ORIGINAL ARTICLE

Older patients (aged ≥60 years) with previously untreated advanced-stage classical Hodgkin lymphoma: a detailed analysis from the phase III ECHELON-1 study

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Authors' contributions

Data were collected, and study procedures were overseen, by AME, JMC, AY, SMA, WSK, JR, TF, JT, KJS, YO, AG, CP, MD-D, and AGal. Data were verified by KF, AF-T, RL, HT, and AGal, analyzed by RL, and interpreted by all authors. The manuscript was prepared by all authors with the assistance of a medical writer funded by the sponsor. All authors vouch for completeness and accuracy of the data and had final responsibility for the manuscript content and decision to submit.

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Data sharing statement

The datasets, including the redacted study protocol, redacted statistical analysis plan, and individual participant's data supporting the results reported in this article, will be made available within 3 months from initial request, to researchers who provide a methodologically sound proposal. The data will be provided after its de-identification, in compliance with applicable privacy laws, data protection, and requirements for consent and anonymization.

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ABSTRACT

Effective and tolerable treatments are needed for older patients with classical Hodgkin lymphoma (cHL). We report results for older patients with cHL treated in the large phase III ECHELON-1 study of frontline brentuximab vedotin plus doxorubicin, vinblastine, and dacarbazine (A+AVD) *versus* doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD). Modified progression-free survival (PFS) per independent review facility (IRF) for older *versus* younger patients (aged ≥60 *versus* <60 years) was a prespecified subgroup analysis; as the ECHELON-1 study was not powered for these analyses, reported *P*-values are descriptive. Of 1,334 enrolled patients, 186 (14%) were aged ≥60 years (A+AVD: n=84, ABVD: n=102); results below refer to this age group. Modified PFS per IRF was similar between arms at 24 months (A+AVD: 70.3% [95% confidence interval (CI): 58.4–79.4], ABVD: 71.4% [95% CI: 60.5–79.8], hazard ratio (HR): 1.00 [95% CI: 0.58–1.72], *P*=0.993). After a median follow-up of 60.9 months, 5-year PFS per investigator was 67.1% with A+AVD *versus* 61.6% with ABVD (HR: 0.820 [95% CI: 0.494–1.362], *P*=0.443). Comparing A+AVD *versus* ABVD, grade 3/4 peripheral neuropathy occurred in 18% *versus* 3%; any-grade febrile neutropenia in 37% *versus* 17%; and any-grade pulmonary toxicity in 2% *versus* 13%, respectively, with three (3%) pulmonary toxicity-related deaths with ABVD (none with A+AVD). Altogether, A+AVD showed overall similar efficacy to ABVD with survival rates in both arms comparing favorably to prior series in older patients with advanced-stage cHL. Furthermore, A+AVD was associated with higher neuropathy and neutropenia rates, but lower rates of pulmonary-related toxicity than ABVD.

Clinical trial number

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Keywords

Advanced disease, brentuximab vedotin, Hodgkin lymphoma, older patients, previously untreated.

Introduction

Older patients (aged ≥60 years) account for approximately 20–25% of classical Hodgkin lymphoma (cHL) cases in population-based studies.[2-4] While outcomes for younger patients with cHL have improved significantly in recent decades, similar progress has not been seen for older patients,[5] in particular for those with advanced-stage disease.[3,4,6] This has been attributable to biological disease differences and co-morbidities associated with advanced age resulting in poor chemotherapy tolerance and increased incidence of severe toxicities, including treatment-related deaths.[5,7] Intensive regimens, such as bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPP) are too toxic for older patients and may result in increased treatment-related mortality.[8] In addition, bleomycin, a component of the doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) regimen is associated with a significantly elevated risk of pulmonary toxicity in older patients,[6,9-11] particularly in those aged ≥70 years.[12-14]

Brentuximab vedotin has been evaluated as an alternative treatment approach in older, less fit patients with previously untreated cHL, both as monotherapy[15,16] and in combination regimens.[17-19] Results from these early-phase trials demonstrated tolerability and encouraging efficacy, with objective response rates (ORR) of 98–100% and complete response (CR) rates of 44–87%.[17-19] Sequential therapy in a phase II multicenter study with 2 cycles of brentuximab vedotin followed by 6 cycles of doxorubicin, vinblastine, and dacarbazine (AVD) yielded encouraging results.[20]

There has been a relative paucity of randomized phase III clinical trials in the frontline cHL setting that have included older patients in the contemporary era. In the primary analysis of the phase III ECHELON-1 study performed after a median follow-up of 24.6 months, frontline administration of brentuximab vedotin in combination with AVD (A+AVD) significantly improved the primary endpoint, modified progression-free survival (PFS) per independent review facility (IRF), compared with ABVD (hazard ratio [HR]: 0.77 [95% confidence interval (CI): 0.60–0.98], *P*=0.035).[21] Exploratory 3- and 5-year analyses reported continued provision of per-investigator PFS benefits for A+AVD compared with ABVD.[22,23] Here, we report the results of pre-specified analyses and *post hoc* analyses with extended follow-up of the efficacy and safety of A+AVD *versus* ABVD in 186 older cHL patients aged ≥60 years.

Methods

Study design and assessments

The study design and patient population for the open-label, global, randomized, phase III ECHELON-1 study have been described previously.[21] Briefly, patients aged ≥18 years (no upper age limit) with histologically confirmed, advanced (Ann Arbor stage III/IV) cHL who had received no prior systemic chemotherapy or radiotherapy were randomized 1:1 to receive A+AVD (brentuximab vedotin 1.2 mg/kg, doxorubicin 25 mg/m^2, vinblastine 6 mg/m^2, and dacarbazine 375 mg/m^2) or ABVD (doxorubicin 25 mg/m^2, bleomycin 10 units/m^2, vinblastine 6 mg/m^2, and dacarbazine 375 mg/m^2) intravenously on days 1 and 15 of each 28-day cycle for up to 6 cycles. Dose reductions and modifications for brentuximab vedotin, including for the management of peripheral neuropathy (PN), have been described previously.[21]

Patients were assessed for response to study treatment per IRF in accordance with the 2007 Revised Response Criteria for Malignant Lymphoma.[24] Computed tomography scans were performed at screening, at the end of cycle 2, after administration of the last dose of frontline therapy, and during follow-up (every 3 months in the first year, and every 6 months thereafter). PET scans were performed at screening, the end of cycle 2, and the end of treatment. Adverse events (AE) were graded according to the National Cancer Institute Common Terminology Criteria for AE version 4.03.

ECHELON-1 was conducted in accordance with regulatory requirements; the protocol was approved by the institutional review boards and ethics committees at each registered site. Written informed consent per the local ethics committee was mandatory before enrollment. This study was conducted according to the guideline of the International Conference on Harmonization Good Clinical Practice.

Endpoints and analyses

The primary endpoint for ECHELON-1 was modified PFS per IRF, defined as the time to progression, death, or evidence of non-complete response per IRF (Deauville score ≥3) after completion of frontline therapy, followed by subsequent anticancer therapy (chemotherapy and/or radiotherapy). Overall survival (OS) was defined as the time from randomization to death from any cause and was the key secondary endpoint.

Here, we report a pre-specified subgroup analysis of modified PFS per IRF in older patients (defined as ≥60 years of age), as well as exploratory analyses, including PFS per investigator assessment (the time from randomization to relapse/progression or death) and safety. Patient subgroups for efficacy and safety analyses were derived from the intention-to-treat (all randomized patients enrolled in ECHELON-1) and safety (all patients who received

at least one dose of trial drug) populations, respectively. Following the primary analysis, the protocol did not require investigators to submit further information to the IRF, thus extended follow-up for analysis of modified PFS or PFS by IRF was not conducted. Modified PFS and PFS were summarized using Kaplan-Meier methodology. ECHELON-1 was not powered for age-based subgroup analyses; reported *P*-values are descriptive and without multiplicity adjustment.

Results

Patients

As reported previously, 1,334 patients were included in the intention-to-treat population;[21] of whom 186/1334 (14%; A+AVD: n=84, ABVD: n=102) were aged ≥60 years (A+AVD arm: median age 68 years [range: 60–82], ABVD arm: median age 66 years [range: 60–83]) and were included in these sub-analyses. Patient demographics and disease characteristics were well balanced across the treatment arms in both older and younger patients. Within both arms, older patients tended to have a poorer Eastern Cooperative Oncology performance status than younger patients (Table 1).

Efficacy in older patients

At the time of the primary analysis median follow-up for older patients was 25 months (range: 24.2–25.8). Modified PFS per IRF was similar between treatment arms at 24 months (A+AVD: 70.3% [95% CI: 58.4–79.4], ABVD: 71.4% [95% CI: 60.5–79.8], HR: 1.00 [95% CI: 0.58–1.72], *P*=0.993) (Figure 1A, Table 2). At the end of randomized treatment, the CR rate per IRF in older patients was 61% in both arms (difference [A+AVD-ABVD]: -0.1% [95% CI: -14.5–14.3]) (Table S1).

After a median of 60.9 months' (95% CI: 60.6–61.7) follow-up, 5-year PFS per investigator for older HL patients treated on ECHELON-1 was 67.1% (95% CI: 55.1–76.5) with A+AVD *versus* 61.6% (95% CI: 50.9–70.7) with ABVD (HR: 0.820 [95% CI: 0.494–1.362], *P*=0.443) (Figure 1B; Table 2). Among younger patients, 5-year PFS per investigator was 84.3% (95% CI: 81.0–87.1) and 77.8% (95% CI: 74.0–81.1), respectively (HR: 0.665 [95% CI: 0.51–0.88], *P*=0.003) (Figure S1; Table 2).

For older patients, the per investigator PFS was similar in both arms in patients with stage III disease (HR: 1.051 [95% CI: 0.42–2.66], *P*=0.917) or stage IV disease (HR: 0.722 [95% CI: 0.39–1.33], *P*=0.291) (Table 2). In exploratory analyses by interim positron emission tomography scan status after two cycles (PET2), 5-year PFS per investigator for older HL patients in the A+AVD *versus* ABVD arm was 71.9% *versus* 64.9% in PET2-negative patients (HR: 0.720 [95% CI 0.40–1.29], *P*=0.268), and 40.0% versus 25.0% in PET2-

positive patients (HR: 0.923 [95% CI 0.23–3.72], *P*=0.910); however, patient numbers were low in the PET2-positive aged ≥60 years subgroup in the A+AVD arm (n=5) and the ABVD arm (n=8) (Table S2). In both arms for both older and younger HL patients, PFS rates were higher in PET2-negative *versus* PET2-positive patients within each study arm (Table S2).

Per protocol, OS was assessed at the time of the primary analysis (median 28 months' follow-up) and final analysis will be performed once 112 events have occurred in the entire study. Among older patients, 15 patients in the A+AVD arm and 17 in the ABVD arm have died as of the April 20, 2017 data cut. Data on salvage therapy are not available.

Safety

A total of 181 older patients were evaluable for safety (A+AVD: n=83, ABVD: n=98). Older patients received a median of 6 treatment cycles across both treatment arms. In the A+AVD arm, 80% of older patients required ≥1 dose modification of brentuximab vedotin: dose reduction, 31%; dose held, 5%; dose delayed, 61%; brentuximab vedotin discontinued, 20%. The mean relative dose intensity (RDI) in older patients for brentuximab vedotin was 92%; RDI in the A+AVD *versus* ABVD arms for doxorubicin were 97% *versus* 97%; vinblastine 93% *versus* 93%; and dacarbazine 98% *versus* 96% (Table S3). In the ABVD arm, 71% of older patients required ≥1 dose modification of bleomycin: dose reduction, 9%; dose held, 4%; dose interrupted, 1%; dose delayed, 49%; bleomycin discontinued, 28%. The mean RDI for bleomycin was 88.7% (Table S3).

Overall, the incidences of grade ≥3 treatment-emergent AE were higher in older patients compared with younger patients (Table 3). Within both age groups, there was a higher incidence of any-grade pulmonary-related events in the ABVD arm compared with A+AVD. In older patients, a total of eight deaths occurred on-study (within 30 days of last dose of frontline treatment), which yielded a treatment-related mortality rate of 4.4% (8/181; 3/83 [3.6%] in the A+AVD arm and 5/98 [5.1%] in the ABVD arm). Of these eight deaths, three occurred in the A+AVD arm (due to hemophagocytic lymphohistiocytosis, multiple organ dysfunction syndrome, and myocardial infarction [each, n=1]), none of which was associated with pulmonary toxicity (Table S4). The remaining five deaths occurred in the ABVD arm (due to pneumonia [n=2], interstitial lung disease [n=1], respiratory disorder [n=1], and cardiac arrest [n=1]). Treatment-related pulmonary-related toxicity was associated with three of these five deaths in the ABVD arm, occurring in patients aged 78, 80, and 83 years, and could not be ruled out as having a causal relationship with the other two deaths.

The incidence of grade ≥3 neutropenia was higher in the A+AVD arm compared with the ABVD arm in older patients (70% *vs.* 59%). The incidence of any-grade febrile neutropenia (FN) was also higher in the A+AVD arm in older (37% *vs.* 17%) compared with the ABVD arm, which was higher in both arms compared with younger patients (17% *vs.* 6%) (Table 3).

In the A+AVD arm, the use of granulocyte colony-stimulating factor (G-CSF) primary prophylaxis (PP), given per institutional guidelines, was associated with a lower incidence of neutropenia (40% with PP *vs.* 78% without PP) and FN (30% with PP *vs.* 38% without PP) in older patients (Table 4). The incidence of any-grade PN was higher in the A+AVD arm compared with ABVD in both older (65% *vs.* 43%) and younger patients (67% *vs.* 43%) (Table 5). Furthermore, the rate of severe grade 3/4 PN was higher in older patients who received A+AVD arm compared with ABVD (18% *vs.* 3%, respectively). Rates of resolution or improvement in PN appeared similar in older cHL patients treated with A+AVD and ABVD (80% *vs.* 83%, respectively). In older patients, 24 and 12 patients had residual PN, which was grade 1 (n=14 and n=6), grade 2 (n=7 and n=4), and grade 3 (n=3 and n=2) in severity in the A+AVD and ABVD arms, respectively.

Discussion

Outcomes for older patients with cHL, particularly those with advanced disease, have historically been poor compared with younger patients.[3-5,7] We report here one of the largest prospective, randomized clinical trials in cHL completed in the contemporary era that have included and analyzed the outcomes of older patients. Among older patients ≥60 years treated in ECHELON-1, we report that modified PFS per IRF was statistically similar overall for patients treated with A+AVD *versus* ABVD, at 2 years being ~70% in both arms. After a median follow-up of ~5 years, A+AVD demonstrated an apparent treatment benefit, although the numerical improvement in PFS over ABVD was not statistically significant. A+AVD was associated with more frequent neuropathy and FN, but less frequent pulmonary toxicity than ABVD. Additionally, older cHL patients had higher rates of FN and neuropathy compared with younger patients treated in ECHELON-1. In interpreting these observations, several factors should be considered.

As older adults may often have multiple comorbidities that pose challenges to the use of traditional multi-agent treatment options, there is a need to identify tolerable and effective treatment regimens. This may reflect improvements in supportive care as well as patient selection. Several recent phase II studies have assessed the efficacy of multiple brentuximab vedotin-based regimens in the frontline cHL setting in older patients. In a phase II study, a sequential administration approach was assessed, in which patients with unfavourable stage II (IIB, IIAX, or IIBX) to stage IV disease received two lead-in doses of single-agent brentuximab vedotin (1.8 mg/kg once every 3 weeks), followed by 6 cycles of AVD. Patients who responded then received four consolidative doses of brentuximab vedotin.[20] This regimen was well tolerated, with lower rates of grade ≥3 neutropenia (44%) and peripheral sensory neuropathy (4%) compared with those seen in older patients in the

A+AVD arm in ECHELON-1, suggesting potentially better tolerability of sequential treatment.[20] An ORR of 95% (CR: 93%) and 2-year PFS and OS rates of 84% and 93%, respectively, were also reported.[20] Furthermore, survival rates varied based on patient fitness in this study with superior PFS and OS being observed among fit older cHL patients with lower Cumulative Illness Rating Scale-Geriatric co-morbidity scores and those without loss of instrumental activities of daily living, the latter which persisted on multivariate analyses. Unfortunately, baseline or prospective geriatric assessments were not performed in ECHELON-1.

Brentuximab vedotin has also been assessed as monotherapy and in combination with bendamustine, dacarbazine or nivolumab.[15,17,25,26] Importantly, patients enrolled in this study were ineligible for frontline conventional chemotherapy combinations (via investigator's judgement). Initial assessment of brentuximab vedotin monotherapy demonstrated promising efficacy with 92% of patients (median age 78 years) achieving an ORR (CR: 73%).[15] The combinations of brentuximab vedotin with dacarbazine, bendamustine or nivolumab achieved 100% ORR rates with each regimen (CR rates 62%, 88% and 72%, respectively).[17,27] Enrolment was discontinued with the bendamustine combination due to 65% of patients experiencing serious AE.[17] Updated analyses with median follow up 59.4 and 58.6 months in brentuximab vedotin monotherapy and dacarbazine and nivolumab combination therapy arms, respectively, showed median PFS 10.5 and 46.8 months, and OS 77.5 and 64.0 months, respectively. Median PFS and OS had not been reached in the nivolumab arm, with median follow up 19.4 months.[26] The authors concluded that brentuximab vedotin plus dacarbazine or nivolumab were reasonable combinations in this more unfit/frail patient population. The nivolumab combination was associated with a higher rate of Grade ≥3 treatment-related adverse events compared with the dacarbazine combination (60% vs 37%), including peripheral neuropathy (35% vs 26%), but a lower rate of serious treatment-related adverse events (5% vs 11%) and treatment discontinuations due to adverse events (30% vs 42%).[26] Another phase 2 study of brentuximab vedotin plus nivolumab in previously untreated older patients (≥60 years) suggested a lower ORR of 64%, including 52% with CR, at an interim analysis, which indicated that the combination was active in this population but did not meet predefined criteria that required a higher level of activity for further enrolment in the trial to proceed.[28]

The overall incidence of treatment-emergent AE in ECHELON-1 was comparable between the A+AVD and ABVD arms. A lower incidence of pulmonary-related toxicity was observed in the A+AVD arm compared with the ABVD arm for both older and younger patients, with this difference being more marked in older patients. In older patients, three out of five on-study deaths in the ABVD arm were associated with pulmonary toxicity compared with none in the A+AVD arm (Table S4), with 28% of patients in the ABVD treatment arm

requiring bleomycin discontinuation. Since this study was initiated, it has been shown that pulmonary toxicity with ABVD can be reduced without reducing efficacy by omitting bleomycin from the regimen after two cycles in PET2-negative patients.[29] The decision over whether to use this risk-adapted approach over A+AVD requires an assessment of the efficacy benefits, safety, and treatment costs for each individual patient. For older patients receiving PET2-adapted therapy, the increased risk of toxicity during the first two cycles of treatment and for PET2-positive patients (who continue on more intensive therapy) must be considered. However, treatment intensification is not recommended for older patients because of poor tolerance of BEACOPP.[30] In the randomized $HD9_{elderly}$ study comparing baseline-BEACOPP regimen with cyclophosphamide, vincristine, procarbazine, prednisone +ABVD (COPP-ABVD), the treatment-related mortality rate among 75 advanced-stage HL patients aged 66–75 years were 21% and 8%, respectively.[8] A modified regimen incorporating brentuximab vedotin, dacarbazine and dexamethasone (BrECADD) in place of bleomycin, vincristine, procarbazine and prednisone (as used in BEACOPP) is being investigated in a Phase 3 trial (HD21; NCT02661503)[31] after a Phase 2 study found that this regimen was associated with a relatively favourable toxicity profile while maintaining a CR rate of 88%.[32]

Microtubule inhibitors, such as the vinca alkaloids (e.g., vinblastine and vincristine) and the monomethyl auristatin E component of brentuximab vedotin are associated with occurrence of PN.[33-35] The incidence of any-grade PN in older patients was higher with A+AVD compared with ABVD (65% *vs.* 43%), especially grade 3/4 PN (18% *vs.* 3%). Severe PN events were also more frequently seen in older *versus* younger cHL patients treated with A+AVD. In the A+AVD arm, approximately four-fifths of older patients with PN experienced improvement or resolution, a rate similar to that observed in the ABVD arm. With longer follow-up, residual PN continues to improve and resolve.[22,36] These findings highlight the importance of appropriate screening, monitoring, and active clinical management of PN in patients treated with A+AVD (including potential dose reductions particularly in older patients who frequently present with multiple comorbidities).

In the current analyses, the rates of neutropenia and FN were higher in the A+AVD arm overall, and moreover, increased in older *versus* younger patients in both the A+AVD and ABVD arms. Although the use of primary prophylaxis with G-CSF was not mandated in ECHELON-1 and the cohort of older patients who received G-CSF primary prophylaxis was small (n=10), post-protocol amendment use of G-CSF primary prophylaxis was associated with reduced rates of neutropenia and FN in patients treated with A+AVD. Similar effects of G-CSF primary prophylaxis on rates of neutropenia and FN were observed in patients treated with A+AVD in the overall ECHELON-1 study population.[37] Consequently, G-CSF primary prophylaxis is recommended for all patients who receive A+AVD.[38] As the optimal

dosing schedule has not been established, G-CSF should be administered with each cycle, starting at Cycle 1, as recommended in the US prescribing information and EU Summary of Product Characteristics.

Taken together, these data showed overall similar efficacy for A+AVD and ABVD in older patients with stage III/IV cHL. A+AVD was associated with increased neuropathy and neutropenia but with less pulmonary-related toxicity compared with ABVD. Altogether, A+AVD represents treatment option (with primary prophylaxis with G-CSF) for selected fit, older patients with cHL overall, and especially for patients in whom pulmonary toxicity is a concern. Moreover, outcomes reported here set a new benchmark for older patients with untreated cHL when treated with A+AVD or ABVD. However, continued study of new therapeutic regimens is needed to improve outcomes and to decrease toxicity for older cHL patients. This includes continued examination of PET response-adapted strategies, which may be prognostic in brentuximab vedotin-based treatment for older cHL patients,[20,22] as well as analysis of timing of brentuximab vedotin relative to chemotherapy (i.e., sequential *vs.* concurrent), integration of other targeted therapeutic agents (e.g., NCT03907488), and via the incorporation of objective geriatric assessments for prediction of tolerable and individualized therapy.

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Tables

Table 1. Baseline characteristics.

	Patients aged ≥60 years			Patients aged <60 years			ITT population (all ages)[39]		
	A+AVD (n=84)	**ABVD (n=102)**	**Total (n=186)**	**A+AVD (n=580)**	**ABVD (n=568)**	**Total (n=1,148)**	**A+AVD (n=664)**	**ABVD (n=670)**	**Total (N=1,334)**
Median age, years (range)	68 (60–82)	66 (60–83)	67 (60–83)	33 (18–59)	33 (18–59)	33 (18–59)	35 (18–82)	37 (18–83)	36 (18–83)
Male, n (%)	55 (65)	64 (63)	119 (64)	323 (56)	334 (59)	657 (57)	378 (57)	398 (59)	776 (58)
White, n (%)	76 (90)	82 (80)	158 (85)	484 (83)	472 (83)	956 (83)	560 (84)	554 (83)	1114 (84)
Ann Arbor stage, n (%)*									
III	31 (37)	34 (34)	65 (35)	206 (36)	212 (37)	418 (36)	237 (36)	246 (37)	483 (36)
IV	51 (61)	67 (66)	118 (64)	374 (64)	354 (62)	728 (63)	425 (64)	421 (63)	846 (64)
ECOG PS score, n (%)†									
0	30 (36)	36 (36)	66 (36)	346 (60)	342 (60)	688 (60)	376 (57)	378 (57)	754 (57)
1	44 (52)	55 (54)	99 (54)	216 (37)	208 (37)	424 (37)	260 (39)	263 (39)	523 (39)
2	10 (12)	10 (10)	20 (11)	18 (3)	17 (3)	35 (3)	28 (4)	27 (4)	55 (4)

Abbreviations: A+AVD: brentuximab vedotin plus doxorubicin, vinblastine, and dacarbazine; ABVD: doxorubicin, bleomycin, vinblastine, and dacarbazine; ECOG PS: Eastern Cooperative Oncology Group performance status; ITT: intention-to-treat. *Ann Arbor stage at initial diagnosis was not applicable or missing for four patients; one patient had Ann Arbor stage II disease (major protocol violation). †ECOG PS score was not obtained or missing for two patients.

Table 2. Summary of modified progression-free survival per independent review facility and per investigator.

	Aged ≥60 years (n=186)		Aged ≥60 years with stage III disease (n=65)*		Aged ≥60 years with stage IV disease (n=118)*		Aged <60 years (n=1,148)		ITT population (N=1,334)	
	A+AVD (n=84)	**ABVD (n=102)**	**A+AVD (n=31)**	**ABVD (n=34)**	**A+AVD (n=51)**	**ABVD (n=67)**	**A+AVD (n=580)**	**ABVD (n=568)**	**A+AVD (n=664)**	**ABVD (n=670)**
24-month modified PFS[†] per IRF, % (95% CI)[21]	70.3 (58.4–79.4)	71.4 (60.5–79.8)	67.7 (44.9–82.6)	80.9 (66.2–90.9)	71.3 (56.3–81.9)	66.1 (51.8–77.1)	83.7 (80.2–86.6)	78.2 (74.4–81.6)	82.1 (78.8–85.0)	77.2 (73.7–80.4)
24-month PFS[‡] per INV, % (95% CI)	74.4 (62.2–82.7)	70.8 (60.6–78.8)	74.8 (54.2–87.1)	85.3 (68.2–93.6)	74.1 (59.6–84.1)	62.7 (49.5–73.5)	86.5 (83.4–89.1)	80.4 (76.8–83.5)	84.5 (81.4–87.1)	78.3 (74.9–81.4)
60-month PFS[‡] per INV, % (95% CI)	67.1 (55.1–76.5)	61.6 (50.9–70.7)	70.1 (48.7–83.9)	69.9 (51.3–82.6)	65.1 (49.9–76.8)	57.0 (43.5–68.5)	84.3 (81.0–87.1)	77.8 (74.0–81.1)	80.7 (77.1–83.8)	73.1 (69.0–76.7)

Abbreviations: A+AVD: brentuximab vedotin plus doxorubicin, vinblastine, and dacarbazine; ABVD: doxorubicin, bleomycin, vinblastine, and dacarbazine; CI: confidence interval; INV: investigator; IRF: independent review facility; ITT: intention-to-treat; PFS: progression-free survival. *Three patients aged ≥60 years were excluded from analysis by disease stage due to missing data (n=2) or stage II disease (n=1). [†]2-year modified PFS per IRF based on the primary analysis. [‡]2- and 5-year PFS per INV based on a median of 60.9 months' extended follow-up in patients aged ≥60 years and 60.8 months in patients aged <60 years.

Table 3. Safety summary.

	Patients aged ≥60 years evaluable for safety* (n=181)		Patients aged <60 years evaluable for safety* (n=1,140)		Safety population*,[39] (N=1,321)	
	A+AVD (n=83)	**ABVD (n=98)**	**A+AVD (n=579)**	**ABVD (n=561)**	**A+AVD (n=662)**	**ABVD (n=659)**
Grade ≥3 AE, n (%)	73 (88)	78 (80)	476 (82)	356 (63)	549 (83)	434 (66)
On-study deaths,[†] n (%)	3 (4)	5 (5)	6 (1)	8 (1)	9 (1)	13 (2)
Grade ≥3 neutropenia,[‡] n (%)	58 (70)	58 (59)	372 (64)	259 (46)	430 (65)	317 (48)
Any-grade FN on study, n (%)	31 (37)	17 (17)	97 (17)	35 (6)	128 (19)	52 (8)
Any-grade pulmonary AE, n (%)	2 (2)	13 (13)	10 (2)	31 (6)	12 (2)	44 (7)

Abbreviations: A+AVD: brentuximab vedotin plus doxorubicin, vinblastine, and dacarbazine; ABVD: doxorubicin, bleomycin, vinblastine, and dacarbazine; AE: adverse events; FN: febrile neutropenia.

*Received ≥1 dose of study therapy.

[†]Within 30 days of the last dose of frontline treatment.

[‡]Neutropenia includes preferred terms of 'neutropenia' and 'neutrophil count decreased'.

Table 4. Safety profile according to receipt of granulocyte colony-stimulating factor primary prophylaxis during days 1–5 of cycle 1.

	Patients aged ≥60 years evaluable for safety* (n=181)				Patients aged <60 years evaluable for safety* (n=1,140)			
	A+AVD (n=83)		ABVD (n=98)		A+AVD (n=579)		ABVD (n=561)	
G-CSF received†	**Yes (n=10)**	**No (n=73)**	**Yes (n=9)**	**No (n=89)**	**Yes (n=73)**	**No (n=506)**	**Yes (n=34)**	**No (n=527)**
Any-grade neutropenia, n (%)	4 (40)	57 (78)	1 (11)	64 (72)	25 (34)	368 (73)	8 (24)	288 (55)
FN in cycle 1, n (%)	1 (10)	20 (27)	2 (22)	8 (9)	0	41 (8)	0	16 (3)
Any-grade FN on study, n (%)	3 (30)	28 (38)	2 (22)	15 (17)	6 (8)	91 (18)	1 (3)	34 (6)
Infections and Infestations System Organ Class, n (%)	8 (80)	43 (59)	5 (56)	60 (67)	31 (42)	279 (55)	14 (41)	252 (48)
Any SAE on study, n (%)	5 (50)	53 (73)	2 (22)	44 (49)	22 (30)	204 (40)	5 (15)	127 (24)

Abbreviations: A+AVD: brentuximab vedotin plus doxorubicin, vinblastine, and dacarbazine; ABVD: doxorubicin, bleomycin, vinblastine, and dacarbazine; FN: febrile neutropenia; G-CSF: granulocyte colony-stimulating factor; SAE: serious adverse event. *Received ≥1 dose of study therapy. †G-CSF was given per institutional practice.

Table 5. Peripheral neuropathy incidence and resolution.

	Patients aged ≥60 years evaluable for safety* (n=181)		Patients aged <60 years evaluable for safety* (n=1,140)	
	A+AVD (n=83)	ABVD (n=98)	A+AVD (n=579)	ABVD (n=561)
Any-grade PN, n/N (%)	54/83 (65)	42/98 (43)	389/579 (67)	244/561 (43)
Grade 1 PN, n/N (%)	23/83 (28)	26/98 (27)	219/579 (38)	192/561 (34)
Grade 2 PN, n/N (%)	16/83 (19)	13/98 (13)	114/579 (20)	44/561 (8)
Grade 3/4 PN,† n/N (%)	15/83 (18)	3/98 (3)	56/579 (9)	8/561 (1)
Patients with PN and complete resolution/improvement, n/N (%)	43/54 (80)	35/42 (83)	332/389 (85)	210/244 (86)
PN complete resolution, n/N (%)	30/54 (56)	30/42 (71)	286/389 (74)	197/244 (81)
PN improvement, n/N (%)	13/54 (24)	5/42 (12)	46/389 (12)	13/244 (5)

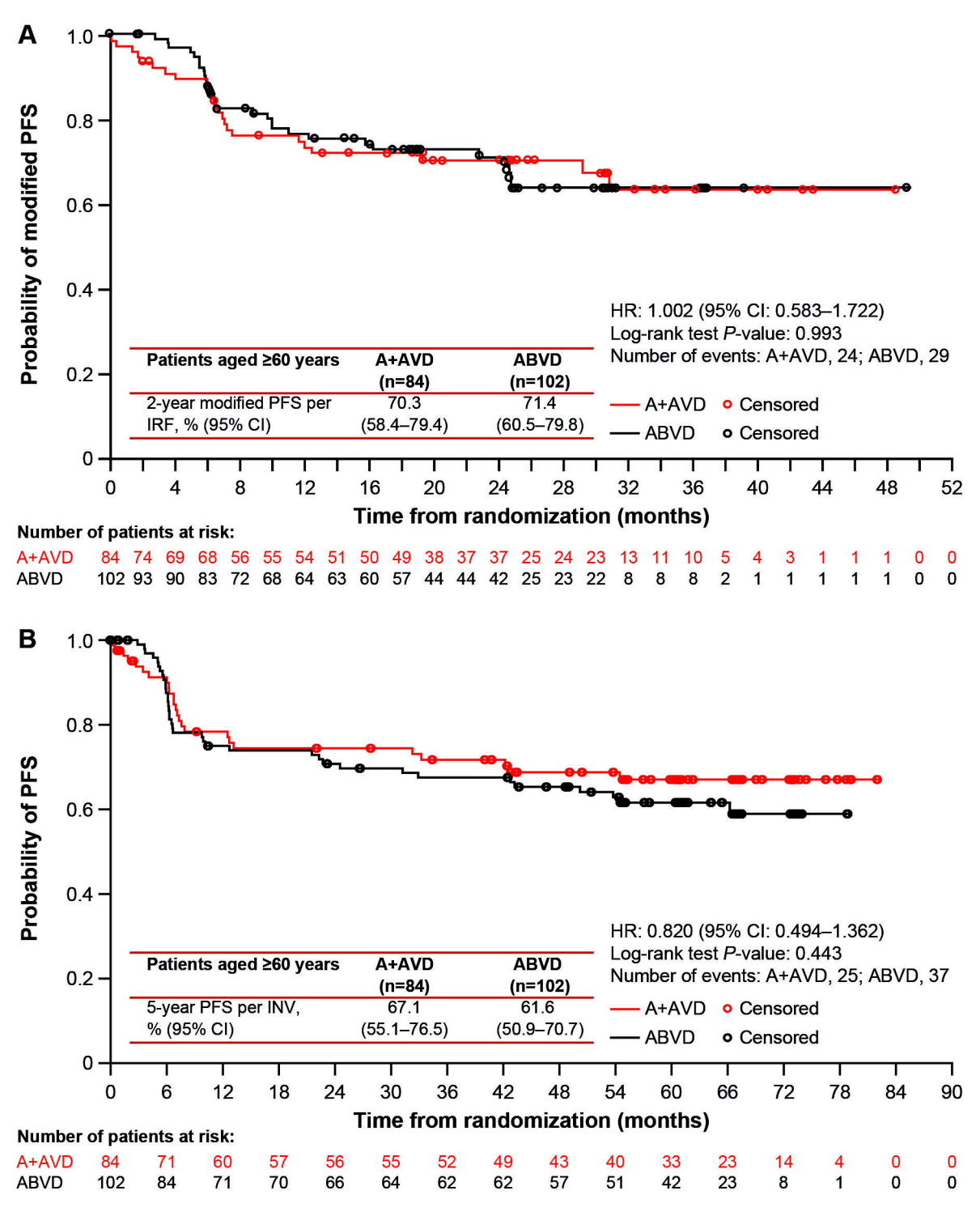
Abbreviations: A+AVD: brentuximab vedotin plus doxorubicin, vinblastine, and dacarbazine; ABVD: doxorubicin, bleomycin, vinblastine, and dacarbazine; PN: peripheral neuropathy.

*Received ≥1 dose of study therapy. †Among all patients evaluable for safety (N=1,321), only one case of grade 4 PN was reported, and this event occurred in a patient aged <60 years in the A+AVD arm.

Figure legends

Figure 1. Progression-free survival (PFS) in patients aged ≥60 years: modified PFS per independent review facility after a median follow-up of 25 months (A); PFS per investigator after a median follow-up of 60.9 months (B).

Abbreviations: A+AVD: brentuximab vedotin plus doxorubicin, vinblastine, and dacarbazine; ABVD: doxorubicin, bleomycin, vinblastine, and dacarbazine; CI: confidence interval; HR: hazard ratio; INV: investigator; IRF: independent review facility; PFS: progression-free survival.


A
Probability of modified PFS
1.0
0.8
0.6
0.4
0.2
0
Patients aged ≥60 years
A+AVD (n=84)
ABVD (n=102)
2-year modified PFS per IRF, % (95% CI)
70.3 (58.4–79.4)
71.4 (60.5–79.8)
HR: 1.002 (95% CI: 0.583–1.722)
Log-rank test P-value: 0.993
Number of events: A+AVD, 24; ABVD, 29
A+AVD Censored
ABVD Censored
0 4 8 12 16 20 24 28 32 36 40 44 48 52
Time from randomization (months)
Number of patients at risk:
A+AVD 84 74 69 68 56 55 54 51 50 49 38 37 37 25 24 23 13 11 10 5 4 3 1 1 1 0 0
ABVD 102 93 90 83 72 68 64 63 60 57 44 44 42 25 23 22 8 8 8 2 1 1 1 1 1 0 0
B
Probability of PFS
1.0
0.8
0.6
0.4
0.2
0
Patients aged ≥60 years
A+AVD (n=84)
ABVD (n=102)
5-year PFS per INV, % (95% CI)
67.1 (55.1–76.5)
61.6 (50.9–70.7)
HR: 0.820 (95% CI: 0.494–1.362)
Log-rank test P-value: 0.443
Number of events: A+AVD, 25; ABVD, 37
A+AVD Censored
ABVD Censored
0 6 12 18 24 30 36 42 48 54 60 66 72 78 84 90
Time from randomization (months)
Number of patients at risk:
A+AVD 84 71 60 57 56 55 52 49 43 40 33 23 14 4 0 0
ABVD 102 84 71 70 66 64 62 62 57 51 42 23 8 1 0 0

Supplementary material

Table S1. Summary of responses.

	Aged ≥60 years (n=186)		Aged <60 years (n=1,148)		ITT population (N=1,334)[1]	
	A+AVD (n=84)	**ABVD (n=102)**	**A+AVD (n=580)**	**ABVD (n=568)**	**A+AVD (n=664)**	**ABVD (n=670)**
CR at end of randomized regimen,* n (%)	51 (61)	62 (61)	437 (75)	410 (72)	488 (73)	472 (70)
Difference (95% CI)[†]	-0.1 (-14.5–14.3)		3.2 (-2.6–9.0)		3.0 (-2.3–8.4)	
ORR at end of randomized regimen,[‡] n (%)	59 (70)	76 (75)	510 (88)	477 (84)	569 (86)	553 (83)
Difference (95% CI)[†]	-4.3 (-18.6–10.2)		4.0 (-1.9–9.7)		3.2 (-2.2–8.6)	
CR at end of frontline regimen,[§] n (%)	50 (60)	62 (61)	438 (76)	412 (73)	488 (73)	474 (71)
Difference (95% CI)[†]	-1.3 (-15.6–13.1)		3.0 (-2.8–8.8)		2.7 (-2.6–8.1)	
CR at cycle 2, n (%)	50 (60)	66 (65)	408 (70)	385 (68)	458 (69)	451 (67)
Difference (95% CI)[†]	-5.2 (-19.5–9.3)		2.6 (-3.3–8.3)		1.7 (-3.7–7.1)	
PET-negative at cycle 2,[¶] n (%)	67 (80)	84 (82)	521 (90)	493 (87)	588 (89)	577 (86)

Difference (95% CI)[†]	-2.6 (-17.0–11.9)		3.0 (-2.8–8.8)		2.4 (-2.9–7.8)	
Deauville score[#]						
≤3 after completion of frontline therapy, n (%)	60 (71)	75 (74)	510 (88)	476 (84)	570 (86)	551 (82)
Difference (95% CI)[†]	-2.1 (-16.5–12.3)		4.1 (-1.7–9.9)		3.6 (-1.8–9.0)	
≤2 after completion of frontline therapy, n (%)	60 (71)	73 (72)	503 (87)	464 (82)	563 (85)	537 (80)
Difference (95% CI)[†]	-0.1 (-14.5–14.3)		5.0 (-0.8–10.8)		4.6 (-0.8–10.0)	

Abbreviations: A+AVD: brentuximab vedotin plus doxorubicin, vinblastine, and dacarbazine; ABVD: doxorubicin, bleomycin, vinblastine, and dacarbazine; CI: confidence intervals; CR: complete response; ITT: intention-to-treat; IRF: independent review facility; ORR: overall response rate; PR: partial response. *CR at the end of the randomized regimen was defined as the proportion of patients with a CR at the end of treatment with either regimen (A+AVD or ABVD), as determined by an IRF assessment. [†]CI were calculated from the exact CI, have not been adjusted for the multiple comparisons, and should not be used for definitive comparisons. [‡]ORR at the end of the randomized regimen was defined as the proportion of patients with a CR or PR at the end of treatment with either regimen (A+AVD or ABVD), as determined by an IRF assessment. [§]CR at the end of frontline therapy was defined as the proportion of patients with a CR after completion of either the randomized regimen (A+AVD or ABVD) or alternate frontline therapy, as determined by an IRF assessment. [¶]PET negativity rate at cycle 2 was defined as the proportion of patients with negative cycle 2 PET results defined as a Deauville score of ≤3 at cycle 2. [#]The Deauville score is a 5-point scale on which higher scores indicate greater uptake of ^{18}F-fluorodeoxyglucose at involved sites on PET. A score of 1 indicates no uptake, a score of 2 indicates uptake at an initial site that is less than or equal to the uptake at the mediastinum, a score of 3 indicates uptake at an initial site that is greater than uptake at the mediastinum but less than or equal to uptake at the liver, a score of 4 indicates uptake at an initial site that is moderately increased as compared with uptake at the liver, and a score of 5 indicates markedly increased uptake at any site or uptake at a new site of disease. The absence of a CR at the end of primary chemotherapy was defined as a Deauville score of 3, 4, or 5.

Table S2. Five-year progression-free survival per investigator in the two treatment arms by PET2 status and age.

60-month PFS* per INV, % (95% CI)	**A+AVD**	**ABVD**	**HR (95% CI) *P*-value**
ITT population	n=664 82.2 (79.0–85.0)	n=670 75.3 (71.7–78.5)	0.681 (0.53–0.87) 0.0017
PET2-negative	n=588 84.9 (81.7–87.6)	n=578 78.9 (75.2–82.1)	0.663 (0.50–0.88) 0.004
PET2-positive	n=47 60.6 (45.0–73.1)	n=58 45.9 (32.7–58.2)	0.702 (0.39–1.26) 0.229
Aged ≥60 years	n=84 67.1 (55.1–76.5)	n=102 61.6 (50.9–70.7)	0.820 (0.49–1.36) 0.443
PET2-negative	n=67 71.9 (59.0–81.3)	n=85 64.9 (53.5–74.2)	0.720 (0.40–1.29) 0.268
PET2-positive	n=5 40.0 (5.2–75.3)	n=8 25.0 (3.7–55.8)	0.923 (0.23–3.72) 0.910
Aged <60 years	n=580 84.3 (81.0–87.1)	n=568 77.8 (74.0–81.1)	0.665 (0.51–0.88) 0.003
PET2-negative	n=521 86.6 (83.3–89.3)	n=493 81.5 (77.7–84.7)	0.675 (0.49–0.93) 0.014
PET2-positive	n=42 63.1 (46.4–75.9)	n=50 49.3 (34.7–62.3)	0.702 (0.37–1.33) 0.274

Abbreviations: A+AVD: brentuximab vedotin plus doxorubicin, vinblastine, and dacarbazine; ABVD: doxorubicin, bleomycin, vinblastine, and dacarbazine; CI: confidence interval; INV: investigator; ITT: intention-to-treat; PET2, positron emission tomography status after cycle 2; PFS: progression-free survival. *5-year PFS per INV based on a median of 60.9 months extended follow-up.

Table S3. Mean relative dose intensity in patients aged ≥60 years.

	Patients aged ≥60 years	
Mean RDI, % (SD)	**A+AVD (n=83)**	**ABVD (n=98)**
Brentuximab vedotin	92.3 (14.0)	NA
Bleomycin	NA	88.7 (21.1)
Doxorubicin	96.6 (7.7)	97.3 (7.1)
Vinblastine	93.3 (13.6)	93.3 (14.8)
Dacarbazine	97.9 (5.4)	95.9 (11.9)

Abbreviations: A+AVD: brentuximab vedotin plus doxorubicin, vinblastine, and dacarbazine; ABVD: doxorubicin, bleomycin, vinblastine, and dacarbazine; NA: not applicable; RDI: relative dose intensity; SD: standard deviation.

Table S4. Cause of death in patients aged ≥60 years.

Age (years)/ gender	Cycle day of last dose	Days from first dose	Days from last dose	Cause of death*	Disease related?†	Treatment related?
A+AVD (n=83)						
On-study deaths‡						
62/F	C1D1	12	12	AE (histiocytosis hematophagic)	Yes	Yes
73/M	C1D15	41	25	AE (multiple organ dysfunction)	No	Yes
79/M	C1D1	3	3	AE (myocardial infarction)	Yes	No
ABVD (n=98)						
On-study deaths‡						
61/M	C5D15	168	19	AE (pneumonia)	No	No
63/M	C6D15	200	25	AE (cardiac arrest)	No	No
78/F	C3D15	109	29	AE (pulmonary toxicity – interstitial lung disease)	No	Yes
80/M	C3D1	83	27	AE (respiratory disorder)	No	Yes
83/F	C5D15	160	21	AE (pneumonia)	Yes	Yes

Abbreviations: A+AVD: brentuximab vedotin plus doxorubicin, vinblastine, and dacarbazine; ABVD: doxorubicin, bleomycin, vinblastine, and dacarbazine; AE: adverse event; C: cycle; D: day; F: female; M: male. *AE are described by their Medical Dictionary for Regulatory Activities (MedDRA) preferred term. †Related to the disease under study or complications thereof. ‡On-study deaths were defined as deaths that occurred within 30 days of the last dose of frontline therapy.

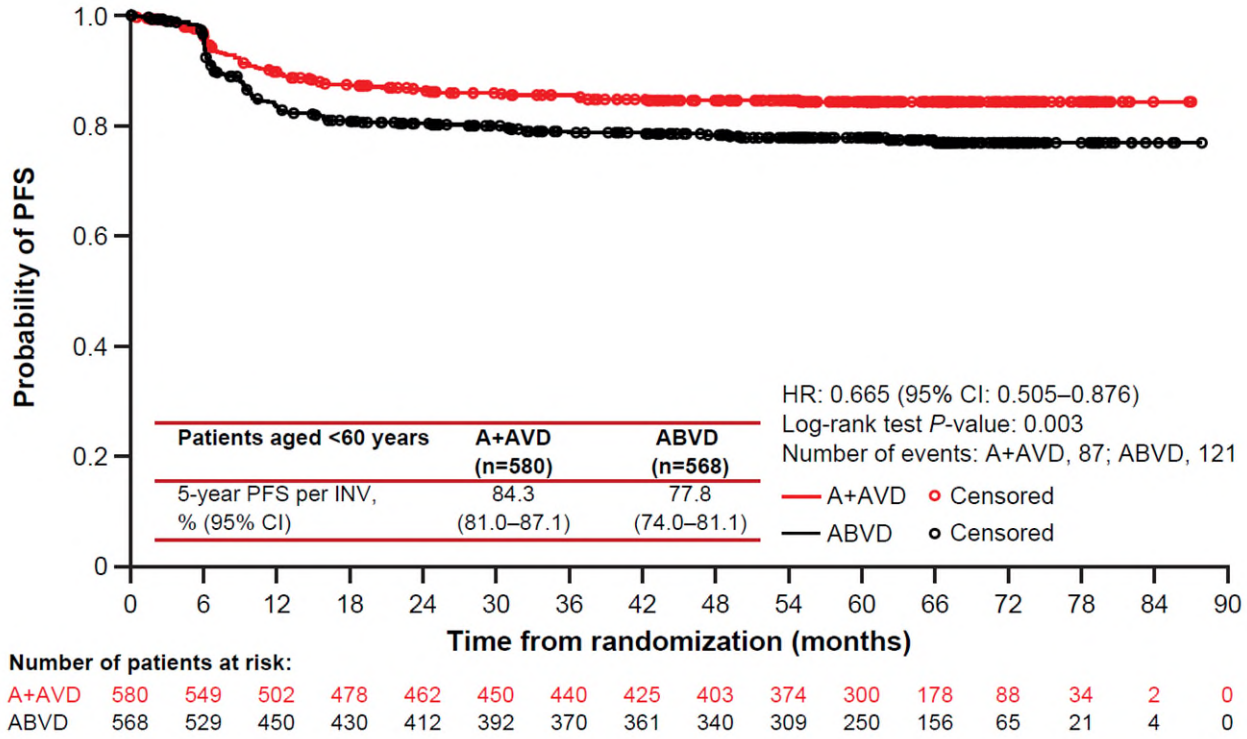
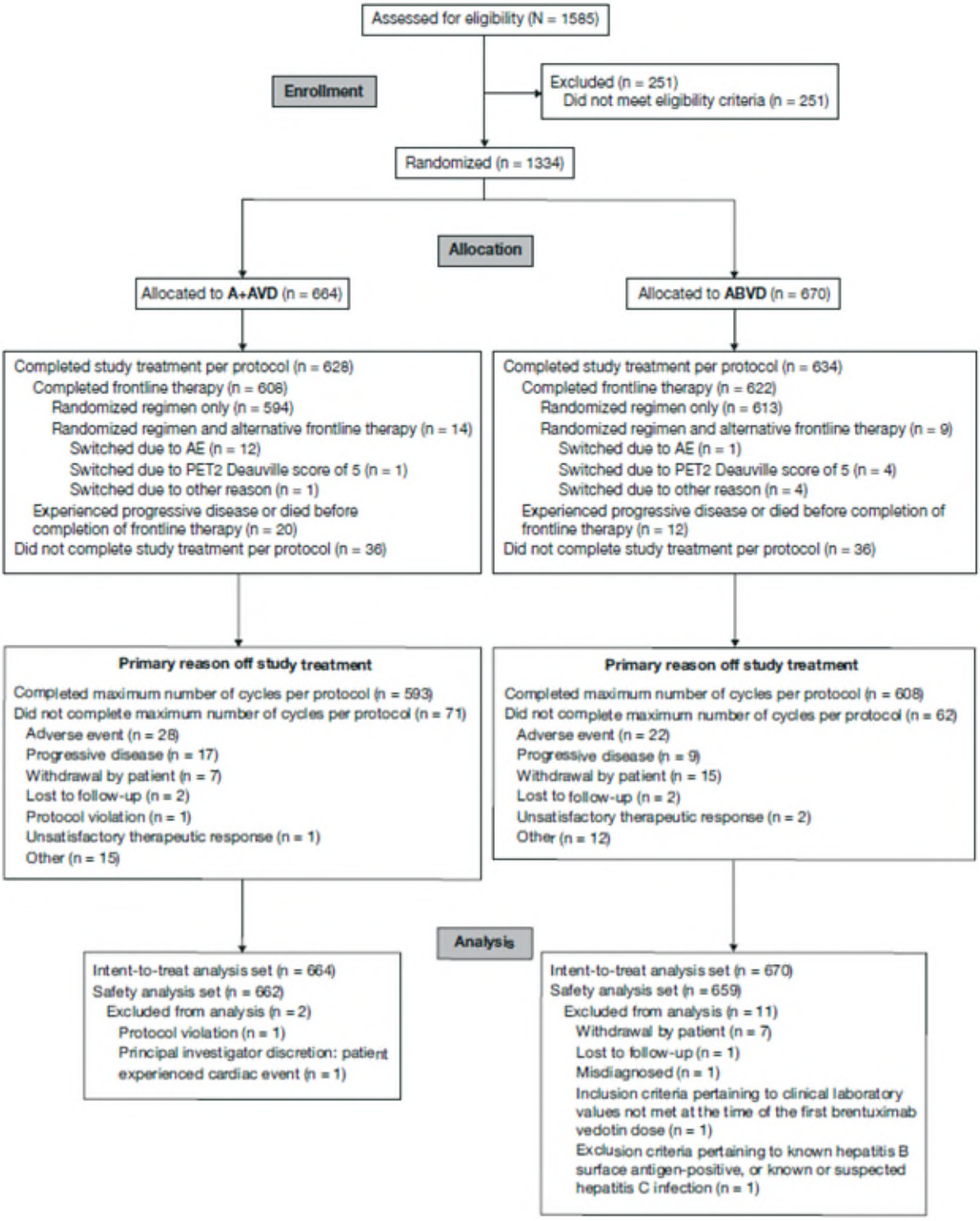


Figure S1. Progression-free survival (PFS) per independent review facility (IRF) in patients aged <60 years.

Abbreviations: A+AVD: brentuximab vedotin plus doxorubicin, vinblastine, and dacarbazine; ABVD: doxorubicin, bleomycin, vinblastine, and dacarbazine; CI: confidence interval; HR: hazard ratio; INV: investigator; IRF: independent review facility; PFS: progression-free survival.



ECHELON-1 CONSORT diagram.

Abbreviations: A+AVD: brentuximab vedotin plus doxorubicin, vinblastine, dacarbazine; ABVD: doxorubicin, bleomycin, vinblastine, dacarbazine; AE: adverse event; PET2: end-of-cycle-2 positron-emission tomography.

References

1. Connors JM, Jurczak W, Straus DJ, Ansell SM, Kim WS, Gallamini A, et al. Brentuximab vedotin with chemotherapy for stage III or IV Hodgkin's lymphoma. N Engl J Med. 2018;378(4):331–344.