# Brentuximab vedotin with chemotherapy in adolescents and young adults with stage III or IV classical Hodgkin lymphoma in ECHELON-1

Doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) have been used as front-line therapy for classical Hodgkin lymphoma (cHL) for decades. However, current literature suggests a significant minority of patients with stage III/IV cHL will relapse, with most relapses within 18 months of treatment initiation. The global, phase III ECHELON-1 trial compared brentuximab vedotin (BV), a CD30-directed antibody-drug conjugate, in combination with doxorubicin, vinblastine, and dacarbazine (A+AVD) *versus* ABVD.[1] cHL is most commonly diagnosed in adolescents and young adults (AYA),[2,3] defined by the National Cancer Institute (NCI) and multiple international oncology groups as 15-39 years of age (AYAO August Report; https://www.cancer.gov). Relapsed or refractory lymphoma and/or long-term sequelae of treatment (e.g., residual effects of bleomycin pneumonitis, infertility, and second malignancies resulting from treatment) have profound negative impacts. Therefore, an AYA subgroup analysis of ECHELON-1 was conducted. Consistent with the intent-to-treat (ITT) population,[1] AYA patients exhibited survival benefit with A+AVD *versus* ABVD with no new safety signals, including low rates of second malignancies and no apparent effect on fertility. These data underscore clinical benefit of A+AVD for AYA patients aged 18-39 years.

Of 1,334 patients with newly diagnosed stage III or IV cHL enrolled in ECHELON-1, median age was 36 years (range 18-83). In the overall population, A+AVD demonstrated a 6-year progression-free survival (PFS) benefit *versus* ABVD (Hazard Ratio [HR] 0.68; 95% Confidence Interval [CI]: 0.53-0.86, *P*=0.0003) independent of disease stage, International Prognostic Score baseline risk, or interim positron emission tomography scan after cycle 2 (PET2) status.[1] Significant overall survival (OS) benefit was shown with 6-year estimates of 93.9% *versus* 89.4% (HR 0.59; 95% CI: 0.40-0.88; *P*=0.009) with A+AVD *versus* ABVD. A+AVD also demonstrated favorable long-term safety with low rates of second malignancies. Although not formally assessed, there was no apparent impact on fertility through assessment of pregnancies.[1]

ECHELON-1 trial design and methodology have been previously reported.[1] To examine differences in AYA across age groups, and because eligibility was limited to ≥18 years, subgroups of patients aged 18-39 and 18-29 years were included. Adverse event grading and statistical analysis have been previously reported.[4] PFS (time from randomization to disease progression or death due to any cause) per investigator was a prespecified, exploratory endpoint in the ITT population and was assessed at six years. PET-positivity was defined as a Deauville score of 4 or 5. Except for the prespecified OS analysis in the ITT population, *P* values are nominal and not adjusted for multiplicity. All patients provided written informed consent. The protocol was approved by individual site institutional review boards and ethics committees as previously described[1,4] and was in accordance with the Declaration of Helsinki. This study was registered with clinicaltrials.gov identifier: NCT01712490 (EudraCT N 2011-005450-60).

Adolescents and young adult patients (58% of the ITT population) received either A+AVD (N=396) or ABVD (N=375). Baseline demographics and disease characteristics (Table 1) were similar across subgroups, treatment arms within subgroups, and the overall population.[1] In the 18-29 years subgroup, 224/244 (92%) of A+AVD patients were $PET2^-$ *versus* 197/224 (88%) ABVD patients; 16/244 (7%) of A+AVD patients were $PET2^+$ *versus* 14/224 (6%) ABVD patients.

Consistent with the ITT population,[1] patients aged 18-39 years exhibited a 6-year PFS benefit with A+AVD (86.4%) *versus* ABVD (79.4%) (HR 0.636; 95% CI: 0.445-0.908; *P*=0.012) (Figure 1A). Similar outcomes occurred for ages 18-29 years: 6-year PFS was 87.3% with A+AVD and 80.0% with ABVD (HR 0.604; 95% CI: 0.378-0.965; *P*=0.033). Numerical PFS benefit was observed with A+AVD *versus* ABVD independent of PET2 status in the 18-39 year subgroup (Figure 1B). Although sample sizes were small, similar outcomes occurred in the 18-29 years subgroup: A+AVD *versus* ABVD, $PET2^-$ (HR 0.505; 95% CI: 0.297-0.859; *P*=0.012); A+AVD *versus* ABVD, $PET2^+$ (HR 1.004; 95% CI: 0.306-3.290; *P*=0.995). Multivariable Cox regression analysis in patients <60 years of age including treatment arm and age (continuous) interaction, and International Prognostic Score category, region, sex, disease stage, extranodal involvement, and body mass index showed no significant interactions between age and treatment effect (*P*=0.865).

At a median 71.7 months OS follow-up, 6-year survival estimates were 98.2% with A+AVD and 94.9% with ABVD (HR 0.391; 95% CI: 0.161-0.951; *P*=0.032) in patients aged 18-39 years (*Online Supplementary Table S1*), comparing favorably with the ITT population. Use of subsequent systemic therapy including chemotherapy, high-dose chemotherapy and transplant, and immunotherapy was numerically lower in the A+AVD *versus* ABVD arms (*Online Supplementary Table S2*). Radiation therapy at any time was used in 10% of patients across arms.

**Table 1.** Patient demographics and disease characteristics in adolescents and young adults.

| Characteristics | Age 18-29 years | | Age 18-39 years | |
|---|---|---|---|---|
| | A+AVD N=244 | ABVD N=224 | A+AVD N=396 | ABVD N=375 |
| Age in years, median (range) | 24 (18-29) | 24 (18-29) | 27 (18-39) | 28 (18-39) |
| BMI, median | 23.0 | 23.3 | 23.1 | 24.0 |
| Female, N (%) | 112 (46) | 99 (44) | 188 (47) | 155 (41) |
| Region, N (%) | | | | |
| Americas[a] | 105 (43) | 81 (36) | 158 (40) | 153 (41) |
| Europe[b] | 118 (48) | 118 (53) | 202 (51) | 187 (50) |
| Asia | 21 (9) | 25 (11) | 36 (9) | 35 (9) |
| Ann Arbor stage, N (%) | | | | |
| Stage III | 96 (39) | 88 (39) | 143 (36) | 150 (40) |
| Stage IV | 148 (61) | 136 (61) | 253 (64) | 225 (60) |
| IPFP risk factors, N (%) | | | | |
| 0-1 | 62 (25) | 62 (28) | 113 (29) | 111 (30) |
| 2-3 | 135 (55) | 124 (55) | 215 (54) | 197 (53) |
| 4-7 | 47 (19) | 38 (17) | 68 (17) | 67 (18) |
| ECOG Score, N (%) | | | | |
| 0 | 146 (60) | 135 (60) | 240 (61) | 223 (59) |
| 1 | 93 (38) | 81 (36) | 145 (37) | 138 (37) |
| 2 | 5 (2) | 8 (4) | 11 (3) | 14 (4) |
| Extranodal disease, N (%) | | | | |
| ≥1 Extranodal site | 147 (60) | 139 (62) | 250 (63) | 236 (63) |
| None | 81 (33) | 76 (34) | 123 (31) | 124 (33) |
| Bone marrow involvement, N (%) | 48 (20) | 48 (21) | 78 (20) | 78 (21) |
| B symptoms[c], N (%) | 146 (60) | 134 (60) | 244 (62) | 226 (60) |
| PET status at cycle 2[d], N (%) | | | | |
| PET2-positive | 16 (7) | 14 (6) | 24 (6) | 28 (7) |
| PET2-negative | 224 (92) | 197 (88) | 366 (92) | 324 (86) |
| Unknown or indeterminate | 4 (2) | 13 (6) | 6 (2) | 23 (6) |

[a]The geographic region of the Americas was defined as Brazil, Canada, and the United States. [b]South Africa and Russia are included in Europe. [c]Patients who present with B symptom for at least one visit before the start of study drug administration. [d]Positivity defined as Deauville 4 or 5. A+AVD: brentuximab vedotin, doxorubicin, vinblastine, and dacarbazine; ABVD: doxorubicin, bleomycin, vinblastine, and dacarbazine; AYA: adolescent and young adult; BMI: body mass index; ECOG: Eastern Cooperative Oncology Group; IPFP: International Prognostic Factors Project; PET2: positron emission tomography scan conducted after cycle 2.

Similar to the ITT population,[1] overall incidence of febrile neutropenia (FN) was greater with A+AVD *versus* ABVD (16% *vs*. 5%). Incidence of FN decreased from 17% (57/343 patients) to 9% (5/53 patients) with A+AVD with use of granulocyte colony-stimulating factor (G-CSF) primary prophylaxis, whereas patients treated with ABVD had similar incidence of FN independent of G-CSF primary prophylaxis (5%). As a result, and per prescribing information label, G-CSF is recommended with A+AVD; current guidelines do not distinguish between younger and older patients. Outcomes with G-CSF primary prophylaxis with A+AVD have been previously reported.[5]

Incidence of all-grade peripheral neuropathy (PN) for patients aged 18-39 years was 64% (255/396 patients) with A+AVD and 40% (149/368 patients) with ABVD. Approximately 13% of PN with A+AVD treatment were grade 3/4 *versus* 3% with ABVD, similar to the ITT population (11%; 70/662).[4] With A+AVD, 89% (227/255) of patients with PN had either complete resolution (78% [198/255]) or improvement (11% [29/255]) at six years (Figure 2); 33 (13%), 15 (6%), 8 (3%), and one patient(s) (<1%) had ongoing PN of maximum severity grade 1, 2, 3, or 4, respectively. Assessment of ongoing PN with maximum severity of grade 3/4 was confounded in 7/9 patients treated with A+AVD (3 were lost to follow-up, 3 withdrew from the study, and one died before resolution/improvement); one patient receiving ABVD was lost to follow-up. Proactive management of PN is required to manage long-term effects. With ABVD, 90% (134/149) of patients with PN had either complete resolution (86% [128/149]) or improvement (4% [6/149]).

Similar to the ITT population,[1] low rates of second malignancies occurred across arms, with fewer observed with A+AVD *versus* ABVD (*Online Supplementary Table S3*). As previously reported,[1] no apparent impact on pregnancy rates was observed with A+AVD. Pregnancy occurred in 131 female patients (44 received A+AVD; 26 received ABVD) or partners of male patients (31 received A+AVD; 30 received ABVD).

Considering relapse patterns in cHL, long-term PFS benefit with A+AVD *versus* ABVD suggests that more AYA patients

will remain relapse-free, yet longer follow-up is needed.[6,7] OS benefit similar to the ITT population was also observed despite subsequent treatment options and the high survival rate of AYA patients. These data broadly compare with escalated BEACOPP outcomes, but potentially without additional second malignancy or infertility risk, particularly in patients who are PET2$^{+}$ and require more BEACOPP cycles.[8-10] Beyond ECHELON-1, the only other recent trial

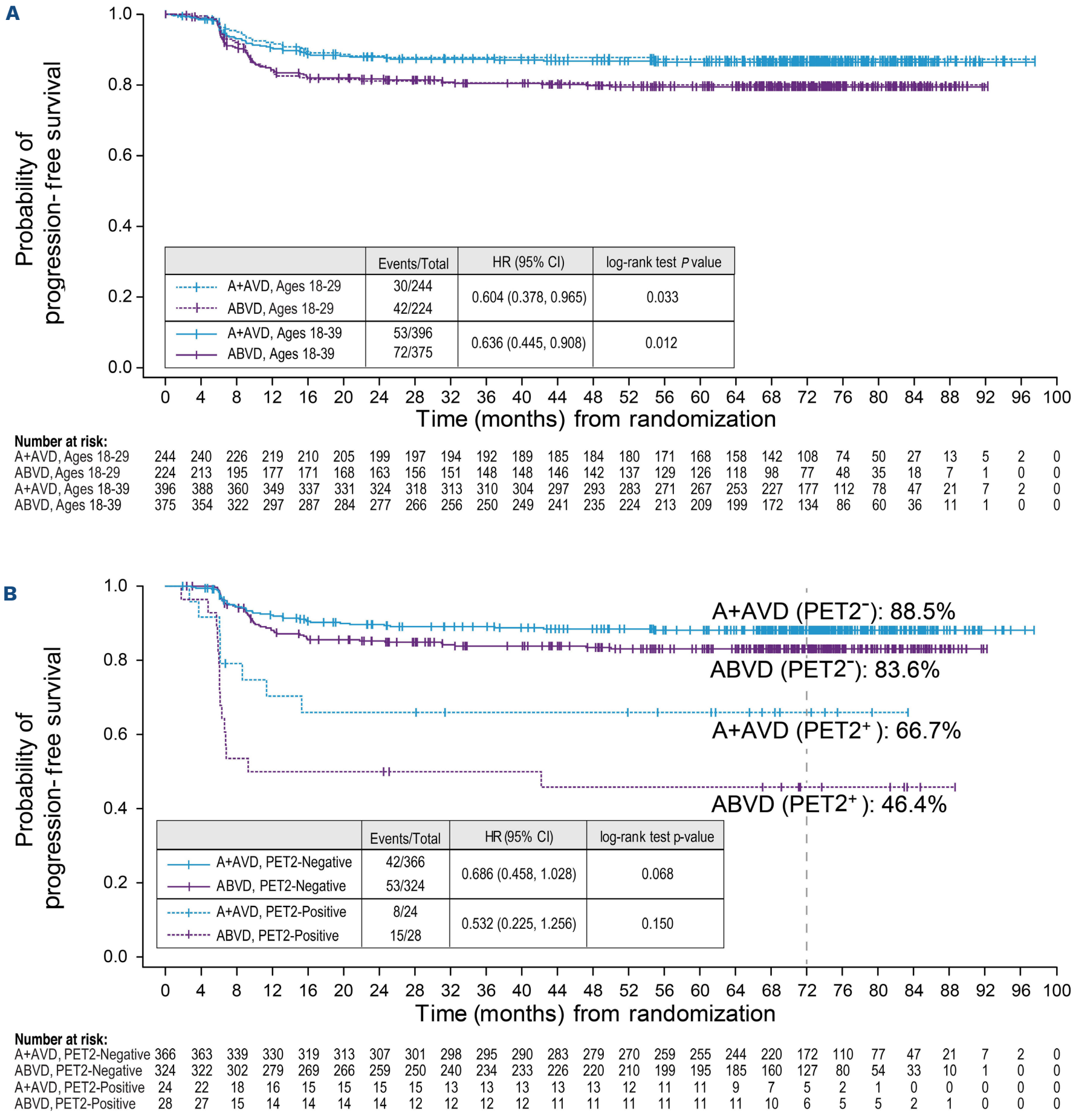


**Figure 1. Progression-free survival per investigator in adolescent and young adult patients in ECHELON-1.** (A) Progression-free survival (PFS) per investigator by treatment group in patients aged 18-29 years and 18-39 years. (B) PFS per investigator by treatment group and PET2 status in patients aged 18-39 years. Median PFS follow-up was 71.3 months (range 0-97.5) for patients aged 18-29 years and 71.5 months (range 0-97.5) for patients aged 18-39 years. A+AVD: brentuximab vedotin, doxorubicin, vinblastine, and dacarbazine; ABVD: doxorubicin, bleomycin, vinblastine, and dacarbazine; AYA: adolescent and young adult; CI: Confidence Interval; HR: Hazard Ratio; PET2: positron emission tomography scan conducted after cycle 2.

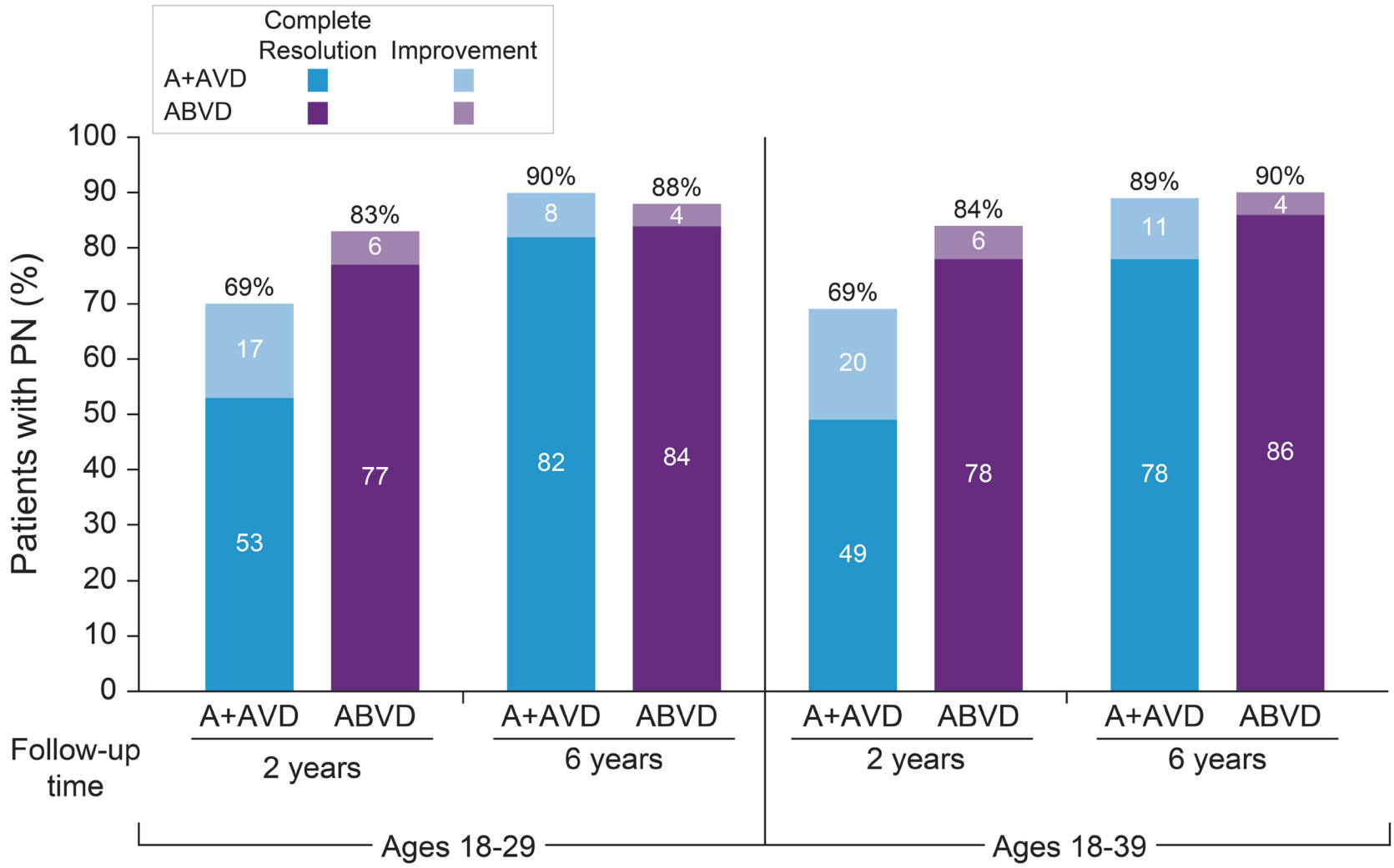


**Figure 2. Peripheral neuropathy resolution and improvement at two years and at six years.** Percentage of patients with peripheral neuropathy with complete resolution or improvement at two years and at six years are shown for the adolescent and young adult (AYA) subgroups 18-29 years and 18-39 years. 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." Percentages are rounded to the nearest integer. A+AVD: brentuximab vedotin, doxorubicin, vinblastine, and dacarbazine; ABVD: doxorubicin, bleomycin, vinblastine, and dacarbazine; CI: Confidence Interval; PN: peripheral neuropathy.

to show OS benefit was the GHSG HD18 trial comparing 4 cycles *versus* 6 or 8 cycles of escalated BEACOPP.[7] With fewer cycles, patients experienced OS benefit, primarily attributed to fewer treatment-related deaths and a lower second malignancy rate.

Other BV-based regimens have been evaluated in pediatric and AYA patients. The HLHR13 trial, which incorporated BV into a standard pediatric chemotherapy regimen, reported a 3-year event-free survival of 97.4% in patients aged ≤18 years with advanced-stage IIB, IIIB, or IV cHL (clinicaltrials.gov identifier: NCT01920932).[11] BV-AVEPC (doxorubicin, vincristine, etoposide, prednisone, and cyclophosphamide) *versus* ABVE-PC (doxorubicin, bleomycin, vincristine, etoposide, prednisone, and cyclophosphamide) were evaluated as front-line therapy for patients aged 2-21 years with high-risk (stage IIB with bulk to IVB) disease in a phase III randomized AHOD1331 trial (clinicaltrials.gov identifier: NCT02166463).[12] BV-AVEPC was approved by the US Food and Drug Administration for this population based on a 59% risk reduction in events (progression, relapse, second neoplasm, or death) *versus* ABVE-PC (HR 0.41; 95% CI: 0.25-0.67; *P*=0.001).[12] Moreover, data from ECHELON-1 have supported inclusion of A+AVD as the control arm *versus* nivolumab + AVD (N+AVD) in the fully enrolled, AYA inclusive (age ≥12 years) SWOG S1826, a phase III NCI Cooperative Group trial in advanced stage (III/IV) cHL (clinicaltrials.gov identifier: NCT03907488).[13] Initial data from S1826 demonstrated strong 3-year PFS with N+AVD but with a short follow-up of 12.1 months; unlike ECHELON-1, OS superiority has not been reached. Furthermore, initial data suggests that N+AVD may perform best for patients aged ≥60 years; this plus data from HOLISTIC suggests the potential benefit of tailoring future treatment approaches based on age.[14]

ECHELON-1, S1826, and AHOD1331 have demonstrated that bleomycin can be eliminated while maintaining efficacy by adding BV to backbone regimens to reduce chemotherapy-associated AE. Furthermore, SGN35-027 Part B (BV-nivolumab with doxorubicin + dacarbazine) provides strong evidence for additional elimination of vinblastine for front-line advanced-stage cHL, with a high ORR of 95% and CR rate of 89% with median duration of CR of 'not reached' at 18.8 months of follow-up. No FN was observed and rates of grade ≥3 PN were 4%. These data support further evaluation in a phase II randomized trial.[15]

With OS benefit of A+AVD in the AYA subgroup consistent with the overall patient population, this subset analysis

of ECHELON-1 reinforces clinical benefit of A+AVD *versus* ABVD for the treatment of AYA patients aged 18-39 with high-risk cHL. Future trials will continue to harmonize management of AYA cHL patients in efforts to minimize late effects without sacrificing long-term efficacy.

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**Disclosures**

HEC served as a consultant for Gilead Sciences, Abbvie, SERVIER, Daiichi Sankyo, and Bristol-Myers Squibb; was an employee of KIYATEC and has equity ownership in KIYATEC, Seagen Inc., and Pfizer. ASL served on advisory boards for Seagen Inc. and Kite Pharma; and served on a speakers bureau for Research to Practice. NLB received research funding from ADC Therapeutics, Autolus, BMS/Celgene, Forty Seven, Gilead/Kite Pharma, Janssen, Merck, Millennium, Pharmacyclics, Roche/Genentech, and Seagen Inc; and served on an advisory board for ADC Therapeutics, Foresight Diagnostics, Kite, Roche/Genentech, and Seagen Inc. KJS served as a consultant for BMS, Seagen Inc., Janssen, and Abbvie; served on a Steering Committee for BeiGene; received research funding from BMS and institutional research funding from Roche; and served on a Data and Safety Monitoring Committee for Regeneron. PLZ served as a consultant for MSD, EUSA Pharma, and Novartis; served on a speakers bureau for Celltrion, Gilead Sciences, Janssen-Cilag, BMS, Servier, MSD, AstraZeneca, Takeda, Roche, EUSA Pharma, Kyowa Kirin Co., Novartis, Incyte, and Beigene; and served on an advisory board for Secura Bio, Celltrion, Gilead Sciences, Janssen-Cilag, BMS, Servier, Sandoz, MSD, AstraZeneca, Takeda, Roche, EUSA Pharma, Kyowa Kirin Co., Novartis, ADC Therapeutics, Incyte, and Beigene. GPC served on advisory boards for Takeda, Roche, Beigene, ADC Therapeutics, Gilead Sciences, and AstraZeneca; received honoraria from Takeda, Roche, Gilead Sciences, Novartis, BMS, Beigene, ADC Therapeutics, Kyowa Kirin Co., and AstraZeneca; and received research funding from Pfizer, Amgen, Beigene, and BMS. MF and KF are employees of and have equity ownership in Seagen Inc. CD is an employee of Takeda and has equity ownership in Takeda and Seagen Inc. HM is an employee of and has equity ownership in Kite Pharma. DJS and APG have no conflicts of interest to disclose.

**Contributions**

HEC, ASL, NLB, DJS, KJS, PLZ, GPC, MF, HM and APG participated in data collection. KF and CD accessed and verified the data. HEC, MF and APG interpreted the data and drafted the manuscript. All authors reviewed the manuscript, had access to study data, and accept responsibility for the decision to submit for publication.

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**Data-sharing statement**

Deidentified patient-level trial data that underlie the results reported in this publication will be made available upon study completion (current est. January 2026) on a case-by-case basis to researchers who provide a methodologically sound proposal. Additional documentation may also be made available. Data availability will begin after approval of the qualified request and end 30 days after receipt of datasets. All requests can be submitted to CTDR@seagen.com and will be reviewed by an internal review committee. Please note that the data sharing policy of this clinical study's sponsor, Seagen Inc., requires all requests for clinical trial data be reviewed to determine the qualification of the specific request. This policy is available at https://www.seagen.com/healthcare-professionals/clinical-data-requests and is aligned with BIO's Principles on Clinical Trial Data Sharing (available at https://www.bio.org/blogs/principles-clinical-trial-data-sharing-reaffirm-commitment).

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