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ORIGINAL ARTICLE

Brentuximab Vedotin with Chemotherapy for Stage III or IV Hodgkin's Lymphoma

J.M. Connors, W. Jurczak, D.J. Straus, S.M. Ansell, W.S. Kim, A. Gallamini, A. Younes, S. Alekseev, Á. Illés, M. Picardi, E. Lech-Maranda, Y. Oki, T. Feldman, P. Smolewski, K.J. Savage, N.L. Bartlett, J. Walewski, R. Chen, R. Ramchandren, P.L. Zinzani, D. Cunningham, A. Rosta, N.C. Josephson, E. Song, J. Sachs, R. Liu, H.A. Jolin, D. Huebner, and J. Radford, for the ECHELON-1 Study Group*

ABSTRACT

BACKGROUND

Brentuximab vedotin is an anti-CD30 antibody–drug conjugate that has been approved for relapsed and refractory Hodgkin's lymphoma.

METHODS

We conducted an open-label, multicenter, randomized phase 3 trial involving patients with previously untreated stage III or IV classic Hodgkin's lymphoma, in which 664 were assigned to receive brentuximab vedotin, doxorubicin, vinblastine, and dacarbazine (A+AVD) and 670 were assigned to receive doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD). The primary end point was modified progression-free survival (the time to progression, death, or noncomplete response and use of subsequent anticancer therapy) as adjudicated by an independent review committee. The key secondary end point was overall survival.

RESULTS

At a median follow-up of 24.9 months, 2-year modified progression-free survival rates in the A+AVD and ABVD groups were 82.1% (95% confidence interval [CI], 78.7 to 85.0) and 77.2% (95% CI, 73.7 to 80.4), respectively, a difference of 4.9 percentage points (hazard ratio for an event of progression, death, or modified progression, 0.77; 95% CI, 0.60 to 0.98; P=0.03). There were 28 deaths with A+AVD and 39 with ABVD (hazard ratio for interim overall survival, 0.72 [95% CI, 0.44 to 1.17]; P=0.19). All secondary efficacy end points trended in favor of A+AVD. Neutropenia occurred in 58% of the patients receiving A+AVD and in 45% of those receiving ABVD; in the A+AVD group, the rate of febrile neutropenia was lower among the 83 patients who received primary prophylaxis with granulocyte colony-stimulating factor than among those who did not (11% vs. 21%). Peripheral neuropathy occurred in 67% of patients in the A+AVD group and in 43% of patients in the ABVD group; 67% of patients in the A+AVD group who had peripheral neuropathy had resolution or improvement at the last follow-up visit. Pulmonary toxicity of grade 3 or higher was reported in less than 1% of patients receiving A+AVD and in 3% of those receiving ABVD. Among the deaths that occurred during treatment, 7 of 9 in the A+AVD group were associated with neutropenia and 11 of 13 in the ABVD group were associated with pulmonary-related toxicity.

CONCLUSIONS

A+AVD had superior efficacy to ABVD in the treatment of patients with advanced-stage Hodgkin's lymphoma, with a 4.9 percentage-point lower combined risk of progression, death, or noncomplete response and of subsequent anticancer therapy at 2 years. (Funded by Millennium Pharmaceuticals and Seattle Genetics; ECHELON-1 ClinicalTrials.gov number, NCT01712490; EudraCT number, 2011-005450-60.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Connors at the Department of Medical Oncology, British Columbia Cancer Agency, Vancouver, BC V5Z 4E6, Canada, or at jconnors@bccancer.bc.ca.

*All ECHELON-1 investigators are listed in the Supplementary Appendix, available at NEJM.org.

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Outcomes for patients with advanced-stage Hodgkin's lymphoma have improved dramatically over the past half century.[1] Although regional differences exist, the most commonly used frontline regimen — doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) — has not been modified since its original description in 1975.

Up to 30% of patients with stage III or IV Hodgkin's lymphoma harbor refractory disease or relapse after frontline treatment with ABVD.[2-4] Bleomycin is associated with unpredictable and sometimes fatal pulmonary toxicity and is often dropped from later cycles of chemotherapy owing to pulmonary symptoms.[5,6] Recent studies suggest that response-adapted therapy guided by interim positron-emission tomography (PET) with ^{18}F-fluorodeoxyglucose can provide a more individualized treatment approach, in which treatment intensity is de-escalated or intensified depending on the early response to treatment.[7,8] Efforts are also being made to incorporate new drugs into established backbone regimens to improve efficacy and reduce toxicity.[9]

CD30 is a characteristic surface antigen expressed on Reed–Sternberg cells in classic Hodgkin's lymphoma.[10] Brentuximab vedotin is an antibody–drug conjugate composed of an anti-CD30 monoclonal antibody conjugated by a protease-cleavable linker to the microtubule-disrupting agent monomethyl auristatin E. Brentuximab vedotin has been approved for the treatment of classic Hodgkin's lymphoma after failure of autologous stem-cell transplantation or after two or more multiagent chemotherapy regimens in patients who are not candidates for transplantation. The drug has also been approved as post-transplantation consolidation therapy for patients with Hodgkin's lymphoma who are at increased risk for relapse or progression.[11,12]

A previous phase 1, dose-escalation trial involving patients with advanced Hodgkin's lymphoma evaluated the use of frontline brentuximab vedotin combined with either ABVD or doxorubicin, vinblastine, and dacarbazine (AVD).[13] Brentuximab vedotin plus AVD (A+AVD) had an acceptable side-effect profile and resulted in complete response in 24 of 25 patients (96%). Long-term follow-up showed a 5-year failure-free survival rate of 92% and an overall survival rate of 100% with A+AVD.[14] On the basis of these findings, ECHELON-1, a large, international, open-label, randomized, multicenter, phase 3 trial was conducted to compare A+AVD with ABVD as frontline therapy in patients with stage III or IV classic Hodgkin's lymphoma.

Methods

Trial Design

Patients were randomly assigned in a 1:1 ratio to receive A+AVD (1.2 mg of brentuximab vedotin per kilogram of body weight, 25 mg of doxorubicin per square meter of body-surface area, 6 mg of vinblastine per square meter, and 375 mg of dacarbazine per square meter) or ABVD (25 mg of doxorubicin per square meter, 10 units of bleomycin per square meter, 6 mg of vinblastine per square meter, and 375 mg of dacarbazine per square meter) intravenously on days 1 and 15 of each 28-day cycle for up to 6 cycles. Brentuximab vedotin was administered over 30 minutes, starting within approximately 1 hour after completion of AVD. Dose reductions and modifications are described in Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org. Patients were stratified according to region (Americas vs. Europe vs. Asia) and International Prognostic Score (IPS) risk group (low risk vs. intermediate risk vs. high risk). The IPS ranges from 0 to 7, with a score of 0 or 1 indicating low risk of treatment failure, a score of 2 or 3 intermediate risk, and a score of 4 to 7 high risk (see Table S2 in the Supplementary Appendix).[15] The results of PET conducted at the end of the second 28-day cycle of treatment (hereafter referred to as PET2) guided an optional switch to alternative frontline therapy at the treating physician's discretion for patients with a Deauville score of 5. 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 uptake at an initial site that is less than or equal to the uptake at the mediastinum, a score of 3 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 uptake at an initial site that is moderately increased as compared with the uptake at the liver, and a score of 5 markedly increased uptake at any site or uptake at a new site of disease.[16]

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OVERSIGHT

The ECHELON-1 trial was conducted in accordance with regulatory requirements; the protocol (available at NEJM.org) was approved by institutional review boards and ethics committees at individual sites, and adhered to Good Clinical Practice guidelines (as defined by the International Conference on Harmonisation). A steering committee and an independent data and safety monitoring committee oversaw the conduct of the trial, and all the patients provided written informed consent.

The trial was designed by a committee consisting of six authors plus representatives of the sponsors, Millennium Pharmaceuticals and Seattle Genetics. Data were collected and trial procedures were overseen by trial investigators. Data were verified by the sponsors, analyzed by sponsor statisticians, and interpreted by academic authors and sponsor representatives. The manuscript was prepared by the authors with the assistance of a medical writer funded by the sponsors. All the authors had full access to the data, vouch for the completeness and accuracy of the data and adherence of the trial to the protocol, and had final responsibility for the manuscript content and the decision to submit the manuscript for publication.

PATIENTS

Patients were 18 years of age or older and had histologically confirmed advanced classic Hodgkin's lymphoma (Ann Arbor stage III or IV, as determined on a 4-point scale, with higher stages indicating more widespread disease),[17] according to the World Health Organization classification system.[18] Patients who had not been previously treated with systemic chemotherapy or radiotherapy were eligible. Patients were required to have an Eastern Cooperative Oncology Group performance status of 0, 1, or 2 (on a scale of 0 to 5, with higher scores indicating greater disability)[19]; satisfactory absolute neutrophil counts (≥1500 per cubic millimeter), platelet counts (≥75,000 per cubic millimeter), and hemoglobin levels (≥8 g per deciliter) (with the exception of patients with involvement of the marrow); satisfactory levels of markers of liver function (total bilirubin level, <1.5 times the upper limit of normal [with the exception of patients with Gilbert's syndrome] and alanine aminotransferase or aspartate aminotransferase levels, <3 times the upper limit of normal [with the exception of patients with involvement of the liver]); and satisfactory levels of markers of kidney function (serum creatinine level, <2.0 mg per deciliter [177 μmol per liter]; creatinine clearance or calculated creatinine clearance, >40 ml per minute; or both). Patients with nodular lymphocyte-predominant Hodgkin's lymphoma were ineligible, as were those with peripheral sensory or motor neuropathy, a positive pregnancy test, known cerebral or meningeal disease, any evidence of residual disease from another cancer, diagnosis of another cancer within 3 years before the first dose, or any clinically relevant cardiovascular conditions.

END POINTS

The primary end point was modified progression-free survival, defined as time to disease progression, death, or modified progression (with the latter defined as evidence of noncomplete response after completion of frontline therapy according to review by an independent committee, followed by subsequent anticancer therapy). This end point was chosen specifically to evaluate the effectiveness of the primary chemotherapy and encompasses three possible outcomes, each of which represents a failure of the primary chemotherapy to eliminate Hodgkin's lymphoma: documented progression[20] at any time after initiation of primary chemotherapy, death from any cause, and detection of a response that was less than complete at the end of primary chemotherapy (Deauville score of 3, 4, or 5 on a PET scan), followed by the delivery of subsequent anticancer therapy. The latter outcome was considered to be an event only if noncomplete response was confirmed during review by an independent committee, whose members were unaware of group assignments, and was followed by the delivery of subsequent anticancer treatment that was not specified in the protocol. Additional justifications for, and explanation of, this choice of primary end point are provided in the Supplementary Appendix. Timing of the modified progression event was the date on which the first PET scan was obtained after completion of frontline therapy, showing the absence of complete response. In the absence of disease progression, a switch to an alternative frontline therapy before com-

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pletion of primary chemotherapy with the randomized regimen was not considered to be an event.

The key secondary end point was overall survival, defined as the time from randomization to death from any cause. Other secondary and exploratory end points are described in the protocol.

ASSESSMENTS

Response and progression were evaluated in accordance with the Revised Response Criteria for Malignant Lymphoma.[20] Computed tomographic scans were obtained at screening, at the end of cycle 2, after administration of the last dose of frontline therapy, and during the follow-up period (every 3 months for the first year and every 6 months thereafter). PET scans were obtained at screening, at the end of cycle 2, and at the end of treatment. Safety outcomes were the incidence of adverse events (defined according to the Medical Dictionary for Regulatory Activities [MedDRA], version 19.0, and the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03) and changes in vital signs and laboratory test results.

STATISTICAL ANALYSIS

According to statistical calculations, an estimated 260 modified progression-free survival events would give the trial 90% power to detect a hazard ratio for disease progression, death, or modified progression of 0.67 at a one-sided significance level of 0.025. The trial was powered on the following assumption: a 2-year modified progression-free survival of 81% for patients in the A+AVD group and 73% for patients in the ABVD group. Randomization of approximately 1240 patients was planned to achieve (with 95% probability) 260 modified progression-free survival events. The primary end point was summarized with the use of the Kaplan–Meier method and evaluated with the use of a stratified log-rank test. A stratified Cox regression model was used to estimate the hazard ratio and the 95% confidence interval for the treatment effect. The stratification factors included region and IPS risk group at baseline. The interim analysis for overall survival was to be performed if the result of the primary analysis was statistically significant. The final overall survival analysis will be performed after 112 deaths have occurred. Overall type I error for the overall survival analysis will be controlled with the use of the O'Brien–Fleming method with the Lan–DeMets alpha spending function.

All efficacy evaluations were performed in the intention-to-treat population unless otherwise specified. Safety was analyzed in patients who received at least one dose of the trial drug (the safety population).

RESULTS

PATIENTS

From November 19, 2012, through January 13, 2016, a total of 1334 patients at 218 sites in 21 countries were randomly assigned to receive A+AVD (664 patients) or ABVD (670 patients) (intention-to-treat population) (Fig. S1 in the Supplementary Appendix). Overall, 58% of the patients were men, 64% had stage IV disease, 62% had extranodal involvement at diagnosis, 58% had B symptoms (i.e., weight loss, night sweats, and fever), and the median age was 36 years (34% of patients were ≥45 years of age). Baseline characteristics were generally well balanced between the two groups (Table 1, and Table S3 in the Supplementary Appendix).

EFFICACY

After a median follow-up of 24.9 months (range, 0 to 49.3), the rate of the primary end point of independently determined modified progression-free survival was significantly higher in the A+AVD group than in the ABVD group (2-year modified progression-free survival rate, 82.1% [95% confidence interval {CI}, 78.7 to 85.0] vs. 77.2% [95% CI, 73.7 to 80.4]; hazard ratio for progression, death, or modified progression, 0.77 [95% CI, 0.60 to 0.98]; P=0.03), corresponding to a 23% risk reduction (Fig. 1A). Events of progression, death, or modified progression occurred in 117 patients in the A+AVD group and in 146 patients in the ABVD group; disease progression occurred in 90 and 102 patients, respectively; death from any cause in 18 and 22 patients, respectively, and receipt of subsequent anticancer therapy after failure to achieve a complete response at the completion of frontline therapy (modified progression) in 9 and 22 patients, respectively (Table 2). The majority (71%) of these subsequent anticancer therapies consisted of salvage chemotherapy (7 of 9 patients

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Table 1. Patient Demographic and Clinical Characteristics at Baseline (Intention-to-Treat Population).*

Characteristic	A+AVD (N=664)	ABVD (N=670)	Total (N=1334)
Male sex — no. (%)	378 (57)	398 (59)	776 (58)
Age — yr			
Median	35	37	36
Range	18–82	18–83	18–83
Age categories — no. (%)			
<45 yr	451 (68)	423 (63)	874 (66)
45–59 yr	129 (19)	145 (22)	274 (21)
60–64 yr	24 (4)	40 (6)	64 (5)
≥65 yr	60 (9)	62 (9)	122 (9)
Regions — no. (%)			
Americas	261 (39)	262 (39)	523 (39)
Europe	333 (50)	336 (50)	669 (50)
Asia	70 (11)	72 (11)	142 (11)
Ann Arbor stage at initial diagnosis — no. (%)†			
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, or missing	1 (<1)	3 (<1)	4 (<1)
International Prognostic Score — no. (%)§			
0 or 1	141 (21)	141 (21)	282 (21)
2 or 3	354 (53)	351 (52)	705 (53)
4 to 7	169 (25)	178 (27)	347 (26)
ECOG performance status — no. (%)¶			
0	376 (57)	378 (57)	754 (57)
1	259 (39)	262 (39)	521 (39)
2	28 (4)	26 (4)	54 (4)
Not obtained or missing	1 (<1)	4 (<1)	5 (<1)
Extranodal involvement at diagnosis — no. (%)			
Yes	411 (62)	416 (62)	827 (62)
1 extranodal site	217 (33)	223 (33)	440 (33)
>1 extranodal sites	194 (29)	193 (29)	387 (29)
No	217 (33)	228 (34)	445 (33)
Unknown or missing	36 (5)	26 (4)	62 (5)
Patients with any B symptom — no. (%)‖	399 (60)	381 (57)	780 (58)

* A full description of patient demographics and clinical characteristics at baseline can be found in Table S3 in the Supplementary Appendix. Percentages may not total 100 because of rounding. A+AVD denotes brentuximab vedotin plus doxorubicin, vinblastine, dacarbazine, and ABVD doxorubicin, bleomycin, vinblastine, and dacarbazine.
† The Ann Arbor staging system ranges from I to IV, with higher stages indicating more widespread disease.
‡ Patients in this category had a major protocol violation.
§ The International Prognostic Score ranges from 0 to 7, with higher scores indicating increased risk of treatment failure. Scores of 0 to 1 denote low risk, scores of 2 to 3 intermediate risk, and scores of 4 to 7 high risk.
¶ Values for Eastern Cooperative Oncology Group (ECOG) performance status range from 0 to 5, with higher scores indicating greater disability.
‖ B symptoms consist of night sweats, unexplained fever (temperature >38°C), or loss of more than 10% of body weight.

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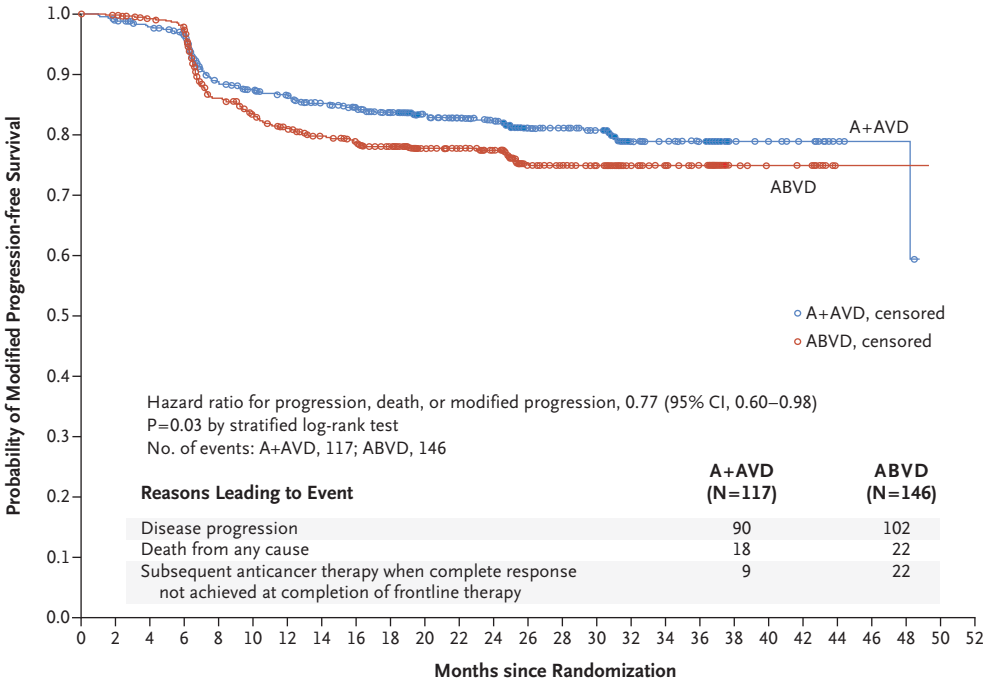
A Modified Progression-free Survival as Assessed by Independent Review Facility



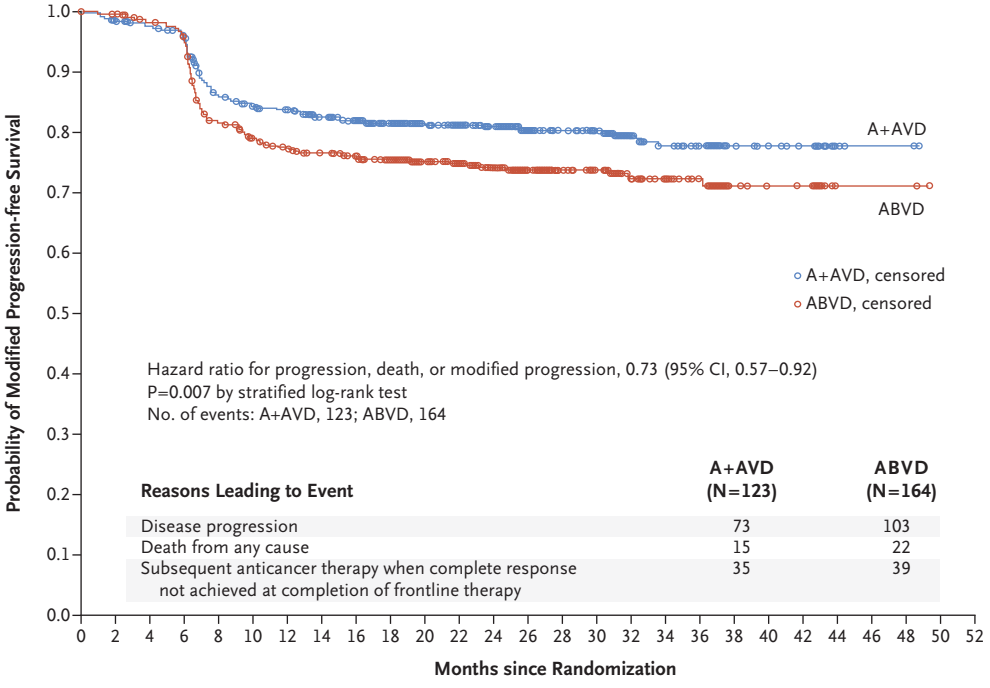
Hazard ratio for progression, death, or modified progression, 0.77 (95% CI, 0.60–0.98)
P=0.03 by stratified log-rank test
No. of events: A+AVD, 117; ABVD, 146

Reasons Leading to Event	A+AVD (N=117)	ABVD (N=146)
Disease progression	90	102
Death from any cause	18	22
Subsequent anticancer therapy when complete response not achieved at completion of frontline therapy	9	22

No. at Risk

A+AVD	664	640	623	606	544	530	516	496	474	447	350	334	311	200	187	174	99	85	77	27	24	21	6	4	4	0	0
ABVD	670	644	626	613	522	496	476	459	439	415	328	308	294	179	168	153	78	68	62	16	13	12	1	1	1	0	0

B Modified Progression-free Survival as Assessed by Investigator



Hazard ratio for progression, death, or modified progression, 0.73 (95% CI, 0.57–0.92)
P=0.007 by stratified log-rank test
No. of events: A+AVD, 123; ABVD, 164

Reasons Leading to Event	A+AVD (N=123)	ABVD (N=164)
Disease progression	73	103
Death from any cause	15	22
Subsequent anticancer therapy when complete response not achieved at completion of frontline therapy	35	39

No. at Risk

A+AVD	664	643	626	613	540	524	516	497	479	456	361	347	325	206	192	180	102	87	79	28	24	21	5	3	3	0	0
ABVD	670	643	628	611	514	492	476	463	448	426	343	319	299	186	171	157	82	71	63	16	13	12	2	2	2	0	0

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Table 2. Summary of Modified Progression-free Survival According to the Independent Review Committee and Concordance with Events Noted by Trial Investigators (Intention-to-Treat Population).

Events	A+AVD (N=664)	ABVD (N=670)	Total (N=1334)
Patients with events per independent review committee — no.	117	146	263
Progression — no./total no. (%)	90/117 (77)	102/146 (70)	192/263 (73)
Death — no./total no. (%)	18/117 (15)	22/146 (15)	40/263 (15)
Positive PET scan and subsequent treatment — no./total no. (%)*	9/117 (8)	22/146 (15)	31/263 (12)
Patients with positive PET scan and subsequent treatment — no.	9	22	31
Salvage chemotherapy — no./total no. (%)†	7/9 (78)	15/22 (68)	22/31 (71)
Met criteria for PFS event			
PFS event or modified event reported by investigator — no.	7	15	22
PFS event reported by investigator — no./total no. (%)	7/7 (100)	13/15 (87)	20/22 (91)
PFS event reported by independent review committee — no./total no. (%)	2/7 (29)	3/15 (20)	5/22 (23)
Deauville score at end of treatment — no./total no. (%)‡			
1	0	0	0
2	0	0	0
3	0	2/15 (13)	2/22 (9)
4	3/7 (43)	4/15 (27)	7/22 (32)
5	4/7 (57)	9/15 (60)	13/22 (59)
Radiation — no./total no. (%)	2/9 (22)	7/22 (32)	9/31 (29)
Met criteria for PFS event			
PFS event or modified event reported by investigator — no.	2	7	9
PFS event reported by investigator — no./total no. (%)	0	1/7 (14)	1/9 (11)
PFS event reported by independent review committee — no./total no. (%)	0	1/7 (14)	1/9 (11)
Deauville score at end of treatment — no./total no. (%)‡			
1	0	0	0
2	0	0	0
3	2/2 (100)	3/7 (43)	5/9 (56)
4	0	3/7 (43)	3/9 (33)
5	0	1/7 (14)	1/9 (11)

* There were 58 patients at risk for a modified progression event (end-of-treatment Deauville score ≥3 and no progressive disease at the end of treatment): 19 in the group receiving A+AVD versus 39 in the group receiving ABVD. However, only 9 patients in the A+AVD group and 22 patients in the ABVD group actually had a modified progression event because they received subsequent treatment. PET denotes positron-emission tomography, and PFS progression-free survival.

† Salvage chemotherapy included the terms chemotherapy, high-dose chemotherapy plus transplantation, and immunotherapy according to medical review.

‡ 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 uptake at an initial site that is less than or equal to the uptake at the mediastinum, a score of 3 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 uptake at an initial site that is moderately increased as compared with uptake at the liver, and a score of 5 markedly increased uptake at any site or uptake at a new site of disease. The absence of complete response at the end of primary chemotherapy was defined as a Deauville score of 3, 4, or 5.

Figure 1 (facing page). Modified Progression-free Survival in the Intention-to-Treat Population.

Panel A shows Kaplan–Meier estimates of modified progression-free survival, by treatment group, according to the independent review committee. The hazard ratio for treatment with A+AVD versus ABVD and the 95% confidence intervals (CIs) were based on a stratified Cox proportional-hazards regression model, with treatment as the explanatory variable. Stratification factors included region and International Prognostic Score risk group at baseline. Panel B shows Kaplan–Meier estimates of modified progression-free survival, by treatment group, according to investigators. In Panels A and B, circles indicate censored data. A+AVD denotes brentuximab vedotin plus doxorubicin, vinblastine, and dacarbazine, and ABVD doxorubicin, bleomycin, vinblastine, and dacarbazine.

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Table 3. Summary of Responses in the Intention-to-Treat Population.

Measure	A+AVD (N=664)	ABVD (N=670)	Difference (95% CI)*
	no. (%)		%
Complete response at end of randomized regimen†	488 (73)	472 (70)	3.0 (–2.3 to 8.4)
Overall response at end of randomized regimen‡	569 (86)	553 (83)	3.2 (–2.2 to 8.6)
Complete response at end of frontline therapy§	488 (73)	474 (71)	2.7 (–2.6 to 8.1)
Deauville score¶			
≤3 After completion of frontline therapy)	570 (86)	551 (82)	3.6 (–1.8 to 9.0)
≤2 After completion of frontline therapy	563 (85)	537 (80)	4.6 (–0.8 to 10.0)
Summary at cycle 2			
1	435 (66)	414 (62)	
2	131 (20)	133 (20)	
3	22 (3)	30 (4)	
4	26 (4)	28 (4)	
5	21 (3)	30 (4)	
Unavailable	29 (4)	35 (5)	
Summary after completion of primary chemotherapy¶			
1	444 (67)	425 (63)	
2	119 (18)	112 (17)	
3	7 (1)	14 (2)	
4	12 (2)	20 (3)	
5	46 (7)	45 (7)	
Unavailable	36 (5)	54 (8)	

* Confidence intervals (CIs) were calculated from the exact confidence interval, have not been adjusted for the multiple comparisons, and should not be used for definitive comparisons.
† Complete response at the end of the randomized regimen is defined as the proportion of patients who had complete response[20] at the end of treatment with either regimen (A+AVD or ABVD).
‡ Overall response at the end of the randomized regimen is defined as the proportion of patients who had complete or partial response[20] at the end of treatment with either regimen (A+AVD or ABVD).
§ Complete response at the end of frontline therapy is defined as the proportion of patients who had complete response after the completion of either the randomized regimen (A+AVD or ABVD) or alternate frontline therapy.
¶ 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 uptake at an initial site that is less than or equal to the uptake at the mediastinum, a score of 3 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 uptake at an initial site that is moderately increased as compared with uptake at the liver, and a score of 5 markedly increased uptake at any site or uptake at a new site of disease. The absence of complete response at the end of primary chemotherapy was defined as a Deauville score of 3, 4, or 5.

in the A+AVD group and 15 of 22 patients in the ABVD group), with radiotherapy given to the remainder of patients in both groups (Table S4 in the Supplementary Appendix). Modified progression events assigned because of an end-of-treatment PET scan and subsequent treatment were predominantly associated with a Deauville score of 4 or 5 (a score of 3 was recorded in 7 of 31 patients [23%], a score of 4 in 10 of 31 patients [32%], and a score of 5 in 14 of 31 patients [45%]); these events also met the criteria for a progression event according to investigator assessment. Of note, only 7 of the 21 patients with a Deauville score of 3 on the end-of-treatment PET scan went on to receive additional therapy and were therefore determined to have had a modified progression event (2 patients in the A+AVD group and 5 patients in the ABVD group) Tables 2 and 3.

According to investigator assessment, the 2-year modified progression-free survival rate was 81.0% (95% CI, 77.6 to 83.9) with the A+AVD regimen

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Subgroup	A+AVD	ABVD	Hazard Ratio (95% CI)
	no. of events/total no. (%)		
Overall	117/664 (17.6)	146/670 (21.8)	0.77 (0.60–0.98)
Age			
<60 yr	93/580 (16.0)	117/568 (20.6)	0.73 (0.56–0.96)
≥60 yr	24/84 (28.6)	29/102 (28.4)	1.01 (0.59–1.73)
<65 yr	99/604 (16.4)	128/608 (21.1)	0.74 (0.57–0.96)
≥65 yr	18/60 (30.0)	18/62 (29.0)	1.01 (0.53–1.95)
<45 yr	70/451 (15.5)	83/423 (19.6)	0.73 (0.53–1.01)
≥45 yr	47/213 (22.1)	63/247 (25.5)	0.86 (0.59–1.26)
Geographic region			
Americas	41/261 (15.7)	58/262 (22.1)	0.65 (0.44–0.97)
North America	38/250 (15.2)	57/247 (23.1)	0.60 (0.39–0.90)
Europe	62/333 (18.6)	74/336 (22.0)	0.83 (0.59–1.17)
Asia	14/70 (20.0)	14/72 (19.4)	0.91 (0.43–1.93)
IPS			
0–1	22/141 (15.6)	25/141 (17.7)	0.83 (0.47–1.48)
2–3	57/354 (16.1)	68/351 (19.4)	0.79 (0.56–1.13)
4–7	38/169 (22.5)	53/178 (29.8)	0.70 (0.46–1.07)
Baseline Ann Arbor stage			
Stage III	40/237 (16.9)	43/246 (17.5)	0.92 (0.60–1.42)
Stage IV	77/425 (18.1)	102/421 (24.2)	0.71 (0.53–0.96)
Baseline B symptoms			
Yes	77/399 (19.3)	94/381 (24.7)	0.74 (0.55–1.01)
No	40/265 (15.1)	52/289 (18.0)	0.79 (0.52–1.20)
Baseline extranodal sites			
0	40/217 (18.4)	39/228 (17.1)	1.04 (0.67–1.62)
1	36/217 (16.6)	45/223 (20.2)	0.75 (0.48–1.16)
>1	39/194 (20.1)	57/193 (29.5)	0.67 (0.44–1.00)
Baseline ECOG status			
0	61/376 (16.2)	79/378 (20.9)	0.74 (0.53–1.03)
1	48/259 (18.5)	57/262 (21.8)	0.83 (0.56–1.21)
2	8/28 (28.6)	10/26 (38.5)	0.54 (0.21–1.37)
Sex			
Male	64/378 (16.9)	90/398 (22.6)	0.71 (0.51–0.97)
Female	53/286 (18.5)	56/272 (20.6)	0.86 (0.59–1.26)

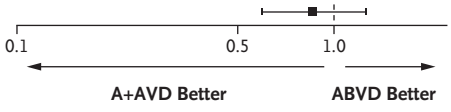

Figure 2. Forest-Plot Analysis of Modified Progression-free Survival.

This forest plot shows modified progression-free survival according to the independent review committee in key prespecified subgroups. The hazard ratio for treatment with A+AVD versus ABVD and the 95% confidence intervals (CIs) were based on an unstratified Cox proportional-hazards regression model, with treatment as the explanatory variable. The intention-to-treat population included all the patients who underwent randomization. The International Prognostic Score (IPS) ranges from 0 to 7, with higher scores indicating increased risk of treatment failure: low risk, 0 or 1; intermediate risk, 2 or 3; and high risk, 4 to 7. The Ann Arbor staging system ranges from I to IV, with higher stages indicating more widespread disease. B symptoms consist of night sweats, unexplained fever (temperature >38°C), or loss of more than 10% of body weight. Values for the Eastern Cooperative Oncology Group (ECOG) performance status range from 0 to 5, with higher scores indicating greater disability.

versus 74.4% (95% CI, 70.7 to 77.7) with the ABVD regimen, corresponding to a 27% lower overall risk of an event among patients treated with A+AVD than among those treated with ABVD (hazard ratio for progression, death, or modified progression, 0.73; 95% CI, 0.57 to 0.92; P=0.007) (Fig. 1B). There was 91% concordance between independent review and investigator determination of a modified progression-free survival event.

Prespecified subgroup analyses of modified progression-free survival showed a hazard ratio of less than 1 for the A+AVD regimen versus the ABVD regimen in the majority of subgroups (Fig. 2). Certain subgroups of patients appeared to benefit more with A+AVD than with ABVD.

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These subgroups included patients from North America, patients with involvement of more than one extranodal site, patients with an IPS indicating a high risk of treatment failure (scores of 4 to 7), men, patients with stage IV disease, and patients younger than 60 years of age. The rates of negativity at PET2 (Deauville score, 1 to 3) were 89% with A+AVD versus 86% with ABVD.

There were 28 deaths in the A+AVD group (9 during treatment [within 30 days after the last dose of frontline therapy] and 19 during follow-up [31 days or more after the last dose of frontline therapy]) and 39 deaths in the ABVD group (13 during treatment and 26 during follow-up). The interim 2-year overall survival rate for the A+AVD group was 96.6% (95% CI, 94.8 to 97.7) and that for the ABVD group was 94.9% (95% CI, 92.9 to 96.4), which corresponded to a reduction in the risk of death of 28% in favor of the A+AVD regimen (hazard ratio, 0.72; 95% CI, 0.44 to 1.17; P=0.19) (Fig. S2 in the Supplementary Appendix). Results for other secondary end points are shown in Table 3. Only 15 of 662 patients who received A+AVD and 9 of 659 patients who received ABVD switched to alternative chemotherapy during frontline therapy for reasons other than progressive disease (a Deauville score of 5 in 1 of 15 and 4 of 9 patients, respectively; adverse events in 12 of 15 and 1 of 9 patients, respectively; and other reasons in 2 of 15 and 4 of 9 patients, respectively) (Table S5 in the Supplementary Appendix).

Overall, fewer patients in the A+AVD group than in the ABVD group received subsequent anticancer therapies. Recipients of these therapies in the A+AVD group versus the ABVD group were as follows: radiation (in 52 patients in each group), chemotherapy (66 vs. 99), high-dose chemotherapy plus transplantation (36 vs. 54), immunotherapy (10 vs. 16), and chemotherapy plus radiation (2 vs. 3).

SAFETY

The median duration of treatment and the number of completed cycles were similar in the two groups (Table S6 in the Supplementary Appendix). The proportions of patients who received the regimens as intended, without dose modification such as delays, holds, or reductions, are shown in Table S6 in the Supplementary Appendix.

The safety profiles for both groups are summarized in Table 4, and in Table S7 in the Supplementary Appendix. Overall, neutropenia was reported in 58% of the patients receiving A+AVD and in 45% of the patients receiving ABVD, and febrile neutropenia was reported in 19% and 8%, respectively. In both groups, the incidence of febrile neutropenia was higher among patients 60 years of age or older than among those younger than 60 years of age (37% vs. 17% in the A+AVD group and 17% vs. 6% in the ABVD group). The incidence of febrile neutropenia was also higher in earlier rather than later cycles of therapy in both groups (9% in cycle 1 vs. 1 to 6% in cycles 2 through 6 in the A+AVD group and 4% in cycle 1 vs. ≤1% in cycles 2 through 6 in the ABVD group). The incidence of discontinuation of any trial drug due to neutropenia or febrile neutropenia was 1% or less in both groups.

The rate of infections (determined in accordance with the MedDRA primary system organ-class term of "infections and infestations") in the A+AVD group was 55% (361 of 662 patients) and the rate in the ABVD group was 50% (331 of 659 patients); rates of infection of grade 3 or higher were 18% (116 of 662 patients) and 10% (66 of 659 patients), respectively. Discussion with the independent data and safety monitoring committee (after 76% of enrollment was complete) led to the recommendation of primary prophylaxis with granulocyte colony-stimulating factor (G-CSF) for patients who were yet to be enrolled and who would receive the A+AVD regimen, owing to the higher incidence of febrile neutropenia in that group. In the A+AVD group, the incidence of febrile neutropenia was lower among the 83 patients who received primary prophylaxis with G-CSF (defined as use of G-CSF by day 5 of treatment) than among those who did not (11% [9 of 83] vs. 21% [119 of 579]) (Table 5). The occurrence of infections and infestations of grade 3 or higher was also lower among the patients who received G-CSF than among those who did not (11% [9 of 83 patients] vs. 18% [107 of 579 patients]).

Peripheral neuropathy (determined on the basis of a standardized MedDRA query; see Table S8 in the Supplementary Appendix) occurred in 67% of the patients (442 of 662) receiving A+AVD and 43% of the patients (286 of 659) receiving ABVD. Grade 2 peripheral neuropathy occurred in 20% of the patients (130 of 662) in the A+AVD group versus 9% of the patients (57 of 659) in the ABVD group, and peripheral neuropathy of grade 3 or higher occurred in 11% of the patients (70 of 662) in the former group

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(with grade 4 occurring in 1 patient) versus 2% of the patients (11 of 659) in the latter. Among patients with peripheral neuropathy, a trial drug was discontinued in 10% in the A+AVD group (44 of 442) versus 4% in the ABVD group (11 of 286). Two thirds of the patients in the A+AVD group (295 of 442) who had peripheral neuropathy had resolution (43%, 191 of 442) or improvement by at least one grade (24%, 104 of 442) in terms of events related to peripheral neuropathy at the time of the last follow-up visit; at that time, 92% of ongoing events related to peripheral neuropathy were grade 1 (64%) or grade 2 (29%) in the A+AVD group. Pulmonary toxicity, defined as events related to interstitial lung disease (in accordance with a standardized MedDRA query), was reported in 2% of the patients (12 of 662) in the A+AVD group versus 7% (44 of 659) in the ABVD group; events of grade 3 or higher were reported in less than 1% of the patients (5 of 662) in the former group and 3% of the patients (21 of 659) in the latter.

During treatment, there were 9 deaths in the A+AVD group and 13 deaths in the ABVD group. In the A+AVD group, 7 deaths were associated with neutropenia (all occurred in patients who had not received primary prophylaxis with G-CSF before the onset of neutropenia, with the exception of 1 patient who entered the trial with preexisting neutropenia) and 2 deaths were due to myocardial infarction. In the ABVD group, 11 deaths were due to or associated with pulmonary-related toxicity and 1 death was due to cardiopulmonary failure. The cause of 1 death was unknown. Among the patients enrolled in the trial, 37% (242 of 662) in the A+AVD group and 28% (186 of 659) in the ABVD group were hospitalized during the trial.

Fertility was not formally assessed; however, similar numbers of pregnancies were reported in each treatment group, which suggests that there was no significant difference in the effect on fertility. At the time of this analysis, a total of 78 pregnancies were reported among trial participants and their partners (42 in the A+AVD group and 36 in the ABVD group).

Table 4. Summary of Adverse Events in the Safety Population.*

Events	A+AVD (N=662)	ABVD (N=659)
	no. (%)	
Adverse events		
Any adverse event	653 (99)	646 (98)
Grade ≥3 adverse event	549 (83)	434 (66)
Serious adverse event	284 (43)	178 (27)
Adverse event resulting in drug discontinuation	88 (13)	105 (16)
Death during treatment†	9 (1)	13 (2)
Death due to drug-related adverse events	8 (1)	7 (1)
Hospitalizations	242 (37)	186 (28)
Common adverse events‡		
Neutropenia		
Any grade	382 (58)	295 (45)
Grade ≥3	357 (54)	260 (39)
Constipation		
Any grade	279 (42)	241 (37)
Grade ≥3	11 (2)	4 (<1)
Vomiting		
Any grade	216 (33)	183 (28)
Grade ≥3	23 (3)	9 (1)
Fatigue		
Any grade	211 (32)	211 (32)
Grade ≥3	19 (3)	7 (1)
Peripheral sensory neuropathy		
Any grade	189 (29)	111 (17)
Grade ≥3	31 (5)	3 (<1)
Diarrhea		
Any grade	181 (27)	121 (18)
Grade ≥3	19 (3)	5 (<1)
Pyrexia		
Any grade	179 (27)	147 (22)
Grade ≥3	19 (3)	13 (2)
Peripheral neuropathy		
Any grade	174 (26)	85 (13)
Grade ≥3	27 (4)	6 (<1)
Abdominal pain		
Any grade	142 (21)	65 (10)
Grade ≥3	21 (3)	4 (<1)
Stomatitis		
Any grade	138 (21)	104 (16)
Grade ≥3	10 (2)	3 (<1)

* For a full summary of adverse events, including rates of drug-related adverse events and deaths, see Table S7 in the Supplementary Appendix.
† Death during treatment is a death that occurred within 30 days after the last dose of frontline therapy.
‡ The events listed include the most clinically important common adverse events. Adverse events (those of any grade that occurred in at least 20% of the patients in either group) excluded from the table are nausea, alopecia, weight loss, and anemia.

DISCUSSION

This large, international, randomized phase 3 trial involving patients who had received a recent diagnosis of stage III or IV classic Hodgkin's lymphoma showed that treatment with brentuxi-

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Table 5. Summary of Adverse Events in Patients Who Did and Those Who Did Not Receive Primary Prophylaxis with Granulocyte Colony-Stimulating Factor.

Events	A+AVD (N=662)		ABVD (N=659)	
	No (N=579)	Yes (N=83)	No (N=616)	Yes (N=43)
	number (percent)			
Febrile neutropenia during treatment	119 (21)	9 (11)	49 (8)	3 (7)
Any neutropenia*	425 (73)	29 (35)	352 (57)	9 (21)
Neutropenia grade ≥3*	406 (70)	24 (29)	309 (50)	8 (19)
Grade ≥3 adverse event	502 (87)	47 (57)	414 (67)	20 (47)
Infections and infestations (SOC)	322 (56)	39 (47)	312 (51)	19 (44)
Grade ≥3 infections and infestations (SOC)	107 (18)	9 (11)	63 (10)	3 (7)
Serious adverse event	257 (44)	27 (33)	171 (28)	7 (16)
Serious adverse events of febrile neutropenia, neutropenia, sepsis, neutropenic sepsis, pyrexia, or infections and infestations (SOC)	190 (33)	20 (24)	107 (17)	4 (9)
Deaths during treatment†	8 (1)	1 (1)‡	12 (2)	1 (2)

* Neutropenia and neutropenia grade 3 or higher (neutrophil count <1000 per cubic millimeter) include the preferred terms of "neutropenia" and "neutrophil count decreased." SOC denotes system organ class for the noted event.
† Death during treatment is a death that occurred within 30 days after the last dose of frontline therapy.
‡ The patient in the A+AVD group who had G-CSF primary prophylaxis received G-CSF for treatment of neutropenia, which occurred before day 5.

mab vedotin plus AVD, as compared with standard treatment with ABVD, resulted in a statistically significant and clinically meaningful improvement in the rate of modified progression-free survival, with a difference at 2 years of 4.9 percentage points as assessed by an independent committee, whose members were unaware of group assignments and 6.6 percentage points as assessed by the trial investigators. These outcomes were associated with reductions in the overall risk of failure of the primary chemotherapy treatment of 23% as assessed by an independent review committee and 27% as assessed by the trial investigators.

The goal of frontline chemotherapy for Hodgkin's lymphoma is to cure patients without the need for additional therapy. Because metabolically detectable residual disease is a reliable predictor of imminent progression, it is accepted practice to initiate subsequent chemotherapy or radiotherapy on the basis of a positive PET scan at the end of frontline treatment.[21-23] In this context, the conventional end point of progression-free survival does not accurately assess the curative intent of frontline chemotherapy. Thus, in the ECHELON-1 trial, the primary end point was "modified" progression-free survival, which, in addition to disease progression or death, included modified progression, defined as evidence of noncomplete response after the completion of frontline chemotherapy (based on independently assessed PET results) followed by subsequent anticancer therapy, as an event, thus accurately assessing the curative potential of the frontline chemotherapy.

The results of the interim overall survival analysis and all other secondary efficacy end points favored A+AVD, further supporting the conclusion that A+AVD is a more effective frontline treatment for advanced Hodgkin's lymphoma than ABVD. Furthermore, the benefit of A+AVD was observed consistently in the majority of prespecified subgroups, including patients in whom there was involvement of more than one extranodal site, patients with an IPS indicating high risk for treatment failure (4 to 7), and patients with stage IV disease. The rate of positivity at PET2 was low, and a higher proportion of the patients treated with A+AVD than those treated with ABVD had negative results at PET2 (89% vs. 86%).

This trial shows that the addition of brentuxi-

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mab vedotin and the elimination of bleomycin from frontline therapy in the A+AVD regimen lowers the incidence of pulmonary toxicity while improving efficacy as compared with the ABVD regimen. No new types of risk to patient safety were identified, although the incidence of febrile neutropenia was higher than expected and an increased incidence of infections was noted in the A+AVD group. The majority of the deaths during treatment in the A+AVD group were associated with febrile neutropenia; however, primary prophylaxis with G-CSF appeared to mitigate the increased risk of febrile neutropenia and its sequelae in the subgroup of 83 patients who received primary prophylaxis, resulting in reduced rates of neutropenia, febrile neutropenia, and serious infection. Peripheral neuropathy occurred more frequently in patients in the A+AVD group. The incidence of peripheral neuropathy of grade 3 or higher was increased by 9 percentage points in this group as compared with the ABVD group, and peripheral neuropathy was largely reversible, either resolving or abating in 67% of the patients in whom the condition had developed. Both the percentage of patients who received subsequent salvage chemotherapy and the percentage of patients who received high-dose chemotherapy followed by transplantation were approximately 33% lower among patients treated with A+AVD than among patients treated with ABVD; those treated with A+AVD were therefore less likely to be subject to the toxicities associated with aggressive salvage therapies.

The results of the ECHELON-1 trial are particularly important considering the opportunity A+AVD provides to administer a treatment to older patients that is at least equivalent in its effectiveness to ABVD, and to do so safely. Older patients with advanced Hodgkin's lymphoma represent a special group, considering their incidence of disease (approximately 20% of all cases), lower rates of treatment efficacy, and typically higher rates of severe toxicity, particularly the pulmonary toxicity that is associated with bleomycin.[6,24,25] When choosing frontline treatment, it is important to consider the lifetime burden of late and long-term adverse effects from salvage chemotherapy, radiotherapy, and transplantation (including infertility, pulmonary and cardiac toxicities, and secondary cancers).[26,27] The A+AVD regimen is associated with more myelotoxicity (which can be ameliorated with prophylactic G-CSF) and neurotoxicity (which is largely reversible) than ABVD but substantially less pulmonary toxicity and appears to be more effective for the frontline treatment of advanced-stage classic Hodgkin's lymphoma.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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APPENDIX

The authors' full names and academic degrees are as follows: Joseph M. Connors, M.D., Wojciech Jurczak, M.D., Ph.D., David J. Straus, M.D., Stephen M. Ansell, M.D., Ph.D., Won S. Kim, M.D., Ph.D., Andrea Gallamini, M.D., Anas Younes, M.D., Sergey Alekseev, M.D., Árpád Illés, M.D., D.Sci., Marco Picardi, M.D., Ewa Lech-Maranda, M.D., Ph.D., Yasuhiro Oki, M.D., Tatyana Feldman, M.D., Piotr Smolewski, M.D., Ph.D., Kerry J. Savage, M.D., Nancy L. Bartlett, M.D., Jan Walewski, M.D., Robert Chen, M.D., Radhakrishnan Ramchandren, M.D., Pier L. Zinzani, M.D., Ph.D., David Cunningham, M.B. Ch.B., M.D., Andras Rosta, Ph.D., Neil C. Josephson, M.D., Eric Song, Ph.D., Jessica Sachs, M.D., Rachael Liu, Ph.D., Hina A. Jolin, Pharm.D., Dirk Huebner, M.D., and John Radford, M.D.

The authors' affiliations are as follows: the University of British Columbia and the Department of Medical Oncology, British Columbia Cancer Agency Centre for Lymphoid Cancer, Vancouver, Canada (J.M.C., K.J.S.); the Department of Hematology, Jagiellonian University, Krakow (W.J.), the Department of Hematology, Institute of Hematology and Transfusion Medicine, Warsaw (E.L.-M.), the Department of Hematology and Transfusion Medicine, Center of Postgraduate Medical Education, Warsaw (E.L.-M.), the Department of Experimental Hematology, Medical University of Lodz, Lodz (P.S.), and the Department of Lymphoid Malignancy, the Maria Sklodowska-Curie Memorial Institute and Oncology Center, Warsaw (J.W.) — all in Poland; Lymphoma Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York (D.J.S., A.Y.); the Department of Internal Medicine, Division of Hematology, Mayo Clinic, Rochester, MN (S.M.A.); the Division of Hematology and Oncology, Sungkyunkwan University School of Medicine, Samsung Medical Center, Seoul, South Korea (W.S.K.); Research Innovation and Statistics, Antoine-Lacassagne Cancer Center, Nice, France (A.G.); Petrov Research Institute of Oncology, St. Petersburg, Russia (S.A.); the Department of Hematology, Faculty of Medicine, University of Debrecen, Debrecen (Á.I.), and the Department of Hematology, National Institute of Oncology, Budapest (A.R.) — both in Hungary; the Department of Advanced Biomedical Science, Federico II University Hospital, Naples (M.P.), and the Institute of Hematology Seràgnoli, University of Bologna, Bologna (P.L.Z.) — both in Italy; the Department of Lymphoma and Myeloma, M.D. Anderson Cancer Center, Houston (Y.O.); John Theurer Cancer Center, Hackensack University Medical Center, Hackensack, NJ (T.F.); the Department of Medicine, Division of Oncology, Washington University School of Medicine, St. Louis (N.L.B.); the Department of Hematology and Hema-

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topoietic Cell Transplantation, City of Hope National Medical Center, Duarte, CA (R.C.); the Department of Hematology–Oncology, Barbara Ann Karmanos Cancer Center, Detroit (R.R.); Gastrointestinal and Lymphoma Unit, The Royal Marsden NHS Foundation Trust, Sutton (D.C.), and the Department of Medical Oncology, University of Manchester and the Christie NHS Foundation Trust, Manchester Academic Health Science Centre, Manchester (J.R.) — both in the United Kingdom; the Department of Clinical Development, Seattle Genetics, Bothell, WA (N.C.J., E.S.); and Oncology Clinical Research (J.S., H.A.J., D.H.) and Global Biostatistics (R.L.), Millennium Pharmaceuticals, Cambridge, MA.

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