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# Brentuximab vedotin plus chemotherapy for stage III/IV classical Hodgkin lymphoma: 4-year update of the ECHELON-1 study

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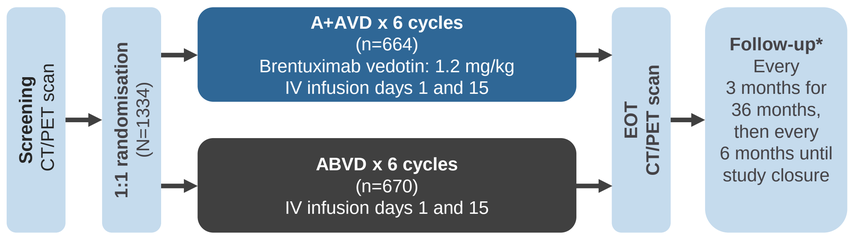
## INTRODUCTION

- Approximately 30% of patients with advanced stage classical Hodgkin lymphoma (cHL) are primary refractory or will relapse after receiving frontline doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD).[1–3]
- In the primary analysis, the international, phase 3 ECHELON-1 study demonstrated that brentuximab vedotin with doxorubicin, vinblastine and dacarbazine (A+AVD) was superior to ABVD for patients with previously untreated stage III/IV cHL (NCT01712490).[4]
  - 2-year modified progression-free survival (PFS) per independent review facility: A+AVD=82.1%, ABVD=77.2%; hazard ratio (HR)=0.77 (95% confidence interval [CI]: 0.60, 0.98; P=0.035).
- At a median of 3 years' follow-up, PFS results support durable benefit of A+AVD versus ABVD; the difference is stable and favourable.[5]
  - 3-year PFS per investigator (INV): A+AVD=83.1%, ABVD=76.0%; HR=0.704 (95% CI: 0.550, 0.901; P=0.005).
- Here, we present a median 4-year follow-up update of the ECHELON-1 trial, including PFS per INV and extended follow-up of peripheral neuropathy (PN).
- ECHELON-1 was an open-label, international, randomised, non–positron emission tomography (PET)-adapted, phase 3 study of A+AVD versus ABVD in patients with newly diagnosed, advanced (stage III/IV) cHL.[4]

## METHODS

- The study design is displayed in Figure 1.
- PFS per INV in the intent-to-treat (ITT) population, an exploratory endpoint, was evaluated post hoc at 4 years.
- Additional analyses of PFS per INV, such as those by PET status and age, are post hoc.
- All P values reported are nominal values.
- PFS per INV was defined as time from randomisation to first documentation of progressive disease (PD) or death due to any cause.[6]
- Resolution and improvement of PN were monitored during extended follow-up.
- An overall survival analysis will be performed after 112 deaths have occurred, consistent with the protocol.

**Figure 1: ECHELON-1 study design**




CT, computed tomography; IV, intravenous
*Per protocol: During post-treatment follow-up, patients are to be followed for survival disease status every 3 months for 36 months and then every 6 months until death/study closure. Investigators are requested to document response assessed from any scans performed either as standard-of-care or based on clinical judgement before initiation of any subsequent anticancer therapy for cHL. Investigators are also requested to document best response to any subsequent salvage anticancer therapies and any multimodality therapy that includes brentuximab vedotin as a component of the regimen

## RESULTS

- Enrolment period: November 2012 through January 2016.
- Total enrolment: 1334 patients at 218 sites in 21 countries (Table 1).
- Baseline patient demographics and disease characteristics for the ITT population were well balanced and have been previously described.[4,7]

**Table 1: Demographics and disease characteristics**

| Baseline patient characteristics | | A+AVD (n=664) | ABVD (n=670) |
|---|---|---|---|
| Male, % | | 57 | 59 |
| Age | Median (range), years | 35 (18–82) | 37 (18–83) |
| | < 60 years, % | 87 | 85 |
| | ≥ 60 years, % | 13 | 15 |
| Region, n (%) | Americas | 39 | 39 |
| | Europe | 50 | 50 |
| | Asia | 11 | 11 |
| IPS, % | 0–1 | 21 | 21 |
| | 2–3 | 53 | 52 |
| | 4–7 | 25 | 27 |
| ECOG PS, % | 0 | 57 | 57 |
| | ≥ 1 | 43 | 43 |
| B symptoms, % | Present | 60 | 57 |
| Baseline extranodal sites, % | 0 | 33 | 34 |
| | 1 | 33 | 33 |
| | > 1 | 29 | 29 |

ECOG PS, Eastern Cooperative Oncology Group performance status; IPS, International Prognostic Score

### PFS per INV at 4 Years of Follow-Up (ITT)

- Treatment with A+AVD versus ABVD resulted in a 31% reduction in the risk of progression or death (HR=0.691 [95% CI: 0.542, 0.881; P=0.003]; Figure 2 and Table 2).
  - PFS rates at 4 years: A+AVD: 81.7% (95% CI: 78.3, 84.6) versus ABVD: 75.1% (95% CI: 71.4, 78.4).
  - Median follow-up: 48.4 months (95% CI: 46.8, 48.6).

**Figure 2. PFS per INV at 4 years of follow-up (ITT)**

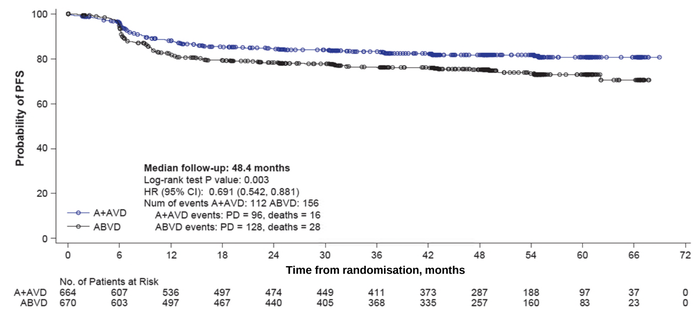



**Table 2: Landmark PFS per INV**

| PFS per INV | A+AVD | ABVD |
|---|---|---|
| **2-year follow-up (primary analysis)[8]** | n=474 | n=440 |
| 2-year PFS rate (95% CI), % | 84.2 (81.1, 86.9) | 78.0 (74.4, 81.1) |
| HR (95% CI) | 0.70 (0.54, 0.91) | |
| P value | P=0.006 | |
| **3-year follow-up[5]** | n=411 | n=368 |
| 3-year PFS rate (95% CI), % | 83.1 (79.9, 85.9) | 76.0 (72.4, 79.2) |
| HR (95% CI) | 0.70 (0.55, 0.90) | |
| P value | P=0.005 | |
| **4-year follow-up** | n=287 | n=257 |
| 4-year PFS rate (95% CI), % | 81.7 (78.3, 84.6) | 75.1 (71.4, 78.4) |
| HR (95% CI) | 0.69 (0.54, 0.88) | |
| P value | P=0.003 | |

- Consistent improvements in PFS were observed for patients treated with A+AVD versus ABVD across subgroups, including both stage III and stage IV disease, age, extranodal sites and IPS (Figure 3).

**Figure 3: PFS per INV at 4 years in prespecified subgroups**

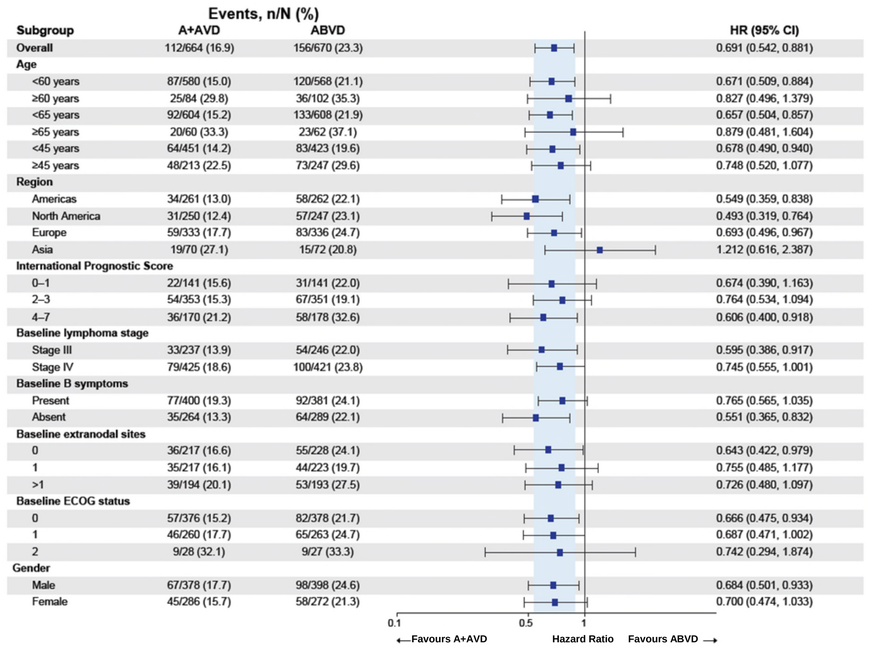



**Table 3: PFS at 4 years according to PET2 status and age (ITT population)**

| Group, % (95% CI) | A+AVD n=664 | ABVD n=670 | Difference at 4 years, % | HR (95% CI)* | P value† |
|---|---|---|---|---|---|
| **All patients (ITT)** | 81.7 (78.3, 84.6) | 75.1 (71.4, 78.4) | **6.6** | 0.691 (0.542, 0.881) | 0.003 |
| PET2– | 84.5 (81.1, 87.3) n=588 | 78.9 (75.2, 82.2) n=578 | **5.6** | 0.680 (0.515, 0.899) | 0.006 |
| PET2+ | 59.8 (43.9, 72.4) n=47 | 44.5 (30.8, 57.4) n=58 | **15.3** | 0.664 (0.371, 1.189) | 0.164 |
| **Age <60 years** | 83.7 (80.3, 86.6) n=580 | 77.3 (73.3, 80.7) n=568 | **6.4** | 0.671 (0.509, 0.884) | 0.004 |
| PET2– | 86.2 (82.7, 89.0) n=521 | 81.0 (77.0, 84.3) n=493 | **5.2** | 0.686 (0.500, 0.942) | 0.019 |
| PET2+ | 62.1 (45.2, 75.2) n=42 | 47.7 (32.5, 61.5) n=50 | **14.4** | 0.652 (0.343, 1.239) | 0.187 |
| **Age ≥60 years** | 67.5 (55.4, 77.0) n=84 | 63.8 (52.9, 72.8) n=102 | **3.7** | 0.827 (0.496, 1.379) | 0.466 |
| PET2– | 72.4 (59.3, 82.0) n=67 | 68.2 (56.7, 77.2) n=85 | **4.2** | 0.745 (0.414, 1.343) | 0.326 |
| PET2+ | 40.0 (5.2, 75.3) n=5 | 25.0 (3.7, 55.8) n=8 | **15.0** | 0.923 (0.229, 3.715) | 0.910 |

PET2, PET scan after cycle 2
*HRs (A+AVD/ABVD) and 95% CIs were based on a Cox proportional hazard regression model, which was stratified for the ITT population and unstratified for subgroup analyses.
†P values were calculated using a log-rank test, which was stratified for the ITT population and unstratified for subgroup analyses.

- Among all enroled patients, 89% (n=588) in the A+AVD arm and 86% (n=578) in the ABVD arm were PET2–; 7% (n=47) and 9% (n=58) were PET2+, respectively.
  - PET2 status was unknown or unavailable in 29 patients (4%) in the A+AVD arm and 35 patients (5%) in the ABVD arm.
- A PFS benefit favouring A+AVD was observed in all patients independent of PET2 status (Table 3).

### Complete Resolution and Improvement of PN at 4 Years

- At the primary analysis, a total of 442 patients (67%) in the A+AVD arm and 286 patients (43%) in the ABVD arm had PN.[4]
- At 4 years' follow-up, among patients with PN, 83% of A+AVD patients and 84% of ABVD patients had experienced complete resolution or improvement of PN (Table 4).
- Median time to complete resolution of PN events that were ongoing at end of treatment (EOT):
  - A+AVD: 30 weeks (range, 0–262 weeks); ABVD: 15 weeks (range, 0–234 weeks).
- Median time to improvement (for patients without complete resolution) of PN events that were ongoing at EOT:
  - A+AVD: 41 weeks (range, 8–205 weeks); ABVD: 12 weeks (range, 2–70 weeks).

**Table 4: Complete resolution and improvement of PN at 4 years**

| Patients with PN, n (%) | | 2 years[4] | 3 years[5] | 4 years |
|---|---|---|---|---|
| **A+AVD n=442** | Complete resolution or improvement of PN | 295 (67) | 345 (78) | 365 (83) |
| | Complete resolution* | 191 (43) | 272 (62) | 300 (68) |
| | Improvement† | 104 (24) | 73 (17) | 65 (15) |
| **ABVD n=286** | Complete resolution or improvement of PN | 214 (75) | 236 (83) | 240 (84) |
| | Complete resolution* | 174 (61) | 209 (73) | 217 (76) |
| | Improvement† | 40 (14) | 27 (9) | 23 (8) |

| | A+AVD n=442 | ABVD n=286 |
|---|---|---|
| Patients with ongoing PN at last follow-up | 142 (32) | 69 (24) |
| Maximum severity Grade 1/2 | 125 (28) | 65 (23) |
| Maximum severity Grade 3/4 | 17 (4) | 4 (1) |

*Resolution was defined as event outcome of "resolved" or "resolved with sequelae." Improvement was defined as "improved by ≥ 1 grade from worst grade as of the latest assessment".
†Improvement is defined as a decrease by ≥ 1 grade from worst grade with no higher grade thereafter. Improvement from EOT for a patient was defined as time from EOT visit to the first improvement date among events that were ongoing at EOT and improved between EOT and last follow-up. Patients with all events resolved were excluded.

## CONCLUSIONS

- **This PFS analysis at 4 years provides further evidence of a robust and durable benefit of A+AVD versus ABVD for the frontline treatment of stage III/IV cHL.**
- **PFS benefit for A+AVD is independent of PET2 status, disease stage, age and IPS.**
- **PN continues to resolve and improve over time, with most patients experiencing complete resolution.**
- **A+AVD compares favourably to PET-adapted strategies without requiring change of therapy based on PET2 status and completely eliminates exposure to bleomycin.**

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