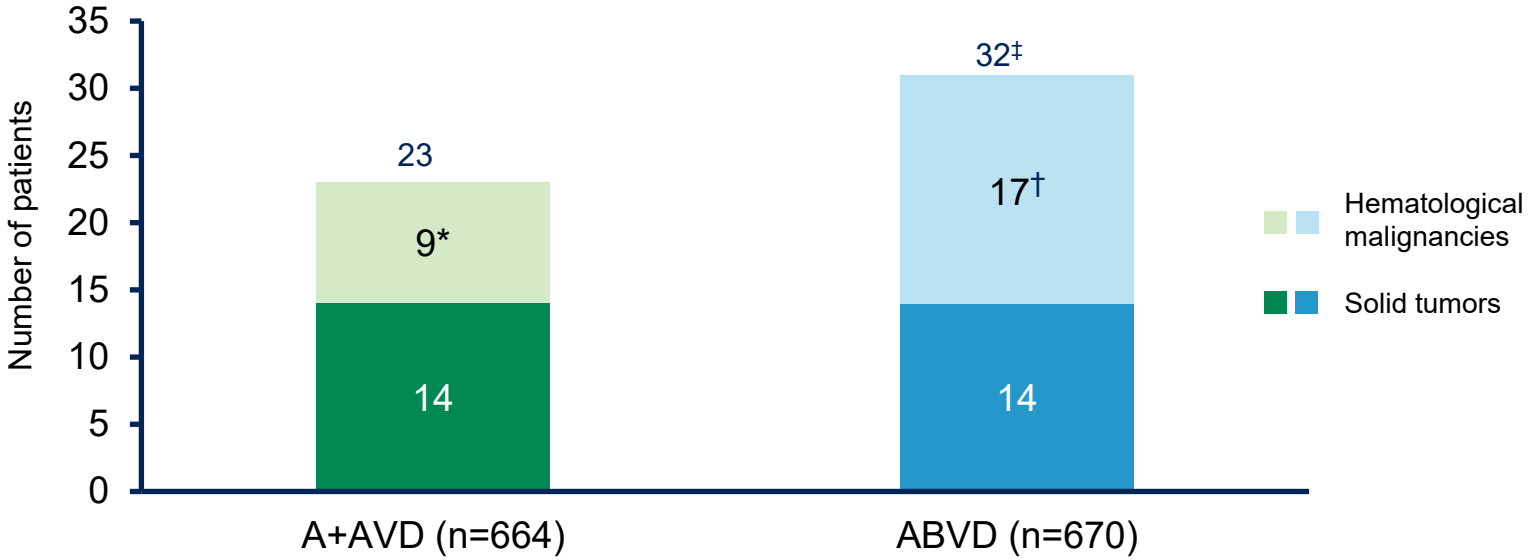
- A+AVD: 19 patients had prior disease progression (not always the cause of death); 18 received subsequent therapy
- ABVD: 28 patients had prior disease progression, 25 received a subsequent therapy (13 received brentuximab vedotin)

Use of subsequent therapy was less common with A+AVD versus ABVD (safety population)

	A+AVD (n=662)	ABVD (n=659)	Total (N=1,321)
Patients with ≥1 subsequent anticancer therapy, n (%)	135 (20)	157 (24)	292 (22)
Type of therapy, n (%)			
Chemotherapy regimens	78 (12)	108 (16)	186 (14)
Brentuximab vedotin monotherapy	8 (1)	49 (7)	57 (4)
Brentuximab vedotin + chemotherapy	2 (<1)	20 (3)	22 (2)
Radiation	54 (8)	54 (8)	108 (8)
Chemotherapy + radiation	1 (<1)	4 (<1)	5 (<1)
High-dose chemotherapy + transplant	44 (7)	59 (9)	103 (8)
Allogeneic transplant	4 (<1)	12 (2)	16 (1)
Immunotherapy*	18 (3)	24 (4)	42 (3)
Brentuximab vedotin + nivolumab	0 (0)	4 (<1)	4 (<1)
Nivolumab	15 (2)	18 (3)	33 (2)
Pembrolizumab	2 (<1)	6 (<1)	8 (<1)
Nivolumab combinations	1 (<1)	1 (<1)	2 (<1)

*Immunotherapy was based predominantly on anti-PD-1 agents.

Fewer second malignancies were reported in the A+AVD vs ABVD arm, consistent with prior reports[1]



*Includes 2 cases of acute myeloid leukemia and 6 cases of B- or T-cell lymphomas.
†includes 1 case each of acute myeloid leukemia, acute promyelocytic leukemia, and myelodysplastic syndrome, and 13 cases of B- or T-cell lymphomas.
‡Includes 1 unknown malignancy.

Among patients with second malignancies:

- Two patients on each arm received transplant
- Three patients on the ABVD arm received prior radiation (none with A+AVD)

1. Straus DJ, et al. Lancet Haematol 2021;8(6):e410–e421.

Pregnancy and peripheral neuropathy data consistent with prior reports

Pregnancies

- Fertility was not formally assessed
- A total of 191 pregnancies were reported among patients and their partners (A+AVD: 113; ABVD: 78)
  - Among female patients with A+AVD and ABVD:
    - Pregnancies: 49 and 28
    - Live births*: 56 and 23
  - Among partners of male patients with A+AVD and ABVD:
    - Pregnancies: 33 and 33
    - Live births*: 40 and 36
- No still births were reported in either arm

Peripheral neuropathy

- Incidence of PN at 2 years of follow-up was greater with A+AVD (67%) vs ABVD (43%)[1]
- In patients with PN in the A+AVD and ABVD arms, after 6 years follow-up:
  - Treatment-emergent PN either resolved or continued to improve† in 86% and 87%
  - Median time to resolution was 16 and 10 weeks

Safety population	A+AVD (n=662)	ABVD (n=659)
Patients with ongoing PN at last follow-up, n (%)	125 (19)	59 (9)
Grade 1	71 (11)	39 (6)
Grade 2	38 (6)	16 (2)
Grade 3‡	15 (2)	4 (<1)
Grade 4‡	1 (<1)	0

*Some female patients (13 on the A+AVD arm and 3 on the ABVD arm)/partners of male patients (8 on the A+AVD arm and 7 on the ABVD arm) recorded more than one live birth; †Resolution was defined as resolved/recovered with or without sequelae or return to baseline or lower severity as of the latest assessment for pre-existing events. Improvement was defined as resolution or a decrease by at least 1 grade from the worst grade with no higher grade thereafter; ‡Patients who were lost to follow-up or died prior to resolution or improvement were not censored (11/16 patients [including the 1 patient with Grade 4 PN] on the A+AVD arm; 4/4 on the ABVD arm).

1. Connors JM, et al. *N Engl J Med* 2018;378:331–44.

Authors' Conclusions

- A+AVD is the first regimen to show an improvement in OS versus classic ABVD in patients with previously untreated advanced cHL
- A+AVD improved OS versus ABVD despite the wide availability and use of active salvage therapies, including substantial use of subsequent brentuximab vedotin in the ABVD arm
- The OS benefit with A+AVD was coupled with fewer second malignancies vs ABVD
- The observed OS benefit with A+AVD, fewer disease-related deaths, and a concomitant reduction in disease progression, suggests that A+AVD has potentially cured more patients of their disease
- 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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