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Nivolumab+AVD in Advanced-Stage Classic Hodgkin's Lymphoma

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ABSTRACT

BACKGROUND

Incorporating brentuximab vedotin into the treatment of advanced-stage classic Hodgkin's lymphoma improves outcomes in adult and pediatric patients. However, brentuximab vedotin increases the toxic effects of treatment in adults, more than half of pediatric patients who receive the drug undergo consolidative radiation, and relapse remains a challenge. Programmed death 1 blockade is effective in Hodgkin's lymphoma, including in preliminary studies involving previously untreated patients.

METHODS

We conducted a phase 3, multicenter, open-label, randomized trial involving patients at least 12 years of age with stage III or IV newly diagnosed Hodgkin's lymphoma. Patients were randomly assigned to receive brentuximab vedotin with doxorubicin, vinblastine, and dacarbazine (BV+AVD) or nivolumab with doxorubicin, vinblastine, and dacarbazine (N+AVD). Prespecified patients could receive radiation therapy directed to residual metabolically active lesions. The primary end point was progression-free survival, defined as the time from randomization to the first observation of progressive disease or death from any cause.

RESULTS

Of 994 patients who underwent randomization, 970 were included in the intention-to-treat population for efficacy analyses. At the second planned interim analysis, with a median follow-up of 12.1 months, the threshold for efficacy was crossed, indicating that N+AVD significantly improved progression-free survival as compared with BV+AVD (hazard ratio for disease progression or death, 0.48; 99% confidence interval [CI], 0.27 to 0.87; two-sided P=0.001). Owing to the short follow-up time, we repeated the analysis with longer follow-up; with a median follow-up of 2.1 years (range, 0 to 4.2 years), the 2-year progression-free survival was 92% (95% CI, 89 to 94) with N+AVD, as compared with 83% (95% CI, 79 to 86) with BV+AVD (hazard ratio for disease progression or death, 0.45; 95% CI, 0.30 to 0.65). Overall, 7 patients received radiation therapy. Immune-related adverse events were infrequent with nivolumab; brentuximab vedotin was associated with more treatment discontinuation.

CONCLUSIONS

N+AVD resulted in longer progression-free survival than BV+AVD in adolescents and adults with stage III or IV advanced-stage classic Hodgkin's lymphoma and had a better side-effect profile. (Funded by the National Cancer Institute of the National Institutes of Health and others; S1826 ClinicalTrials.gov number, NCT03907488.)

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CME

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Combination chemotherapy has been the standard treatment for advanced-stage Hodgkin's lymphoma for decades. Chemotherapy backbones differ worldwide, with doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) and bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPP) being the most commonly used combinations.[1-3] Divergent approaches are taken for adult and pediatric patients, with modifications to these backbones, positron emission tomography (PET)–based response adaptation, and the use of consolidative radiotherapy after completion of chemotherapy in 55 to 76% of pediatric patients.[4-10]

The incorporation of the CD30-directed antibody drug conjugate brentuximab vedotin into the treatment of advanced-stage Hodgkin's lymphoma has led to improved outcomes.[11] Modified progression-free survival and overall survival in adults treated with brentuximab vedotin combined with doxorubicin, vinblastine, and dacarbazine (BV+AVD) are superior to survival with standard ABVD.[12,13] Inclusion of brentuximab vedotin into escalated BEACOPP (BrECADD) has led to reduced toxic effects and better efficacy,[14] and event-free survival is improved in pediatric patients with the integration of brentuximab vedotin into a pediatric chemotherapy backbone.[15] Nevertheless, relapses after treatment of advanced-stage Hodgkin's lymphoma remain problematic, brentuximab vedotin use necessitates more growth factor support than prior regimens, BV+AVD is more toxic than ABVD in adults, and 53% of pediatric patients still receive radiotherapy with brentuximab vedotin-based therapy.[16]

Programmed death receptor 1 (PD-1) ligand expression is ubiquitous on Hodgkin's Reed–Sternberg cells, owing to alteration of PD-1 ligand genes on chromosome 9p24.1.[17] PD-1 blockade is a safe and effective treatment for relapsed or refractory Hodgkin's lymphoma, and high response rates and durable remissions are observed after PD-1 blockade in untreated Hodgkin's lymphoma.[18-22] The SWOG Cancer Research Network collaborated with the pediatric and adult groups of the National Clinical Trials Network to conduct the S1826 trial, a phase 3, international, open-label, randomized trial of nivolumab combined with AVD (N+AVD) as compared with BV+AVD in adolescent and adult patients with newly diagnosed stage III or IV classic Hodgkin's lymphoma.

METHODS

TRIAL OVERSIGHT

The S1826 trial was led by SWOG and conducted at 256 sites across the United States and Canada in the National Cancer Institute (NCI)–funded National Clinical Trials Network. Nivolumab was supplied by Bristol Myers Squibb (one of the trial sponsors) to the NCI through a Cooperative Research and Development Agreement, and SeaGen supplied brentuximab vedotin to patients enrolled in Canada. The authors designed the trial; gathered, analyzed, and interpreted the data; and vouch for the accuracy and completeness of the data and the fidelity of the trial to the protocol. No one who is not an author contributed to writing the manuscript. All the data were maintained by the SWOG Statistical Center, and the trial was monitored by the SWOG data and safety monitoring committee. All the patients provided written informed consent. The trial was approved by the central institutional review board in Rockville, MD, and was conducted in accordance with the principles of the Declaration of Helsinki.

TRIAL DESIGN

Patients were randomly assigned to receive N+AVD intravenously (nivolumab at a dose of 240 mg in adults and 3 mg per kilogram of body weight in children 12 to <18 years of age [capped at 240 mg], doxorubicin at a dose of 25 mg per square meter of body-surface area, vinblastine at a dose of 6 mg per square meter, and dacarbazine at a dose of 375 mg per square meter) or BV+AVD (brentuximab vedotin at a dose of 1.2 mg per kilogram [capped at 100 kg], and AVD at the doses listed above) on days 1 and 15 of each 28-day cycle for six cycles. Dose reductions and modifications are described in the protocol, available with the full text of this article at NEJM.org. Granulocyte colony-stimulating factor (G-CSF) prophylaxis was mandatory in patients who received BV+AVD but optional, at the investigator's discretion, in patients who received N+AVD. Dexrazoxane use was permitted to reduce the risk of doxorubicin-induced cardiac toxic effects. Radiation (30 Gy) treatment of residually meta-

bolically active lesions at the end of treatment was allowed according to protocol-specified criteria but was used sparingly. Patients were stratified according to age (12 to 17 years, 18 to 60 years, or ≥61 years), score group (0 to 3 or 4 to 7) on the International Prognostic Score (IPS, a 7-point scale on which higher numbers indicate poorer prognosis), and the intent to use radiation (yes or no).

PATIENTS

Patients 12 years of age or older were eligible for inclusion in the trial if they had previously untreated stage III or IV classic Hodgkin's lymphoma, Zubrod performance status of 0 to 2 (or Lansky performance status of 50 to 100 in patients 17 years of age or younger), and adequate hematologic and organ function. Zubrod performance status is measured on a 5-point scale, with higher numbers reflecting greater disability, and Lansky performance status is measured on a scale ranging from 0 to 100, with higher numbers indicating better performance on play and activity. Pathological findings were reviewed centrally by three of the authors; as mandated by SWOG policy, patients without pathological confirmation of Hodgkin's lymphoma were deemed to be ineligible. Patients with controlled human immunodeficiency virus (HIV) infection were eligible. Patients with active autoimmune disease, preexisting interstitial lung disease, or peripheral neuropathy of grade 2 or higher were excluded. Full eligibility criteria are provided in the protocol.

END POINTS

The primary end point was progression-free survival, defined as the time from randomization to the first observation of progressive disease or death from any cause. Data from patients who were last known to be alive and without report of progression were censored as of the last date of contact. Key secondary end points were the incidence of adverse events, overall survival (defined as the time from randomization to death from any cause), and event-free survival (defined as the time from randomization to the date of progression or relapse, death from any cause, or administration of non–protocol-specified antilymphoma therapy in the absence of progression).

RESPONSE ASSESSMENT

Disease assessment was performed at baseline and at the end of treatment (4 to 8 weeks after completion of systemic therapy). Patients who received radiotherapy underwent additional response assessment afterwards. PET–computed tomography (PET-CT) was the preferred imaging method, although CT or magnetic resonance imaging (MRI) was acceptable if PET-CT was contraindicated. CT was performed at 1 year and 2 years after randomization. Response and progression were assessed by investigators according to the 2014 Lugano classification.[23]

STATISTICAL ANALYSIS

The primary objective was to assess progression-free survival in patients who received N+AVD as compared with those who received BV+AVD. Randomization was performed in a 1:1 ratio and was dynamically balanced across three stratification factors. On the basis of previous data, 2-year progression-free survival for the BV+AVD group was estimated to be approximately 84%.[13] An exponential cure-rate model was assumed for both groups, with the assumption that 70% of the patients in the BV+AVD group and 74% of the patients in the N+AVD group would have no disease progression or die in the long term. Among the fraction of patients with disease progression, a hazard ratio of 1.67 for disease progression was assumed in the comparison between the groups. On the basis of simulation, the trial was anticipated to have 86% power to detect a between-group difference of 6 percentage points in progression-free survival (i.e., 2-year progression-free survival of 90%). For the power calculations, we assumed uniform patient entry and a one-sided stratified log-rank test at a significance level of 2.5%. Details of the statistical analysis are provided in the Methods section of the Supplementary Appendix, available at NEJM.org. The final analysis was to be conducted when 179 events of disease progression or death occurred across both groups at a one-sided significance level of 0.021 to account for interim testing.

Interim analyses were planned when 25% (for futility only), 50%, and 75% of the anticipated progression-free survival events in the pooled groups had been observed. In accordance with SWOG policy, modified intention-to-treat analysis

was performed — patients who were deemed to be ineligible on the basis of pathology review or violation of the eligibility criteria were excluded. At the 50% information-fraction interim analysis (date of database lock, December 15, 2022), the SWOG data and safety monitoring committee recommended that the primary results be reported because the result for progression-free survival, the primary end point, crossed the protocol-specified efficacy threshold of a one-sided P value of less than 0.005. Two-sided P values are presented here. The database was locked for analysis (at the 70% information fraction) on March 24, 2024.

RESULTS

PATIENTS

A total of 994 patients underwent randomization between July 19, 2019, and October 5, 2022 — 496 were assigned to receive N+AVD and 498 to receive BV+AVD. Overall, 970 patients (97.6%) were eligible for inclusion in the modified intention-to-treat cohort (483 patients in the BV+AVD group and 487 in the N+AVD group) (Fig. 1). The characteristics of the patients at baseline were balanced between the two groups (Table 1). All treatment was discontinued early in 37 patients (7.6%) in the N+AVD group and 58 patients (12.0%) in the BV+AVD group. The reasons for treatment discontinuation are listed in Table S1 of the Supplementary Appendix; adverse events were the most frequent reason in both groups. Any discontinuation of nivolumab occurred in 46 patients (9.4%), and 107 patients (22.2%) discontinued brentuximab vedotin. The dose of brentuximab vedotin was reduced in 129 patients (26.7%); dose reduction of nivolumab was not permitted. Dexrazoxane was administered in 273 patients (28.1%), with similar use across groups and primarily in adolescent patients (188 of 236 patients 12 to <18 years of age [79.7%]). G-CSF was used in 274 patients (56.3%) in the N+AVD group, as compared with 467 patients

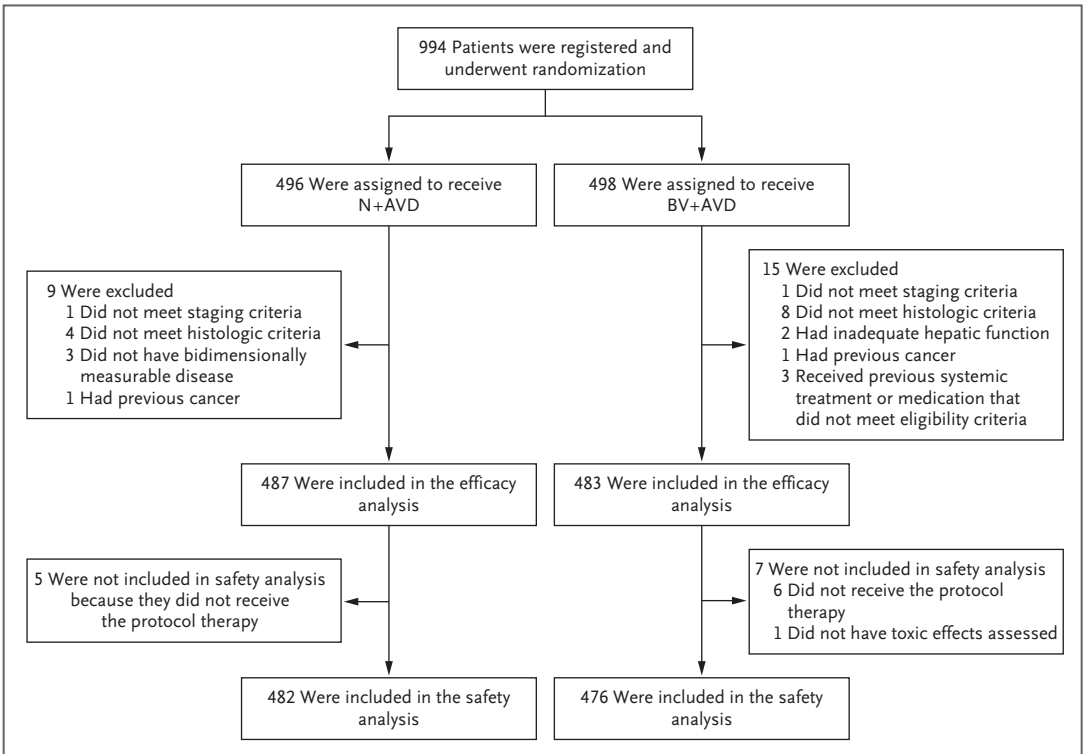

Figure 1. Randomization, Follow-up, and Analysis.

BV+AVD denotes brentuximab vedotin plus doxorubicin, vinblastine, and dacarbazine, and N+AVD nivolumab plus doxorubicin, vinblastine, and dacarbazine.

(96.7%) in the BV+AVD group. Radiation therapy was administered in 7 patients (0.7%) — 3 patients (0.6%) in the N+AVD group and 4 patients (0.8%) in the BV+AVD group (Table S2).

EFFICACY

At the prespecified second interim analysis (50% information fraction), the efficacy threshold for the interim analysis was crossed: N+AVD significantly improved progression-free survival as compared with BV+AVD (hazard ratio for disease progression or death, 0.48; 99% confidence interval [CI], 0.27 to 0.87; two-sided P=0.001). The median follow-up at the primary analysis time point was 12.1 months (range, 0 to 38.6), with disease progression or death occurring in 30 patients in the N+AVD group, as compared with 58 patients in the BV+AVD group. One-year progression-free survival was 94% (95% CI, 91 to 96) with N+AVD, as compared with 86% (95% CI, 82 to 90) with BV+AVD.

Owing to the short follow-up time for the primary analysis, we repeated the analysis after an additional 1 year of follow-up to assess the durability of the progression-free survival benefit. At a median follow-up of 2.1 years (range, 0 to 4.2), 2-year progression-free survival was 92% (95% CI, 89 to 94) after N+AVD and 83% (95% CI, 79 to 86) after BV+AVD (hazard ratio for disease progression or death, 0.45; 95% CI, 0.30 to 0.65) (Fig. 2A). Results were generally consistent across prespecified patient subgroups, including subgroups according to age, disease stage, and IPS score (Fig. 3 and Fig. S1).

The end-of-treatment metabolic response according to trial group is shown in Table S3. Two-year event-free survival was 90% after N+AVD and 81% after BV+AVD (stratified hazard ratio for death, 0.50; 95% CI, 0.36 to 0.71) (Fig. S2). The types of events in each trial group are shown in Table S4. Overall, death from any cause occurred in 7 patients in the N+AVD group (in 3 during treatment) and 14 patients in the BV+AVD group (in 8 during treatment). At 2.1 years of follow-up, 2-year overall survival was 99% in the N+AVD group and 98% in the BV+AVD group (hazard ratio for death, 0.39; 95% CI, 0.15 to 1.03) (Fig. 2B). Causes of death according to group are listed in Table S5, and the number of deaths according to age group are listed in Table S6. Infection or sepsis was the most frequent cause of death; only 3 patients died of lymphoma.

Table 1. Characteristics of the Patients at Baseline (Modified Intention-to-Treat Population).*

Characteristic	N+AVD (N=487)	BV+AVD (N=483)
Age		
Median (range) — yr	27.6 (12.0–83.7)	26.8 (12.0–81.7)
Distribution — no. (%)		
12–17 yr	118 (24)	118 (24)
18–60 yr	321 (66)	318 (66)
>60 yr	48 (10)	47 (10)
Female sex — no. (%)	216 (44)	210 (43)
Race or ethnic group — no. (%)†		
White	372 (76)	361 (75)
Black	58 (12)	56 (12)
Asian	11 (2)	17 (4)
Other or unknown	46 (9)	49 (10)
Hispanic	66 (14)	58 (12)
Disease stage — no. (%)		
III	185 (38)	168 (35)
IV	302 (62)	315 (65)
B symptoms present — no. (%)‡	288 (59)	273 (57)
IPS — no. (%)§		
0–3	332 (68)	328 (68)
4–7	155 (32)	155 (32)
Bulky disease — no. (%)¶	156 (32)	127 (26)
HIV-positive status — no. (%)	11 (2)	5 (1)

* The modified intention-to-treat population consisted of all the patients who underwent randomization except for those who were deemed to be ineligible by pathology review or owing to violation of the eligibility criteria. Percentages may not total 100 because of rounding. Data reflect an information fraction of 70%. BV+AVD denotes brentuximab vedotin plus doxorubicin, vinblastine, and dacarbazine, HIV human immunodeficiency virus, and N+AVD nivolumab plus doxorubicin, vinblastine, and dacarbazine.
† Race and ethnic group were determined by the patient.
‡ B symptoms include fever without an infection, drenching night sweats, and unintentional weight loss (at least 10% of body weight over 6 months).
§ The International Prognostic Score (IPS) is a 7-point scoring system in which 1 point is scored for the presence of each poor prognostic factor and higher scores indicate a poorer prognosis (higher risk).
¶ Bulky disease was defined as the presence of tumor mass larger than 10 cm in the greatest dimension.

SAFETY

The most frequent adverse events in each group are shown in Table 2 (all adverse events are listed in Table S7), with nearly all adverse events except neutropenia and arthralgia occurring more frequently with BV+AVD. The most commonly reported adverse events of grade 3 or higher are shown in Table S8; high-grade adverse events were

more frequent with BV+AVD, except neutropenia. Neutropenia of any grade occurred in 272 patients (56%) with N+AVD and in 160 patients (34%) with BV+AVD; 232 patients (48%) had neutropenia of grade 3 or higher with N+AVD, as compared with 126 patients (26%) with BV+AVD. Occurrences of febrile neutropenia, sepsis, and infection and infestation were similar in the groups, but these events occurred more frequent in older patients (in 18% of those aged 12 to 17 years, 20% of those aged 18 to 60 years; and 33% of those aged >60 years), especially among the patients who received BV+AVD.

Peripheral sensory neuropathy of any grade occurred in 139 patients (29%) who received N+AVD, as compared with 266 patients (56%) who received BV+AVD; 3% of those in the N+AVD group and 32% of those in the BV+AVD group had peripheral sensory neuropathy of grade 2 or higher. Occurrences of pneumonitis, gastritis, rash, and colitis were similar in the two groups (Table S9). Alanine aminotransaminase levels outside the normal range occurred in 160 patients (33%) treated with N+AVD and in 201 patients (42%) treated with BV+AVD. Hypothyroidism and hyperthyroidism occurred more

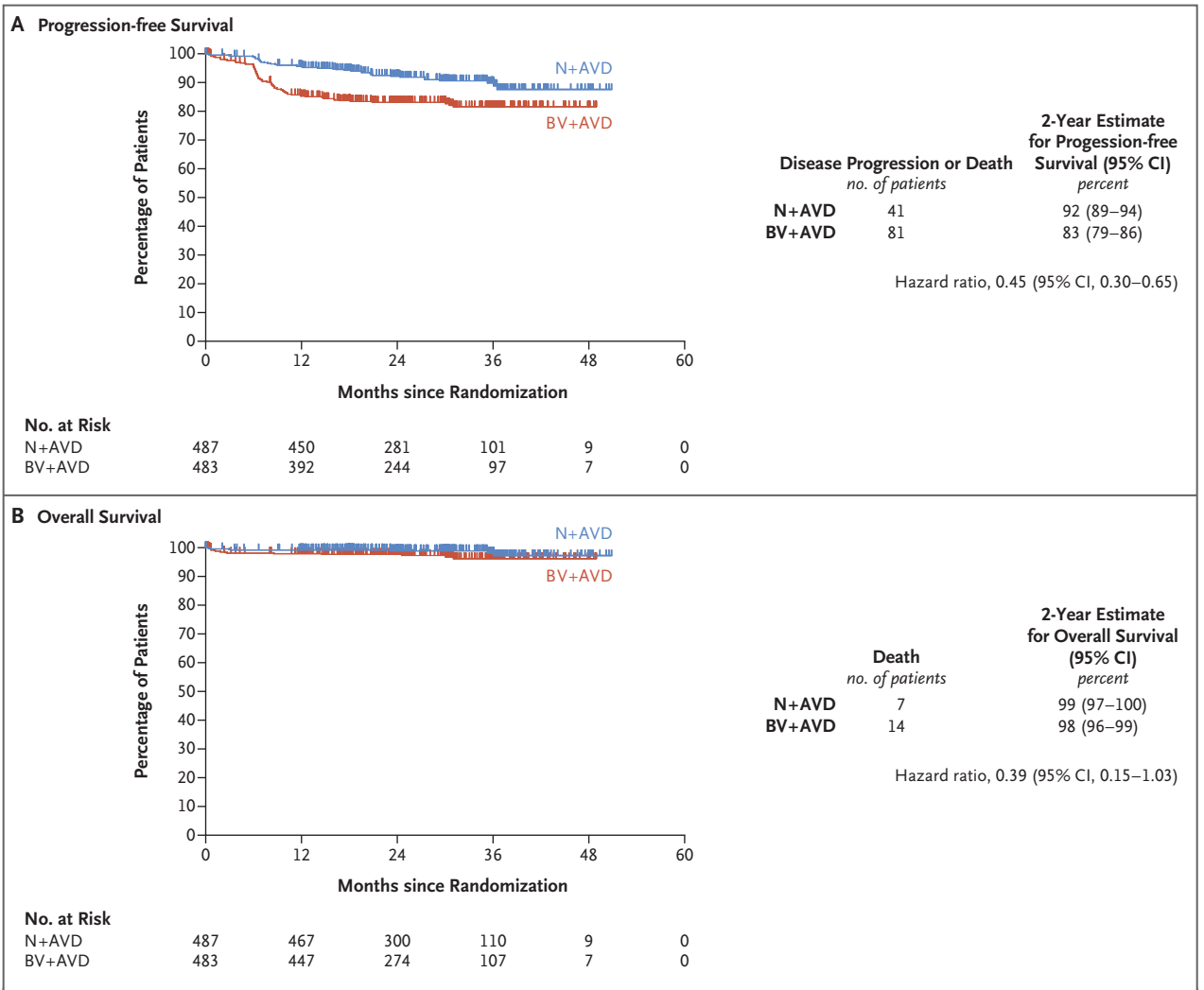

Figure 2. Progression-free Survival and Overall Survival (Modified Intention-to-Treat Population).

The modified intention-to-treat population consisted of all the patients who underwent randomization, except for those who were deemed to be ineligible on the basis of pathology review or violation of the eligibility criteria.

frequently after treatment among the patients in the N+AVD group (in 7% and 3%, respectively) than among those in the BV+AVD group (in <1% and 0%, respectively).

DISCUSSION

The S1826 trial showed that N+AVD significantly improved progression-free survival as compared with BV+AVD in adolescent and adult patients with advanced-stage classic Hodgkin's lymphoma. Event-free survival was also longer in patients receiving N+AVD. N+AVD had a better side-effect profile than BV+AVD — fewer patients stopped treatment early, fewer deaths occurred during treatment, and the incidence of immune-related toxic effects was low. Very few patients (<1%) received end-of-treatment radiotherapy, a dramatic reduction in the use of radiation in adolescent patients as compared with contemporary regimens. The S1826 trial was inclusive and representative of the population of patients with advanced-stage classic Hodgkin's lymphoma: approximately one quarter of the patients were younger than 18 years of age, 10% were older than 60 years of age, one quarter were from underrepresented backgrounds, and one third had IPS scores greater than 3 (Table S10).

The progression-free survival advantage observed with N+AVD was substantial and consistent across age, disease stage, and IPS-score subgroups. In the context of a disease in which a high proportion of patients are cured with standard therapy and the bar to change practice is set high, the improvement in efficacy and in the risk of adverse events was clinically meaningful. The interim efficacy-analysis threshold was crossed during a preplanned interim analysis with a median follow-up of only 1 year, and the improvement in progression-free survival with N+AVD was sustained with longer follow-up.

PD-1 blockade is a uniquely targeted treatment for Hodgkin's lymphoma, exploiting a therapeutic vulnerability caused by the genetic alteration of 9p24.1 in Hodgkin's Reed–Sternberg cells.[17] A randomized trial of PD-1 blockade as compared with brentuximab vedotin monotherapy in patients with relapsed or refractory Hodgkin's lymphoma showed improved progression-free survival with PD-1 blockade.[24] The results of our trial are consistent with that result, with PD-1 blockade being more effective than brentuximab vedotin when combined with

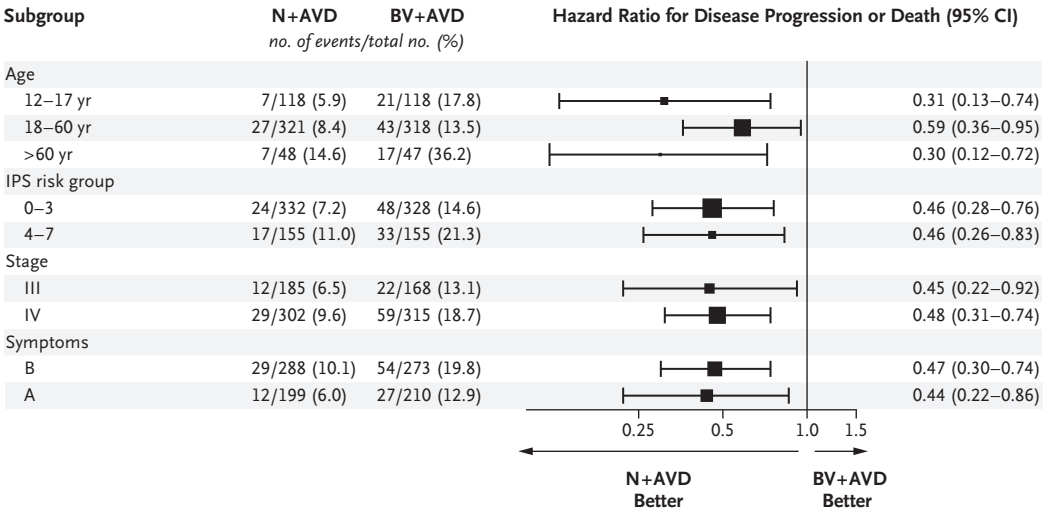

Figure 3. Subgroup Analysis of Progression-free Survival (Modified Intention-to-Treat Population).

The International Prognostic Score (IPS) is a 7-point scoring system in which 1 point is scored for the presence of each poor prognostic factor and higher scores indicate a poorer prognosis (higher risk). Symptom category B is the presence of fever without an infection, drenching night sweats, and unintentional weight loss (at least 10% of body weight over 6 months). Symptom category A indicates the absence of these symptoms.

Table 2. Adverse Events of Any Grade (Modified Intention-to-Treat Population).*

Event	N+AVD (N = 482)	BV+AVD (N = 476)
	number (percent)	
Nausea	312 (65)	331 (70)
Fatigue	228 (47)	242 (51)
Neutrophil count decreased	272 (56)	160 (34)
Anemia	190 (39)	217 (46)
Peripheral sensory neuropathy	139 (29)	266 (56)
Constipation	193 (40)	204 (43)
ALT increased	160 (33)	201 (42)
White-cells decreased	197 (41)	128 (27)
Vomiting	134 (28)	157 (33)
AST increased	125 (26)	160 (34)
Diarrhea	100 (21)	129 (27)
Alopecia	103 (21)	124 (26)
Lymphocyte count decreased	103 (21)	109 (23)
Mucositis, oral	107 (22)	100 (21)
Anorexia	61 (13)	106 (22)
Abdominal pain	58 (12)	107 (22)
Headache	69 (14)	75 (16)
Platelet count decreased	52 (11)	86 (18)
Bone pain	40 (8)	96 (20)
Alkaline phosphatase increased	54 (11)	81 (17)
Fever	62 (13)	61 (13)
Arthralgia	64 (13)	58 (12)
Hyperglycemia	57 (12)	63 (13)
Maculopapular rash	54 (11)	58 (12)
Myalgia	52 (11)	57 (12)
Dyspnea	42 (9)	58 (12)
Weight loss	25 (5)	71 (15)
Dysgeusia	35 (7)	59 (12)

* Shown are adverse events occurring in more than 10% of the patients in either group. Data reflect an information fraction of 70%. ALT denotes alanine aminotransferase, and AST aspartate aminotransferase.

chemotherapy in advanced-stage Hodgkin's lymphoma.

In addition to N+AVD providing greater efficacy, N+AVD also had a better side-effect profile than BV+AVD. More patients discontinued treatment with brentuximab vedotin than with nivolumab, and overall, most of the adverse events occurred less frequently in the N+AVD group than in the BV+AVD group. As expected with dual microtubule inhibition (vinblastine and vedotin), a substantially higher incidence of peripheral neuropathy was seen with BV+AVD than with N+AVD.[25] Immune-related adverse events that were associated with checkpoint inhibition were infrequent among patients treated with N+AVD.[26] Although neutropenia was observed in more patients in the N+AVD group, the frequency of neutropenia with BV+AVD was probably ameliorated by the required use of G-CSF as compared with the optional use of G-CSF with N+AVD. Febrile neutropenia, sepsis, and infections did not occur more frequently with N+AVD than with BV+AVD, and the reduced use of G-CSF led to less bone pain in the N+AVD group. The high incidence of neutropenia without increased risk of infection in the N+AVD group is similar to what has been seen for decades with ABVD, another regimen in which G-CSF primary prophylaxis is not used.

The S1826 trial was a collaborative lymphoma trial involving patients from the Children's Oncology Group (COG) and adult patient groups of the National Clinical Trials Network. The S1826 trial allowed for the earlier integration of new agents into pediatric Hodgkin's lymphoma protocols, thereby accelerating the harmonization of treatment guidelines for adolescent and young adult patients with Hodgkin's lymphoma. Historically, COG trials for patients with untreated pediatric advanced-stage Hodgkin's lymphoma have used a different chemotherapy backbone than adult studies, have included patients with stage IIB bulky disease (defined as the presence of tumor mass larger than 10 cm in the greatest dimension) and excluded patients with stage IIIA disease, and administered consolidative radiotherapy in 50 to 76% of the pediatric patients.[4,9,15] This last difference is notable because younger patients are particularly vulnerable to the late toxic effects (occurring after cessation of therapy) of radiation, such as secondary cancers and latent cardiopulmonary disease.[27-29] The criteria for end-of-treatment radiotherapy in the S1826 trial represent a major change to the radiotherapy guidelines in COG studies. The resulting extremely low use of radiotherapy in our trial (<1%), combined with the excellent outcomes observed after treatment with N+AVD, suggests that radiotherapy has limited utility in adolescent patients after they have received N+AVD. Although six cycles of ABVD-type therapy with a cumulative

doxorubicin dose of 300 mg per square meter is an established standard in the treatment of adults with advanced-stage Hodgkin's lymphoma, the dose of doxorubicin in six cycles of N+AVD is higher than in contemporary pediatric Hodgkin's lymphoma regimens[10,15] as well as in BEACOPP and BrECADD (140 to 200 mg per square meter). The concomitant use of dexrazoxane may be protective against late-onset cardiac disease, especially in the absence of radiotherapy.[30,31] Likewise, higher cumulative doses of doxorubicin are associated with increased breast-cancer risk,[32] but the considerable decrease in radiation is expected to help mitigate future breast-cancer risk in patients treated with N+AVD. Longer term follow-up in the current trial will be helpful in the assessment of the relative effects of doxorubicin dose and radiation levels on breast-cancer risk. Considering the excellent efficacy observed with N+AVD, future studies could evaluate modification of the regimen and anthracycline dose levels, potentially using biomarkers to deescalate therapy while maintaining efficacy.

The inclusive eligibility criteria in the S1826 trial resulted in enrollment of almost 100 patients over 60 years of age, a group historically underrepresented in Hodgkin's lymphoma trials.[33,34] Older patients with advanced-stage Hodgkin's lymphoma have shown markedly inferior outcomes owing to unacceptable side-effect profiles with conventional therapy and more treatment-resistant tumor biology.[35] In a previous National Clinical Trials Network trial of ABVD, the treatment-related mortality among older patients was 9%, owing in large part to bleomycin-induced pulmonary toxic effects.[36] A subset analysis of the ECHELON-1 trial, which avoided bleomycin, still showed inferior outcomes and high toxic effects among older patients.[37] In the current trial, BV+AVD was associated with a particularly unacceptable side-effect profile among older patients, with one third discontinuing all treatment early, as well as high mortality. On the basis of these findings, the use of BV+AVD should probably be avoided in older patients. Of note, in the S1826 trial, older patients who received N+AVD had outcomes similar to those among younger patients without significantly greater morbidity or mortality. Thus, we consider N+AVD to be an important new treatment option for fit older patients; unfit and frail older patients, a group of patients for whom alternative approaches are often used, were not included in our trial.[38]

Our trial has several limitations, including the short follow-up time. Secondary analyses and subgroup analyses that involved specified stratification factors were preplanned, but these analyses did not have adequate statistical power. Nevertheless, the results were consistent across subgroups.

The preliminary results of the HD21 trial were similar to those of the S1826 trial in that they showed an improved side-effect profile and superior efficacy of BrECADD as compared with escalated BEACOPP in advanced-stage classic Hodgkin's lymphoma. The balance of efficacy and toxic effects shown with BrECADD and N+AVD is the most favorable observed to date with a BEACOPP- or ABVD-derived regimen, respectively. There are key differences in the trial populations — for example, the HD21 trial included patients with stage IIB disease, and the S1826 trial included patients younger than 18 years and older than 60 years and enrolled a racially and ethnically diverse trial population. The use of end-of-treatment consolidative radiation was much lower in our trial (<1% with N+AVD vs. 14% with BrECADD), and N+AVD spares the use of brentuximab vedotin, which has had toxic effects when combined with chemotherapy, particularly in older adults. A direct comparison of the trial results of the S1826 and HD21 trials is not possible because of these differences. Future comparative studies would be appropriate to determine a definitive answer regarding the relative efficacy and safety of the regimens, including potential incorporation of biomarkers to identify precision approaches for patients who are more likely to benefit from a particular regimen.

The S1826 trial showed that N+AVD resulted in longer progression-free survival, as compared with BV+AVD, in advanced-stage classic Hodgkin's lymphoma. On the basis of the clinically meaningful improvement in progression-free survival and excellent side-effect profile of N+AVD, the opportunity to avoid potentially toxic consolidative radiation therapy, and the decreased drug-acquisition and supportive-care costs, N+AVD should be a strong candidate for primary treatment in adolescent and adult patients with stage III or IV Hodgkin's lymphoma.

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APPENDIX

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