ORIGINAL ARTICLE

Overall Survival with Brentuximab Vedotin in Stage III or IV Hodgkin's Lymphoma

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ABSTRACT

BACKGROUND

Five-year follow-up in a trial involving patients with previously untreated stage III or IV classic Hodgkin's lymphoma showed long-term progression-free survival benefits with first-line therapy with brentuximab vedotin, a CD30-directed antibody–drug conjugate, plus doxorubicin, vinblastine, and dacarbazine (A+AVD), as compared with doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD). A planned interim analysis indicated a potential benefit with regard to overall survival; data from a median of 6 years of follow-up are now available.

METHODS

We randomly assigned patients in a 1:1 ratio to receive up to six cycles of A+AVD or ABVD. The primary end point, modified progression-free survival, has been reported previously. The key secondary end point was overall survival in the intention-to-treat population. Safety was also assessed.

RESULTS

A total of 664 patients were assigned to receive A+AVD and 670 to receive ABVD. At a median follow-up of 73.0 months, 39 patients in the A+AVD group and 64 in the ABVD group had died (hazard ratio, 0.59; 95% confidence interval [CI], 0.40 to 0.88; P=0.009). The 6-year overall survival estimates were 93.9% (95% CI, 91.6 to 95.5) in the A+AVD group and 89.4% (95% CI, 86.6 to 91.7) in the ABVD group. Progression-free survival was longer with A+AVD than with ABVD (hazard ratio for disease progression or death, 0.68; 95% CI, 0.53 to 0.86). Fewer patients in the A+AVD group than in the ABVD group received subsequent therapy, including transplantation, and fewer second cancers were reported with A+AVD (in 23 vs. 32 patients). Primary prophylaxis with granulocyte colony-stimulating factor was recommended after an increased incidence of febrile neutropenia was observed with A+AVD. More patients had peripheral neuropathy with A+AVD than with ABVD, but most patients in the two groups had resolution or amelioration of the event by the last follow-up.

CONCLUSIONS

Patients who received A+AVD for the treatment of stage III or IV Hodgkin's lymphoma had a survival advantage over those who received ABVD. (Funded by Takeda Development Center Americas and Seagen; ECHELON-1 ClinicalTrials.gov number, NCT01712490; EudraCT number, 2011-005450-60.)

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*The full list of the investigators in the ECHELON-1 Study Group was included with an earlier published trial; see the Supplementary Appendix, available at NEJM.org, for detailed information.

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For decades, first-line treatment with doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) has been the standard of care for the treatment of advanced-stage classic Hodgkin's lymphoma.[1] However, a substantial proportion of patients with stage III or IV disease have a relapse or disease that is refractory to ABVD.[1-3]

Trials involving patients with advanced disease have not shown an overall survival advantage with various therapies and treatment strategies as compared with ABVD alone.[4-11] In an effort to maintain or improve disease control while limiting toxic effects, several response-adapted strategies that have been based on positron-emission tomography status at end of the second cycle of treatment (PET2) have been studied. Although various treatment strategies have succeeded in improving the side-effect profile or progression-free survival, as compared with ABVD, an overall survival advantage has not been observed.[5,7-11] In a post hoc analysis, the HD9 trial[6] showed an overall survival advantage at 10 years with escalated bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPP) as compared with cyclophosphamide, vincristine, procarbazine, and prednisone alternating with doxorubicin, bleomycin, vinblastine, and dacarbazine (COPP-ABVD). However, BEACOPP-based regimens are toxic and have not been shown to prolong overall survival as compared with ABVD alone. This finding may be due to the improved ability to provide salvage therapy to patients who have a relapse after ABVD therapy as well as due to treatment-related deaths associated with BEACOPP.[6,12] In addition, BEACOPP-based regimens can have an adverse effect on fertility and are associated with an increased risk of second cancers.[13,14]

Regimens that incorporate targeted agents, such as brentuximab vedotin, an antibody–drug conjugate (a CD30-directed monoclonal antibody conjugated by protease-cleavable linker to the microtubule-disrupting agent monomethyl auristatin E), have also been studied. In the phase 3 ECHELON-1 trial, first-line treatment with brentuximab vedotin plus doxorubicin, vinblastine, and dacarbazine (A+AVD) significantly improved modified progression-free survival (the time to progression, death, or noncomplete response and use of subsequent anticancer therapy), as compared with ABVD, among patients with newly diagnosed stage III or IV Hodgkin's lymphoma, and a planned interim analysis indicated a potential benefit with regard to overall survival.[15] At 5 years, a long-term benefit with regard to progression-free survival with A+AVD as compared with ABVD was shown (hazard ratio for disease progression or death, 0.68; 95% confidence interval [CI], 0.53 to 0.87).[16] Here, we report the results of an overall survival analysis of A+AVD as compared with ABVD from the ECHELON-1 trial, as well as long-term safety data, after approximately 6 years of follow-up.

Methods

Trial Design and Procedures

We conducted a multicenter, randomized, open-label trial of A+AVD as compared with ABVD in patients with stage III or IV Hodgkin's lymphoma. The trial design and protocol (available with the full text of this article at NEJM.org) have been published previously.[15] Adult patients (≥18 years of age) with histologically confirmed advanced Hodgkin's lymphoma (Ann Arbor stage III or IV, as determined on a 4-point scale, with higher stages indicating more widespread disease) were randomly assigned in a 1:1 ratio to receive A+AVD or ABVD. The A+AVD regimen consisted of 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. The ABVD regimen consisted of 25 mg of doxorubicin per square meter, 10 U of bleomycin per square meter, 6 mg of vinblastine per square meter, and 375 mg of dacarbazine per square meter. In each regimen, drugs were administered intravenously on days 1 and 15 of each 28-day cycle for up to six cycles.

Randomization was stratified according to geographic region and International Prognostic Score (IPS) risk group (0 or 1 [low], 2 or 3 [intermediate], or ≥4 [high]). The IPS is a 7-point scoring system in which 1 point represents the presence of each poor prognostic factor; higher scores indicate a poorer prognosis (higher risk). The use of granulocyte colony-stimulating factor (G-CSF), which was permitted according to institutional guidelines, was subsequently recommended after an increased incidence of febrile neutropenia was observed with A+AVD therapy during an interim safety analysis.[15]

The protocol was approved by the institutional review boards and ethics committees at individual sites and adhered to Good Clinical Practice guidelines (as defined by the International Council for Harmonisation). All the patients provided written informed consent.

The trial was designed by a committee consisting of five of the authors, one of the investigators who is not an author, and representatives of the sponsors (Takeda Development Center Americas and Seagen). Data were collected and trial procedures overseen by the trial investigators. Data were verified by the sponsors, analyzed by statisticians employed by the sponsors, and interpreted by academic authors and representatives of the sponsors.[15] The conduct of the trial was overseen by an independent data and safety monitoring committee and an independent review committee.[15] The manuscript was prepared by the authors with the assistance of medical writers funded by Takeda Pharmaceuticals USA. All the authors had full access to the data and vouch for the completeness and accuracy of the data and for the adherence of the trial to the protocol.

END POINTS

The primary end point of the trial, modified progression-free survival, has been reported previously.[15] The key secondary end point, overall survival, was assessed in a prespecified, type I error–controlled, event-driven analysis. Additional analyses of overall survival in prespecified subgroups and exploratory analyses involving patients who were PET2-negative (Deauville score, 1 to 3) or PET2-positive (Deauville score, 4 or 5) were also performed. (The Deauville score is a 5-point scale on which higher scores indicate greater uptake of ^{18}F-fluorodeoxyglucose at involved sites on PET.[17] 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.) Deaths during follow-up were recorded, including reported causes of death as assessed by the investigator. Progression-free survival as assessed by the investigator was also assessed at 6 years of follow-up.[16]

Safety outcome measures included the resolution and amelioration of peripheral neuropathy, the incidence of second cancer, and the incidence and outcomes of pregnancy among patients and their partners; all these events were assessed by the investigator. A multivariate Cox regression model was used to evaluate the treatment effect on survival after simultaneous adjustment for clinically relevant demographic and disease characteristics of the patients at baseline. Geographic region and IPS risk group were prespecified stratification factors. Sex, treatment, age, race, Eastern Cooperative Oncology Group (ECOG) performance-status score, extranodal involvement, disease stage, B symptoms (i.e., weight loss, night sweats, and fever), and PET2 results were included as covariates.

ASSESSMENTS

Overall survival was defined as the time from randomization to death from any cause. Progression-free survival was defined as the time from randomization to the first occurrence of disease progression or death. Progression was evaluated according to the Revised Response Criteria for Malignant Lymphoma.[18] A mandatory PET2 evaluation was conducted. Post-treatment follow-up assessments for new primary cancers and other safety events were performed every 3 months until 36 months after the end of treatment and then every 6 months thereafter. The grade of peripheral neuropathy was defined according to the *Medical Dictionary for Regulatory Activities*, version 19.0, and the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03, and was assessed as the last observation carried forward. Patients who were lost to follow-up or who died before the resolution or amelioration of peripheral neuropathy did not have their data censored.

STATISTICAL ANALYSIS

Overall survival and progression-free survival were estimated with the use of Kaplan–Meier methods. Between-group differences in overall survival (hazard ratios for death with 95% confidence intervals) were analyzed by means of a stratified Cox proportional-hazards regression model. Overall survival was to be tested only if a significant result was observed for the primary

analysis of modified progression-free survival. The type I error in the analysis of overall survival was controlled with the use of the O'Brien–Fleming method with a Lan–DeMets alpha-spending function. We projected that 112 deaths would occur approximately 5 years after the randomization of the last patient, but a notable decrease in the incidence of death was observed, which suggested that several additional years would be necessary in order for the analysis to capture the final expected deaths. Given the maturity of the data (103 observed deaths, 92% of the expected total) and in consultation with regulatory agencies, a second interim analysis was conducted that used the already-implemented alpha-spending approach; a benefit in favor of A+AVD over ABVD was considered to be significant at a P value of less than 0.0365 on the basis of a stratified log-rank test (two-sided).

Efficacy evaluations were performed in the intention-to-treat population (defined as all the patients who underwent randomization). All the 95% confidence intervals, except those associated with the type I error–controlled analysis of overall survival in the intention-to-treat population, are descriptive and were not adjusted for multiplicity. The safety population included all the patients who received at least one dose of trial drug.

RESULTS

CHARACTERISTICS OF THE PATIENTS

A total of 1334 patients were enrolled in the trial; 664 patients were assigned to the A+AVD group and 670 to the ABVD group (intention-to-treat population) (Fig. S1 in the Supplementary Appendix, available at NEJM.org). The demographic characteristics of the patients and their disease characteristics at baseline, which were similar in the two treatment groups, have been described previously (Table S1).[15] Approximately 14% of the patients in the trial were 60 years of age or older. The trial population was similar to the expected patient population on the basis of overall demographic and epidemiologic real-world data on Hodgkin's lymphoma; however, no patients from Africa were enrolled in the trial, and Black patients were underrepresented (Table S2). The data-cutoff date for the current analysis was June 1, 2021.

EFFICACY

The median follow-up in the overall survival analysis was 73.0 months (95% CI, 72.3 to 73.6; range, 0.0 to 100.6). A total of 39 deaths occurred in the A+AVD group and 64 in the ABVD group. The analysis of overall survival significantly favored A+AVD over ABVD (hazard ratio for death,

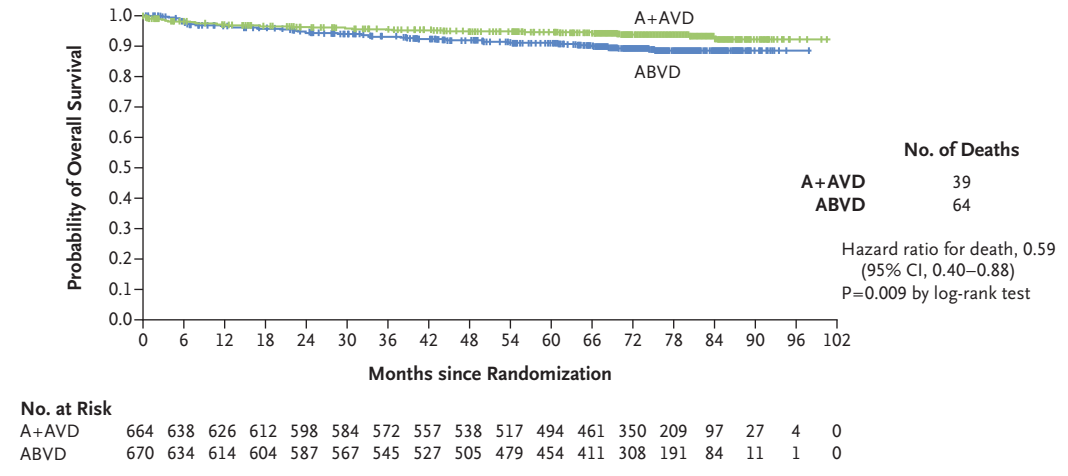

Figure 1. Overall Survival (Intention-to-Treat Population).

The intention-to-treat population included all the patients who underwent randomization. Tick marks indicate censored data. A+AVD denotes brentuximab vedotin plus doxorubicin, vinblastine, and dacarbazine; and ABVD doxorubicin, bleomycin, vinblastine, and dacarbazine.

0.59; 95% CI, 0.40 to 0.88; P=0.009) (Fig. 1). The 6-year overall survival estimates were 93.9% (95% CI, 91.6 to 95.5) in the A+AVD group and 89.4% (95% CI, 86.6 to 91.7) in the ABVD group.

Overall survival was examined in prespecified subgroups (Fig. 2 and Table S3). We observed more favorable estimates of the treatment effect with A+AVD than with ABVD among patients younger than 60 years of age, among those with stage IV disease, among those in the high-risk IPS subgroup, and among those in North America. We observed less favorable estimates of the treatment effect with A+AVD than with ABVD among patients 60 years of age or older, among women, and among patients in the low-risk IPS subgroup.

In a multivariate analysis that included simultaneous adjustment for demographic and baseline disease characteristics, we found that the overall

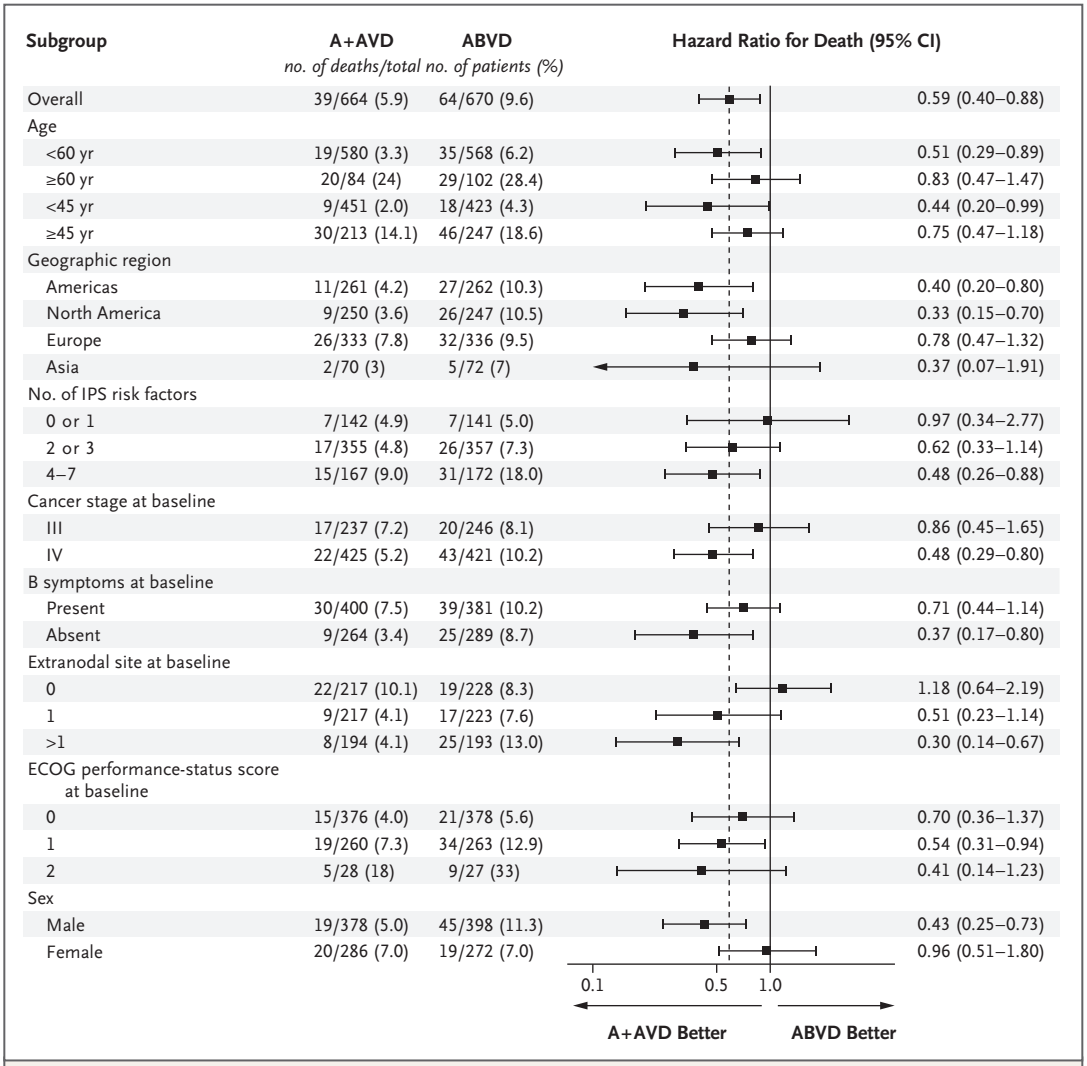

Figure 2. Overall Survival in Prespecified Subgroups (Intention-to-Treat Population).

The geographic region of the Americas was defined as Brazil, Canada, and the United States, and North America was defined as Canada and the United States. International Prognostic Score (IPS) risk groups were characterized with the use of a 7-point scoring system, with 1 point for the presence of each poor prognostic factor (0 or 1 [low], 2 or 3 [intermediate], vs. ≥4 [high]) and with higher scores indicating a poorer prognosis. B symptoms were defined as weight loss, night sweats, and fever. Eastern Cooperative Oncology Group (ECOG) performance-status scores are assessed on a 5-point scale, with higher scores indicating greater disability. The dashed vertical line indicates the treatment effect in the overall trial population. The arrow related to the hazard ratio in the Asia subgroup indicates that the 95% confidence interval extends outside the graphed area.

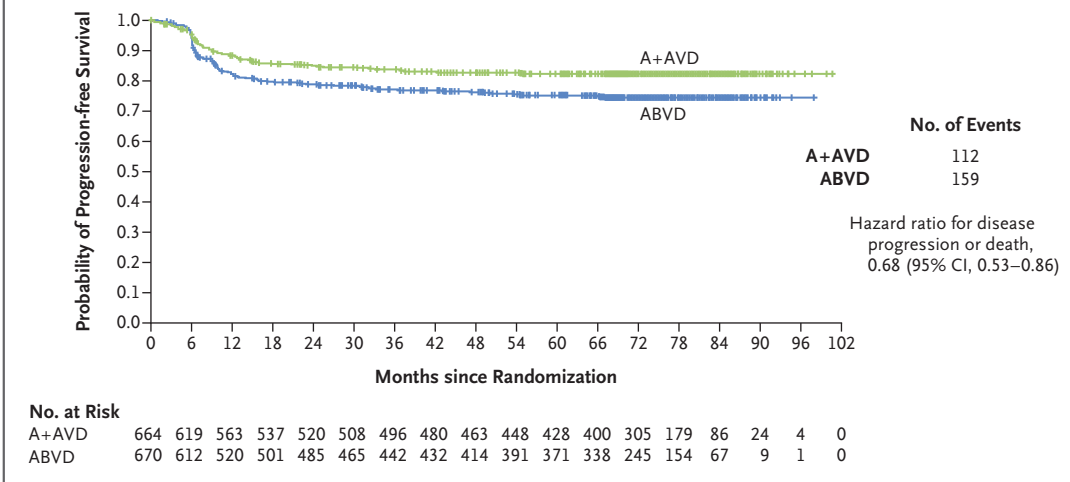

Figure 3. Progression-free Survival According to Investigator Assessment (Intention-to-Treat Population).
Tick marks indicate censored data.

survival benefit with A+AVD as compared with ABVD was preserved (hazard ratio for death, 0.53; 95% CI, 0.34 to 0.83). Age, non-White race, ECOG performance-status score, and PET2 status (negative or positive) were identified as the covariates with greatest evidence of association with overall survival. The 6-year overall survival estimates favored A+AVD over ABVD among both PET2-negative patients (94.9% vs. 90.6%; hazard ratio for death, 0.54; 95% CI, 0.34 to 0.86) and PET2-positive patients (95% vs. 77%; hazard ratio, 0.16; 95% CI, 0.04 to 0.72).

In a finding that was consistent with previous reports,[16,19] progression-free survival outcomes favored A+AVD over ABVD. At a median follow-up of 72.6 months, the 6-year progression-free survival estimates were 82.3% with A+AVD and 74.5% with ABVD (hazard ratio for disease progression or death, 0.68; 95% CI, 0.53 to 0.86) (Fig. 3). The 6-year progression-free survival estimates also favored A+AVD over ABVD across various subgroups, including subgroups defined according to disease stage (III or IV) and PET2-negative status (Fig. S2 and Table S4).

SAFETY

Most patients (593 [89.3%] in the A+AVD group and 608 [90.7%] in the ABVD group) completed all six cycles of trial treatment. In each trial group, the median number of cycles received was six (range, one to six). Details regarding the duration of therapy, treatment exposure, and dose modifications have been reported previously.[15]

In the A+AVD group, 32 of 39 deaths were related to Hodgkin's lymphoma or treatment complications, and there was 1 additional death due to a second cancer (Tables 1 and S5). In the ABVD group, 45 of 64 deaths were related to Hodgkin's lymphoma or treatment complications, and there were 11 additional deaths due to a second cancer. Two patients in the ABVD group with an unknown cause of death had previously had disease progression. Treatment-related deaths (in 8 patients in the A+AVD group and in 7 in the ABVD group) are described in Table S6. Deaths that occurred during treatment (in 9 patients in the A+AVD group, with 7 deaths being associated with neutropenia, and in 13 patients in the ABVD group, with 11 deaths being due to or associated with pulmonary toxic effects) have been previously described.[15]

In the safety population, the use of subsequent therapy was less frequent with A+AVD than with ABVD (in 135 of 662 patients [20.4%] vs. 157 of 659 [23.8%]), including fewer autologous transplantations (in 44 [6.6%] vs. 59 [9.0%]) and allogeneic stem-cell transplantations (in 4 [0.6%] vs. 12 [1.8%]) (Table S7). Brentuximab vedotin, either alone or in combination with another therapy, was the most common subsequent therapy in the ABVD group (in 69 patients [10.5%]). Immunotherapies, primarily nivolumab, were used less

frequently in the A+AVD group than in the ABVD group (in 18 patients [2.7%] vs. 28 [4.2%]).

The use of any subsequent radiation therapy was similar in the two groups (in 55 patients [8.3%] in the A+AVD group and in 58 [8.8%] in the ABVD group), as was radiation used as the first subsequent therapy (in 45 [6.8%] and 42 [6.4%], respectively). There was notable use of subsequent therapies among patients who died: 19 patients in the A+AVD group had previously had disease progression, which was not necessarily related to the cause of death, and 18 had received any subsequent therapy. In the ABVD group, 28 patients had previously had disease progression, and 25 received any subsequent therapy, of whom 13 received brentuximab vedotin (Table S8).

A second cancer was reported in 23 patients (3.5%) who received A+AVD and in 32 (4.9%) who received ABVD (Table S9). In the A+AVD group, 14 solid tumors and 9 hematologic cancers were reported, including 2 cases of acute myeloid leukemia and 6 cases of B-cell or T-cell lymphoma. In the ABVD group, 14 solid tumors and 17 hematologic cancers were reported, including 1 case each of acute myeloid leukemia, acute promyelocytic leukemia, and myelodysplastic syndrome and 13 cases of B-cell or T-cell lymphoma. Among the patients with a second cancer, 2 in each group received a transplant and 3 in the ABVD group had received radiation therapy previously. Overall, 42% of second cancers occurred in patients 60 years of age or older (9 of 23 [39%] in patients in the A+AVD group and 14 of 32 [44%] in patients in the ABVD group).

Fertility was not formally assessed, but the number of pregnancies was reported. A total of 195 pregnancies were reported among patients and their partners (114 pregnancies in 82 patients or partners in the A+AVD group and 81 pregnancies in 61 patients or partners in the ABVD group) (Table S10).

Peripheral neuropathy continued to resolve or ameliorate in the two trial groups. Among 443 patients in the A+AVD group who had peripheral neuropathy, 379 (85.6%) had complete resolution (318 [71.8%]) or amelioration (61 [13.8%]) at the last follow-up. In the ABVD group, 286 patients had peripheral neuropathy, of whom 249 (87.1%) had either complete resolution (227 [79.4%]) or amelioration (22 [7.7%]) at the last follow-up (Table S11). At the last follow-up, 125 of 662 patients (18.9%) in the A+AVD group and 59 of 659 (9.0%) in the ABVD group had ongoing peripheral neuropathy. Most events were of grade 1 (in 71 patients [10.7%] in the A+AVD group and in 39 [5.9%] in the ABVD group) or grade 2 (in 38 [5.7%] and 16 [2.4%], respectively). Assessment of ongoing grade 3 or 4 peripheral neuropathy was limited in 11 of 16 patients in the A+AVD group (3 patients had died, 4 were lost to follow-up, and 4 withdrew from the trial before the resolution or amelioration of symptoms) and in 4 patients in the ABVD group (2 patients had died and 2 were lost to follow-up).

Table 1. Summary of Causes of Death (Safety Population).*

Cause of Death	A+AVD (N=662)	ABVD (N=659)
Any cause — no. (%)	39 (5.9)	64 (9.7)
Hodgkin's lymphoma or complications — no.	32	45
Second cancer — no.	1	11
Other cause — no.	6	8
Unknown cause	1	5†
Accident or suicide	3	0
Covid-19	0	1
Heart failure	1	1
Intracranial hemorrhage	1	0
Lower respiratory tract infection	0	1

* The safety population included all the patients who received at least one dose of trial medication. A+AVD denotes brentuximab vedotin plus doxorubicin, vinblastine, and dacarbazine; ABVD doxorubicin, bleomycin, vinblastine, and dacarbazine; and Covid-19 coronavirus disease 2019.

† In two patients in the ABVD group, death was reported to be of indeterminate cause, but the deaths occurred after the patients had had disease progression (documented by the investigators).

DISCUSSION

In this trial involving patients with previously untreated stage III or IV Hodgkin's lymphoma, treatment with A+AVD resulted in a risk of death that was significantly lower by 41% than that observed with ABVD therapy. This result translated to an overall difference in mortality of 4.5 percentage points in favor of A+AVD at 6 years.

Other regimens have resulted in prolonged overall survival among patients with advanced Hodgkin's lymphoma. In a post hoc analysis, the HD9 trial showed a survival benefit at 10 years with escalated BEACOPP therapy over alternating COPP-ABVD therapy.[6] There were significant be-

tween-group differences in treatment duration, and the findings have not been replicated in subsequent randomized trials of various therapies and treatment strategies as compared with ABVD.[20,21] Given the clinically significant short- and long-term toxic sequelae of BEACOPP, including infertility and a risk of second cancer, as well as limitations for use in older adults, BEACOPP has not been widely adopted despite the reported improvement in disease control. PET-adapted strategies have been investigated in subsequent trials, most notably the Risk-Adapted Therapy in Hodgkin Lymphoma (RATHL) trial, the Southwest Oncology Group (SWOG) S0816 trial, the German Hodgkin Study Group (GSHG) HD18 trial, and the AHL2011 trial.[4,7-9] Although the desired advantage with regard to the side-effect profile can be realized, to date, no evidence of improved overall survival with PET-adapted strategies as compared with ABVD has been reported. Of all the contemporary PET-adapted studies, only the GHSG HD18 trial showed an overall survival benefit, with four cycles of escalated BEACOPP as compared with six to eight cycles — a benefit that was primarily attributed to fewer treatment-related deaths in the group that received fewer cycles.[4]

In the ECHELON-1 trial, the improvement in overall survival with A+AVD as compared with ABVD was observed despite the wide availability and use of active salvage therapies. Historically, it has been difficult to show a survival benefit in the context of first-line therapy, in part because approximately half the patients with relapsed or refractory disease can receive salvage therapy. Such therapy includes the use of various salvage chemotherapy regimen combinations, transplantation, nivolumab, or more recently, brentuximab vedotin combined with bendamustine or nivolumab. The proportion of patients in the ABVD group who received subsequent therapy, including transplantation and subsequent use of brentuximab vedotin, as well as the consistency of these outcomes with other contemporary studies of ABVD, suggests that the observed survival benefit with A+AVD was not due to undertreatment of disease or underperformance of salvage agents administered in patients in the ABVD group. Instead, the survival benefit and reduction in the risk of disease-related death with A+AVD may be attributed to the additional mechanisms of action that have been observed in other studies of brentuximab vedotin, including antibody-dependent cellular phagocytosis, bystander activity in the tumor microenvironment (owing to the release of monomethyl auristatin E), induction of immunogenic cell death, and depletion of CD30-expressing regulatory T cells.[22-28]

The risk of second cancer is a critical consideration in patients with Hodgkin's lymphoma owing to its potential effects on long-term survival.[29,30] A pooled analysis of four randomized trials showed that a second cancer occurred in 4.0% of the patients treated with ABVD (with no cases of myelodysplastic syndrome or acute myeloid leukemia), as compared with 6.5% of those treated with BEACOPP (with 13 patients having myelodysplastic syndrome or acute myeloid leukemia).[13] In our trial, fewer second cancers were reported with A+AVD (in 23 patients [3.5%]) than with ABVD (in 32 [4.9%]), with a greater number of hematologic cancers, primarily B-cell and T-cell lymphomas, occurring in the ABVD group. Overall, approximately 42% of the second cancers occurred in patients 60 years of age or older, even though these patients constituted approximately 14% of the total trial population. Given that historical and contemporary trials often did not enroll older adults, these percentages may better approximate the expected incidence of second cancer with A+AVD and ABVD in clinical practice. In addition, although the use of subsequent therapy was more common with ABVD than with A+AVD, overall use of radiation therapy was nearly identical in the two groups. Among patients who had a second cancer, 3 in the ABVD group had received radiation therapy previously (vs. no patients in the A+AVD group), and 2 patients in each group received a transplant — findings that suggest that the imbalance of subsequent therapy use alone, including transplantation or radiation, did not drive the observed difference.

Other potential long-term sequelae must be considered. Treatment with chemotherapy may negatively affect fertility; however, ABVD is generally not considered to be associated with a greater risk of premature menopause than alkylating chemotherapy or pelvic radiotherapy.[31] A case–control study showed no substantial effect on fertility among patients treated with ABVD, particularly in contrast to intensified regimens, such as BEACOPP.[14,32-34] Although fertility was not formally assessed in our trial, a higher number of pregnancies was reported in patients (or

in partners of male patients) treated with A+AVD than in those treated with ABVD: 114 pregnancies in 82 patients or partners in the A+AVD group and 81 pregnancies in 61 patients or partners in the ABVD group. Although these data are inconclusive without a more complete assessment of hormone status and the goals of the couples, it is likely that A+AVD was not associated with more infertility than ABVD.

Although the incidence of peripheral neuropathy was higher with A+AVD than with ABVD and more ongoing neuropathy was noted at the last follow-up (18.9% vs. 9.0%), most patients (85.6%) had complete resolution or amelioration of their symptoms. However, 5.7% of the patients in the A+AVD group had ongoing grade 2 neuropathy at last follow-up (vs. 2.4% in the ABVD group), a finding that highlights the importance of monitoring for neuropathy and making appropriate dose modifications in a timely manner. No additional long-term toxic effects were observed with A+AVD, but the important long-term concern regarding pulmonary fibrosis was not systematically assessed after the completion of therapy. During treatment, a higher incidence of pulmonary toxic effects, including fatal events, was observed with ABVD than with A+AVD, particularly among older adults. Given that a reduction in bleomycin use led to reductions in the incidence of pulmonary toxic effects in the RATHL trial, the elimination of bleomycin from first-line therapy with A+AVD may be an important consideration in the treatment of some patients.[35,36]

As previously reported, a higher incidence of febrile neutropenia was observed with A+AVD (19.3%) than with ABVD (7.9%), but the incidence was lower and was similar to that observed with ABVD among patients who received A+AVD with G-CSF primary prophylaxis (10.8%).[15] A detailed analysis of G-CSF primary prophylaxis with A+AVD has been published previously.[37]

Three limitations of this trial are notable. Studies involving individual subgroups are hypothesis-generating and should be interpreted with caution and with consideration for the many potential overlapping characteristics that define an individual patient. Second, the cause of death was investigator-assessed as either being related or unrelated to Hodgkin's lymphoma or its complications, with additional contextual information provided in some but not all cases. Consequently, a detailed breakdown of cause of death among patients whose death was classified as being related to Hodgkin's lymphoma or its complications was not available, except for the deaths that occurred during treatment, which have been previously reported. Finally, peripheral neuropathy was recorded as the last observation carried forward; data regarding the patients who were lost to follow-up or who died before the resolution or amelioration of symptoms were not censored.

The treatment of advanced Hodgkin's lymphoma has been a success story in oncology, but only modest progress has been made in past decades. However, in this trial, treatment with A+AVD resulted in an improvement in both progression-free survival and overall survival.

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

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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APPENDIX

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