Randomized Phase III Trial Comparing ABVD Plus Radiotherapy With the Stanford V Regimen in Patients With Stages I or II Locally Extensive, Bulky Mediastinal Hodgkin Lymphoma: A Subset Analysis of the North American Intergroup E2496 Trial

Ranjana H. Advani, Fangxin Hong, Richard I. Fisher, Nancy L. Bartlett, K. Sue Robinson, Randy D. Gascoyne, Henry Wagner Jr, Patrick J. Stiff, Bruce D. Cheson, Douglas A. Stewart, Leo I. Gordon, Brad S. Kahl, Jonathan W. Friedberg, Kristie A. Blum, Thomas M. Habermann, Joseph M. Tuscano, Richard T. Hoppe, and Sandra J. Horning

Ranjana H. Advani, Richard T. Hoppe, and Sandra J. Horning, Stanford University, Stanford; Joseph M. Tuscano, University of California, Davis Cancer Center, Sacramento, CA; Fangxin Hong, Dana-Farber Cancer Institute, Boston, MA; Richard I. Fisher and Jonathan W. Friedberg, University of Rochester, Rochester, NY; Nancy L. Bartlett, Washington University School of Medicine, St Louis, MO; K. Sue Robinson, Queen Elizabeth II Health Science Center, Halifax, Nova Scotia; Randy D. Gascoyne, British Columbia Cancer Agency, Vancouver, British Columbia; Douglas A. Stewart, Tim Baker Cancer Institute, Calgary, Alberta, Canada; Henry Wagner Jr, Penn State Cancer Institute, Hershey, PA; Patrick J. Stiff, Loyola University Medical Center, Maywood; Leo I. Gordon, Northwestern University, Chicago, IL; Bruce D. Cheson, Georgetown University Hospital, Washington, DC; Brad S. Kahl, University of Wisconsin, Madison, WI; Kristie A. Blum, Ohio State University, Columbus, OH; and Thomas M. Habermann, Mayo Clinic, Rochester, MN.

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Corresponding author: Ranjana H. Advani, MD, Stanford University, Stanford Cancer Center, 875 Blake Wilbur Dr, Suite CC-2338, Stanford, CA 94305-5821; e-mail: radvani@stanford.edu.

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ABSTRACT

Purpose

The phase III North American Intergroup E2496 Trial (Combination Chemotherapy With or Without Radiation Therapy in Treating Patients With Hodgkin's Lymphoma) compared doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) with mechlorethamine, doxorubicin, vincristine, bleomycin, vinblastine, etoposide, and prednisone (Stanford V). We report results of a planned subgroup analysis in patients with stage I or II bulky mediastinal Hodgkin lymphoma (HL).

Patients and Methods

Patients were randomly assigned to six to eight cycles of ABVD every 28 days or Stanford V once per week for 12 weeks. Two to 3 weeks after completion of chemotherapy, all patients received 36 Gy of modified involved field radiotherapy (IFRT) to the mediastinum, hila, and supraclavicular regions. Patients on the Stanford V arm received IFRT to additional sites ≥ 5 cm at diagnosis. Primary end points were failure-free survival (FFS) and overall survival (OS).

Results

Of 794 eligible patients, 264 had stage I or II bulky disease, 135 received ABVD, and 129 received Stanford V. Patient characteristics were matched. The overall response rate was 83% with ABVD and 88% with Stanford V. At a median follow-up of 6.5 years, the study excluded a difference of more than 21% in 5-year FFS and more than 16% in 5-year OS between ABVD and Stanford V (5-year FFS: 85% v 79%; HR, 0.68; 95% CI, 0.37 to 1.25; $P = .22$; 5-year OS: 96% v 92%; HR, 0.49; 95% CI, 0.16 to 1.47; $P = .19$). In-field relapses occurred in $< 10\%$ of the patients in each arm.

Conclusion

For patients with stage I or II bulky mediastinal HL, no substantial statistically significant differences were detected between the two regimens, although power was limited. To the best of our knowledge, this is the first prospective trial reporting outcomes specific to this subgroup, and it sets a benchmark for comparison of ongoing and future studies.

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INTRODUCTION

Bulky mediastinal involvement is seen in approximately 20% to 25% of patients with stage I or II Hodgkin lymphoma (HL).¹ Traditionally, bulk is defined as a ratio of the maximum width of the mediastinal mass to the maximum intrathoracic diameter on a standing posterior-anterior chest radiograph (mediastinal mass ratio [MMR]) of more than 0.33.² An alternative criterion incorporates a ratio with the intrathoracic width at T5-T6.^{3,4} By

using computed tomography (CT), bulk is defined as a mass greater than 10 cm.⁵ Studies suggest that chest radiograph and newer imaging modalities are concordant in approximately 90% of patients.⁶

Assignment of patients with stage I or II bulky mediastinal disease on clinical trials has varied.⁷ The European Organisation for Research and Treatment of Cancer (EORTC) considers all patients with bulky mediastinal involvement (MMR > 0.35) as having early-stage unfavorable disease, but this category also includes patients with stage I or II disease,

age older than 50 years, involvement of more than three lymph node regions, erythrocyte sedimentation rate more than 50, or “B” symptoms with erythrocyte sedimentation rate more than 30.⁸ In the German Hodgkin Study Group (GHSg), patients with stage I or II bulky disease without B symptoms or extranodal disease are considered early-stage unfavorable, whereas those with the latter symptoms are considered as having advanced disease.⁹ To compare data sets, it is important to understand these differences in assignment of patients on clinical trials because therapy is not uniform.

Combined modality therapy (CMT) has been considered standard of care for patients with stage I or II bulky disease, and algorithms for advanced-stage HL that incorporate radiation therapy (RT) are used in North America.⁷ The most common chemotherapy used is four to six cycles of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) followed by involved field radiation therapy (IFRT).⁷ Other regimens, such as mechlorethamine, doxorubicin, vincristine, bleomycin, vinblastine, etoposide, and prednisone (Stanford V) and escalated bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPP) have also been developed.^{10,11} The Stanford V regimen uses a CMT approach with 12 weeks of once-per-week chemotherapy followed by 36 Gy IFRT to sites ≥ 5 cm at the time of diagnosis. Compared with six cycles of ABVD, this regimen has 50% less anthracycline exposure (150 mg/m^2 v 300 mg/m^2) and 25% less bleomycin (30 U/m^2 v 120 U/m^2). Non-randomized data from Stanford reported excellent tolerability, an overall survival (OS) rate of 96%, and 5-year freedom from progression of 89% in patients with locally extensive and advanced HL.^{12,13} These results were subsequently confirmed in a pilot study by the Eastern Cooperative Oncology Group (ECOG).¹⁴ On the basis of these data, the randomized phase III US Intergroup E2496 Trial was conducted comparing ABVD and Stanford V in patients with newly diagnosed stage III or IV HL or stage I or II bulky disease. Overall study results have been reported, and they show no differences in outcome between the two arms.¹¹ Herein, we report the outcomes of a planned subset analysis of patients with stage I or II bulky disease. To the best of our knowledge, this is the first contemporary trial that reports outcomes on a subset of patients with disease bulk as the defining characteristic.

PATIENTS AND METHODS

ECOG, Cancer and Leukemia Group B (CALGB), and the Southwest Oncology Group (SWOG) participated in this prospective phase III trial. Eligibility criteria included patients with histologically proven, previously untreated HL with stage III or IV or stage I or II bulky disease defined by an MMR of greater than one third on chest radiography or ≥ 10 cm on CT.² Patients were randomly assigned to chemotherapy with six to eight cycles of ABVD or Stanford V once per week for 12 weeks. Two to 3 weeks after completion of chemotherapy, all patients with stage I or II bulky disease received 36 Gy IFRT to the mediastinum, hila, and supraclavicular regions. Patients receiving Stanford V were given IFRT to additional sites ≥ 5 cm. A real-time review of the RT field for each patient was performed by the Quality Assurance Review Center. In addition, RT fields were reviewed retrospectively for quality control.

Complete response (CR) was defined as complete regression of all palpable and demonstrable disease maintained for more than 4 weeks with no B symptoms. Partial response was defined as $\geq 50\%$ reduction in the sum of the products of the pretreatment dimensions of the measurable lesions for more than 4 weeks. Progressive disease (PD) was defined as an increase in size of 25%

Fig 1. CONSORT diagram. ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; Stanford V, mechlorethamine, doxorubicin, vincristine, bleomycin, vinblastine, etoposide, and prednisone.

of the sum of the products of the pretreatment measurements or the appearance of new lesions.

As a planned subset analysis, the primary end point was failure-free survival (FFS), defined as the time from random assignment to progression, relapse, or death. OS was measured from the time of random assignment to death as a result of any cause.

According to study design, the primary analyses of FFS and OS were restricted to eligible patients only. Comparisons were made by using a log-rank test stratified according to the International Prognostic Score (IPS; 0 to 2 v 3 to 7). Treatment groups were used as a stratification factor when necessary. The Kaplan-Meier method and Cox proportional regression model were used to estimate failure rates, hazard ratios (HRs), and 95% CIs.^{15,16} Fisher's exact test and the Wilcoxon rank sum test were used to compare proportions and medians, respectively. Toxicity was evaluated in all patients who received any protocol treatment regardless of eligibility. Patients with B symptoms and/or extranodal involvement at baseline were grouped as a subset with additional risk factors.¹⁷

RESULTS

From April 1999 to June 2006, 854 patients were enrolled. Of these, 264 of the 286 patients with stage I or II bulky disease were eligible. In all, 135 patients were randomly assigned to ABVD and 129 to Stanford V (Fig 1). Table 1 depicts well-matched demographic characteristics between the two study arms. For patients treated with ABVD, 65% received six cycles and 35% received eight cycles of chemotherapy. In total, 94.6% of patients treated with Stanford V received 12 weeks of chemotherapy. Twenty-four patients on the ABVD arm and 15 on the Stanford V arm did not receive any protocol-prescribed RT.

Toxicity

Data were available for 275 patients (142 on the ABVD arm and 133 on the Stanford V arm). Grade 3 to 4 neutropenia was similar between the two arms. In the Stanford V arm compared with the ABVD arm, there were more instances of grade 3 lymphopenia (83% v 46%; $P < .001$) and grade 3 and 4 sensory neuropathy (6% [grade 3] and 1% [grade 4] v 1% [grade 3]). At 5 years, the risk of second cancers

Table 1. Patient Demographic and Clinical Characteristics

Characteristic	ABVD Arm (n = 135)		Stanford V Arm (n = 129)	
	No.	%	No.	%
Age, years				
Median	31		29	
Range	18-62		16-63	
Sex				
Male	57	42.2	65	50.4
Female	78	57.8	64	49.6
ECOG performance status				
0-1	126	92.4	125	97
2	2	1.5	3	2.3
B symptoms	73	54.1	65	50.4
Disease stage				
I	16	11.9	14	10.9
II	99	73.3	95	73.6
IIE	14	10.4	20	15.5
WHO subtype				
Nodular sclerosis	98	72.6	105	81.4
Lymphocyte-rich	2	1.5	1	0.8
Mixed cellularity	5	3.7	6	4.7
Classical Hodgkin lymphoma, not further classifiable	22	16.3	15	11.6
Extranodal sites				
None	116	85.9	107	82.9
1	16	11.9	14	10.9
2	3	2.2	8	6.2
Lung involvement	10	7.4	6	4.7
Risk factors by IPS*				
0-2	102	75.6	106	82.2
≥ 3	28	20.74	23	17.8

Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; ECOG, Eastern Cooperative Oncology Group; IPS, International Prognostic Score; Stanford V, mechlorethamine, doxorubicin, vincristine, bleomycin, vinblastine, etoposide, and prednisone.
*Data not available in five patients.

Table 2. Response Rates According to Treatment Arms

Response	ABVD Arm (%) (n = 135)	Stanford V Arm (%) (n = 129)	Both Arms (%) (n = 264)
CR	74.8	80.6	77.6
PR	8.1	6.2	7.2
SD	5.9	6.2	6.1
Nonevaluable	5.9	5.4	5.7
Missing data	5.2	1.6	3.4

Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine and dacarbazine; CR, complete remission; PR, partial remission; SD, stable disease; Stanford V, mechlorethamine, doxorubicin, vincristine, bleomycin, vinblastine, etoposide, and prednisone.

The median OS has not been reached. In all, there were 14 deaths: five on the ABVD arm (PD, n = 1; respiratory failure/pneumonia, n = 2; sepsis, n = 1; unknown, n = 1) and nine on the Stanford V arm (PD, n = 3; complications from bone marrow transplantation, n = 4; unknown, n = 2). The 5-year OS for ABVD was 96% versus 92% for Stanford V (HR, 0.49; 95% CI, 0.16 to 1.47; $P = .19$), again indicating no significant difference between the two treatment arms (Fig 2B). No differences were noted in the two arms when data were analyzed by excluding patients who did not receive protocol-specified RT (Appendix Fig A1, online only).

With 42 failures and 14 deaths, the study can only detect an HR of 0.37 in FFS and 0.18 in OS with 90% power at a two-sided 0.05 significance level. Therefore, by using the observed rates in ABVD, the study reliably excluded a 5-year FFS difference of 85% versus 64% and a 5-year OS difference of 96% versus 80% between ABVD and Stanford V.

Outcomes According to Prognostic Variables

Outcomes were compared for patients with an IPS score of 0 to 2 (n = 208) versus 3 to 7 (n = 51). The median FFS and OS have not been reached for either group. The 5-year FFS was 82% for IPS 0 to 2 and 84% for IPS 3 to 7 (HR, 1.48; 95% CI, 0.41 to 5.27; $P = .55$; Fig 3A). The 5-year OS was significantly better for IPS 0 to 2 (95%) than for IPS 3 to 7 (91%; HR, 0.30; 95% CI, 0.08 to 1.10; $P = .05$; Fig 3B).

Outcomes were also assessed on the basis of the absence or presence of B symptoms and/or extranodal disease. There were 103 patients without these characteristics (ABVD, n = 48; Stanford V, n = 55) and 143 with additional unfavorable factors (ABVD, n = 73; Stanford V, n = 70). Eighteen patients with missing data were excluded. The 5-year FFS was significantly better for the subset without additional risk factors (89% v 77%; HR, 0.44; 95% CI, 0.21 to 0.93; $P = .03$) with no difference in 5-year OS (97% v 92%; HR, 0.30; 95% CI, 0.08 to 1.11; $P = .06$; Appendix Fig A2, online only). The impact of these additional risk factors was present for both ABVD and Stanford V (Appendix Fig A3 and Appendix Fig A4, online only).

was similar in the two groups ($P = .16$): two patients on the ABVD arm (one renal cell cancer, one breast cancer) and six on the Stanford V arm (one breast cancer, two non-Hodgkin lymphoma, one brain cancer, one acute myeloid leukemia, and one unknown). Details regarding specific histology or exact location of these second cancers were not captured in the ECOG database. No grade 5 toxicities were observed.

Response: FFS and OS

Response rates are provided in Table 2. Comparing ABVD with Stanford V, there were no significant differences in CR rates (75% v 81%; $P = .30$) and overall response rates (83% v 88%; $P = .40$). At a median follow-up of 6.54 years, there were 42 treatment failures (ABVD, n = 19; Stanford V, n = 23). Treatment failed for a majority of patients (63%) less than 1 year after therapy and for 32% between years 2 to 3. Two patients receiving ABVD relapsed after 3 years.

The median FFS was not reached in either arm; the 5-year FFS was 85% for patients on the ABVD arm and 79% for patients on the Stanford V arm (HR, 0.68; 95% CI, 0.37 to 1.25; $P = .22$), indicating no significant difference between the two treatment arms (Fig 2A). There was no difference in the patterns of relapse between the two treatment arms. In-field relapses occurred in less than 10% of patients in both study arms (Table 3).

DISCUSSION

In this randomized phase III trial comparing two CMT approaches in patients with stage I or II bulky HL, no substantial differences were detected in FFS or OS. There were no differences in patterns of failure and less than 10% infield recurrences, suggesting effective local control with IFRT. Hematologic toxicity was similar between the two

Fig 2. (A) Failure-free survival and (B) overall survival by treatment arm. ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; Stanford V, mechlorethamine, doxorubicin, vincristine, bleomycin, vinblastine, etoposide, and prednisone.

arms, except for more grade 3 lymphopenia with Stanford V, likely related to the use of prednisone in the regimen. This did not translate into any increase in infections. Nonhematologic toxicity was also comparable, except for slightly more neuropathy with Stanford V, likely related to the combined use of vincristine and vinblastine. Similar results have also been reported by others.^{18,19} Longer follow-up is required to assess the potential late cardiovascular and pulmonary risks of the higher doses of anthracycline and bleomycin in ABVD compared with Stanford V and the potential greater risks of the larger radiation fields used in Stanford V.

In stage III or IV HL, IPS is the most commonly used prognostic index, but its utility in patients with stage I or II bulky disease is unclear.²⁰ In the IPS data set, 13% of patients had stage I or II disease and were included because they had received therapy on protocols for advanced-stage disease because of bulk and/or B symptoms. A Swedish study of patients (n = 99) with stage IIB HL treated with six to eight cycles of chemotherapy followed by 30 to 40 Gy IFRT demonstrated that bulk was the only statistically significant prognostic factor ($P = .001$) independent of the IPS.²¹ In our study, there were no differences in outcomes in patients with 0 to 2 (good risk) versus 3 to 7 (poor risk) factors (Fig 3).

Trials for patients with unfavorable risk factors conducted by the EORTC and GHSG included patients with bulky mediastinal disease and also included patients with additional risk factors such as B symptoms, extranodal disease, and more than two or three sites of nodal involvement. Thus, it is difficult to assess outcomes specific to the subgroup with stage I or II bulky disease.^{8,9} In the EORTC-GELA (Groupe d'Etude des Lymphomes de l'Adulte) H9-U trial, patients with unfavorable stage I or II disease were randomly assigned to six cycles of ABVD or four cycles of ABVD or four cycles of baseline BEACOPP followed by 30 Gy IFRT in all arms. The 4-year event-free survival was 94%, 89%, and 91% ($P = .23$) and 4-year OS was 96%, 95%, and 93% ($P = .89$), respectively. Chemotherapy-related toxicity was higher with BEACOPP compared with ABVD. Although data were not reported for the subset of patients with bulky mediastinal disease, the EORTC H9-U trial established four cycles of ABVD plus 30 Gy IFRT as a standard for future comparisons in Europe.^{22,23}

In the GHSG, patients with unfavorable disease because of bulky mediastinal involvement are further classified with intermediate or advanced risk depending on additional risk factors. In the HD11 (for Intermediate Stages) trial, patients with stage I or II bulky

Fig 3. (A) Failure-free survival and (B) overall survival by International Prognostic Score (IPS).

Table 3. Patterns of Relapse

Relapse	ABVD (n = 135)		Stanford V (n = 129)	
	No.	%	No.	%
Total relapses	18	13.3	23	17.8
In-field only	8	5.8	7	5.4
Both in-field and distant	3	2.2	5	3.8
Distant	8	5.9	11	8.5
Intrathoracic	6		6	
Intra-abdominal	5		5	
Other	3		9	
Axilla	3		6	
Total in-field	11	8.1	12	9.3
Total distant	11	8.1	16	12.4

Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine and dacarbazine; Stanford V, mechlorethamine, doxorubicin, vincristine, bleomycin, vinblastine, etoposide, and prednisone.

disease (17% to 22% of the study population) without extranodal disease or B symptoms were randomly assigned to one of four treatment arms: four cycles of ABVD plus 30 Gy IFRT, four cycles of ABVD plus 20 Gy IFRT, four cycles of baseline BEACOPP plus 30 Gy IFRT, or four cycles of baseline BEACOPP plus 20 Gy IFRT.²⁴ For the entire cohort of 1,395 patients, the freedom from treatment failure (FFTF) at 5 years was 85%, OS was 94.5%, and progression-free survival was 86.0%. Baseline BEACOPP was more effective than ABVD when followed by only 20 Gy IFRT (5-year FFTF difference of 5.7%), but no difference was seen when 30 Gy IFRT was incorporated into the treatment. The OS was similar in all arms, but grade 3 or 4 toxicities were significantly higher in the BEACOPP group. Notably, no subset analysis was specifically reported for the outcomes of patients with bulky mediastinal disease. The GHSG HD14 trial of dose-intensification in early unfavorable HL (with the same inclusion criteria as the HD11 trial) randomly assigned patients to four cycles of ABVD or two cycles of escalated BEACOPP followed by two cycles of ABVD (2 × 2).⁹ Chemotherapy on both arms was followed by 30 Gy IFRT. Overall, 18.7% of patients had a large mediastinal mass. FFTF was superior in the 2 + 2 arm (difference of 7.2% at 5 years; HR, 0.44; 95% CI, 0.30 to 0.66) with no difference in OS. As in the HD11 study, grade 3 or 4 acute toxicity was significantly more frequent in the BEACOPP arm.⁹ Again, data restricted to patients with large mediastinal adenopathy were not provided.

Patients with stage I or II bulky HL and extranodal sites or B symptoms were treated on GHSG protocols (HD9, HD12, and HD15) for advanced HL. Results across these studies are similar, and none report outcomes specific to patients with stage I or II bulky disease.²⁵⁻²⁸ The HD15 trial established six cycles of escalated BEACOPP as standard treatment for patients with advanced HL within the GHSG, with IFRT added only for patients with residual metabolic activity on positron emission tomography (PET) imaging. The 5-year FFTF was 89.3% and the 5-year OS was 95.3%.²⁸

Within the caveats of nonplanned exploratory subset analyses, in our study, the 5-year FFS was significantly better for the subset of patients without B symptoms and/or extranodal sites with no difference in OS. The impact of these additional risk factors was present for both ABVD and Stanford V arms. A meta-analysis comparing

BEACOPP to ABVD for patients with early-stage unfavorable or advanced-stage HL suggests improved progression-free survival but without significant differences in OS.²⁹

The variable inclusion criteria across studies mentioned herein prevent direct comparison with our results. All of these regimens achieved freedom from progression ranging from 79% to 89% and OS of more than 90% but with different toxicity profiles. Therefore, questions related to the ideal choice of chemotherapy and role of RT remain unanswered.

Another limitation of our study is that responses were assessed by using CT-based criteria that have now largely been replaced by PET assessment to define a CR.³⁰ Trials that used escalated BEACOPP suggest that patients with a PET-negative residual mass at completion of chemotherapy do not require consolidation RT. Retrospective data on the use of RT only in patients who have a positive PET scan after ABVD chemotherapy showed no difference in outcome compared with the PET-negative patients treated without RT.³¹ In contrast, a prospective study evaluated consolidation RT versus observation in patients with bulky HL (> 5 cm) and negative PET scans after chemotherapy with six cycles of vinblastine, etoposide, bleomycin, epirubicin, and prednisone (VEBEP) and reported a significant increase in relapses in the observation group (14%) versus 4% in the CMT group ($P = .03$).³² All relapses involved the bulky site and contiguous nodal regions.

Concern for RT-related late effects, correlation of interim PET imaging results with prognosis, and the ability of PET imaging to discern active versus treated disease have led to studies assessing omission of RT, even for patients with bulky disease at diagnosis. In the ongoing EORTC LYSA (Lymphoma Study Association)/FIL (Fondazione Italiana Linfomi) H10 trial, a risk-adapted strategy incorporates PET imaging after two cycles of ABVD for unfavorable newly diagnosed stage I or II HL, including patients with bulky mediastinal disease.³³ Patients with a negative interim PET were randomly assigned to receive an additional four cycles of ABVD without RT (experimental arm: total of six cycles of ABVD) or two cycles of ABVD plus 30 Gy involved-node radiotherapy (standard arm). Patients with a positive interim PET were treated with two cycles of escalated BEACOPP followed by 30 Gy involved-node radiotherapy. In the standard arm, 74.8% of the patients had a negative early PET scan with seven events versus 16 events in the experimental arm. These results led an independent data monitoring committee to conclude that it was unlikely that noninferiority would be shown in the final results for the experimental arm, and they advised stopping random assignment for early PET-negative patients.³³ The study has been amended, and RT is administered to all patients with interim negative PET scans with no change in the design to escalate therapy if the interim PET scan is positive. As therapy is refined, it is necessary to strike a balance between preserving efficacy and overtreatment. Hopefully, through targeted subgroup analyses like ours, these important issues will be resolved. An ongoing CALGB trial (CALGB-50801; Response-Based Therapy Assessed By PET Scan in Treating Patients With Bulky Stage I and Stage II Classical Hodgkin Lymphoma) is using interim PET response to evaluate whether subsets of patients with stage I or II bulky HL might not require RT or may benefit from escalated BEACOPP.

Advances in the biology of HL have yielded a plethora of novel therapies. The recent approval of brentuximab vedotin is a

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

AUTHOR CONTRIBUTIONS

Conception and design: Fangxin Hong, Henry Wagner Jr, Bruce D.

Cheson, Leo I. Gordon, Richard T. Hoppe, Sandra J. Horning

Provision of study materials or patients: All authors

Collection and assembly of data: Ranjana H. Advani, Fangxin Hong, Randy D. Gascoyne, Henry Wagner Jr, Leo I. Gordon, Brad S. Kahl, Richard T. Hoppe, Sandra J. Horning

Data analysis and interpretation: All authors

Manuscript writing: All authors

Final approval of manuscript: All authors

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Randomized Phase III Trial Comparing ABVD Plus Radiotherapy With the Stanford V Regimen in Patients With Stages I or II Locally Extensive, Bulky Mediastinal Hodgkin Lymphoma: A Subset Analysis of the North American Intergroup E2496 Trial

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Randy D. Gascoyne

Honoraria: Genentech/Roche, Celgene, Janssen Pharmaceuticals, Seattle Genetics

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Henry Wagner Jr

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Patrick J. Stiff

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Honoraria: Celgene, Amgen, Genentech

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Richard T. Hoppe

Stock or Other Ownership: Johnson & Johnson, Pfizer

Honoraria: Clariant, Takeda Pharmaceuticals

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Appendix

Fig A1. (A) Failure-free survival and (B) overall survival by treatment arm, excluding patients who did not receive radiation therapy. ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; Stanford V, mechlorethamine, doxorubicin, vincristine, bleomycin, vinblastine, etoposide, and prednisone.

Fig A2. (A) Failure-free survival and (B) overall survival by absence or presence of B symptoms and/or extranodal disease (E).

ABVD + RT Versus Stanford V in Stage I or II Hodgkin Lymphoma

Fig A3. (A) Failure-free survival and (B) overall survival by treatment arms for patients without additional risk factors (B symptoms and/or extra nodal sites). ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; Stanford V, mechlorethamine, doxorubicin, vincristine, bleomycin, vinblastine, etoposide, and prednisone.

Fig A4. (A) Failure-free survival and (B) overall survival by treatment arm for patients with additional risk factors (B symptoms and/or extranodal disease). ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; Stanford V, mechlorethamine, doxorubicin, vincristine, bleomycin, vinblastine, etoposide, and prednisone.