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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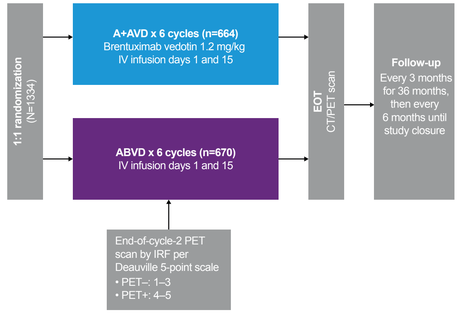
Background

- For the last decade, standard frontline treatments (i.e., ABVD) have set a high bar for survival for patients with advanced cHL[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

Methods

- ECHELON-1 (NCT01712490) is an open-label, randomized phase 3 study (**Figure 1**)

Figure 1: Study design



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

- A total of 1334 patients with previously-untreated Stage III or IV cHL were randomized to treatment with 6 cycles of A+AVD or ABVD
- PET scans were performed after 2 cycles
- Follow up is ongoing; the median follow-up time as of June 2021 (data cut-off for the current analysis) was 73 months
- **Primary endpoint:**
  - Modified PFS per IRF (previously reported[4])
- **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:
    - Second malignancies
    - Outcomes of pregnancy among patients and their partners
    - PN resolution and improvement rates

Results

- Baseline demographics and disease characteristics were well balanced between groups (**Table 1**) and have been previously described

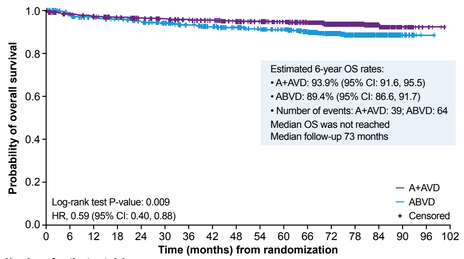
Table 1: Key patient characteristics[3]

Characteristic	A+AVD (n=664)	ABVD (n=670)	Total (N=1334)
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 (%)[a]			
Stage II[b]	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[c], 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[d], n (%)			
Positive	47 (7)	58 (9)	105 (8)
Negative	588 (89)	578 (86)	1166 (87)
Unknown/unavailable	29 (4)	34 (5)	63 (5)

[a]The Ann Arbor staging system ranges from I to IV, with higher stages indicating more widespread disease; [b]Patients in this category have major protocol violation; [c]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; [d]PET status was assessed at post-index whereas other patient characteristics were assessed at baseline.

- A+AVD significantly improved OS with a 41% reduction in risk of death compared with ABVD (HR 0.59; 95% CI: 0.40, 0.88) (**Figure 2**)
- There were a total of 39 deaths in the A+AVD arm, compared with 64 deaths in the ABVD arm
- Median OS has not been reached in either treatment arm

Figure 2: OS at data cutoff

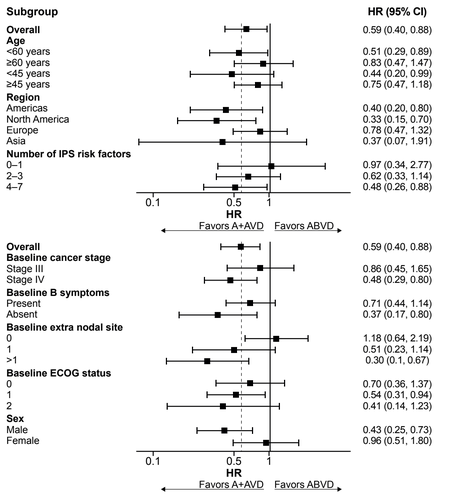


Number of patients at risk

A+AVD	664	638	626	612	598	584	572	557	538	517	494	461	350	209	97	27	4	0
ABVD	670	634	614	604	587	567	545	527	505	479	454	411	308	191	84	11	1	0

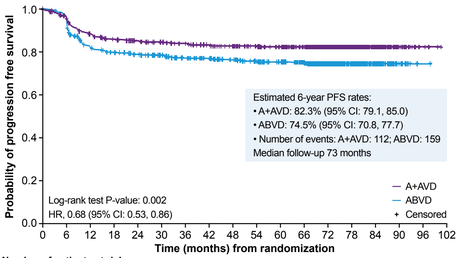
- OS benefit was generally consistent across subgroups (**Figure 3**)
- The OS benefit with A+AVD was preserved in a multivariable analysis when simultaneously adjusting for baseline demographic and disease factors (HR 0.53; 95% CI: 0.34, 0.83)
- Age, non-white race, ECOG performance status score, and PET2 status were identified as the covariates with greatest evidence of association with overall survival

Figure 3: OS benefit across subgroups



- Consistent with previous PFS analyses, at earlier timepoints in ECHELON-1, A+AVD reduced the risk of progression or death by 32% when compared with ABVD (**Figure 4**)

Figure 4: PFS at data cutoff



Number of patients at risk

A+AVD	664	619	563	537	520	508	496	480	463	448	428	400	305	179	86	24	4	0
ABVD	670	612	520	501	485	465	442	432	414	391	371	338	245	154	67	9	1	0

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

- Fewer patients died from cHL and disease, or treatment-related complications with A+AVD vs ABVD (**Table 2**)
- Among those who died:
  - In the A+AVD arm, 19 patients had prior disease progression; 18 received subsequent therapy
  - In the ABVD arm, 28 patients had prior disease progression, 25 received a subsequent therapy (of which 13 received brentuximab vedotin)
- A driver of higher mortality rate in the ABVD arm was due to second malignancies
  - Only 1 patient in the A+AVD arm died from a second malignancy vs 11 patients in the ABVD arm

Table 2: Cause of deaths

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

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

- Use of subsequent therapy was less common with A+AVD versus ABVD (**Table 3**)
  - 1/5 of patients in the A+AVD arm required subsequent therapy, compared with almost 1/4 of patients in the ABVD arm
- Brentuximab vedotin, either alone or in combination with chemotherapy or immunotherapy, was the most common subsequent therapy in the ABVD arm
  - 112 patients (17% of the ABVD arm) received subsequent therapy regimens that included brentuximab vedotin
- More patients in the ABVD arm also received stem cell transplants
  - Of note, however, the proportions of patients receiving transplants was not dramatically imbalanced between arms, suggesting that differing rates of ASCT do not account for other differences observed between arms, for example, in second malignancies

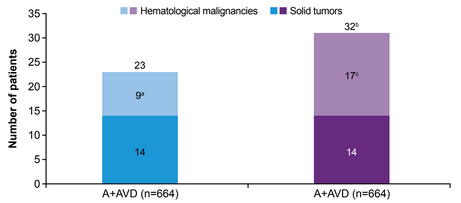
Table 3: Use of subsequent therapy

Characteristic	A+AVD n=662	ABVD n=659	Total N=1321
Patients with ≥1 subsequent anticancer therapy, n (%)	**135 (20)**	**157 (24)**	**292 (22)**
Type of therapy, n (%)			
Brentuximab vedotin or 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[a]	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)
Other	0 (0)	1 (<1)	1 (<1)

[a]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[3] (**Figure 5**)
- 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)
- Pregnancy and PN data were consistent with prior reports[4]
  - More female patients reported pregnancies in the A+AVD than the ABVD arm (49 vs 28)
  - The majority of pregnancies in both arms resulted in live births (a total of 56 and 23, respectively)
  - Incidence of PN at 2 years of follow-up was greater with A+AVD (67%) vs ABVD (43%)[4]
  - 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

Figure 5: Second malignancies



[a]Includes 2 cases of acute myeloid leukemia and 6 cases of B- or T-cell lymphomas. [b]Includes 1 unknown malignancy. [c]Includes 1 case each of acute myeloid leukemia, acute promyelocytic leukemia, and myelodysplastic syndrome, and 13 cases of B- or T-cell lymphomas.

Conclusions

- A+AVD is the first regimen to show an improvement in OS vs classic ABVD in patients with previously untreated advanced cHL
- A+AVD improved OS vs 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, suggest 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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Abbreviations: A+AVD, brentuximab vedotin + doxorubicin, vinblastine, and dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; ASCT, autologous stem cell transplant; BEACOPP, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone; cHL, classical Hodgkin lymphoma; CI, confidence interval; CT, computerized tomography; ECOG, Eastern Cooperative Oncology Group; EOT, end of treatment; HR, hazard ratio; IPS, International Prognostic Score; IRF, independent review facility; IV, intravenous; OS, overall survival; PET, positron emission tomography; PET2, PET status at the end of cycle 2; PFS, progression-free survival; PN, peripheral neuropathy.

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