Eight Cycles of ABVD Versus Four Cycles of BEACOPP<sub>escalated</sub> Plus Four Cycles of BEACOPP<sub>baseline</sub> in Stage III to IV, International Prognostic Score ≥ 3, High-Risk Hodgkin Lymphoma: First Results of the Phase III EORTC 20012 Intergroup Trial

Patrice Carde, Matthias Karnsach, Catherine Fortpied, Pauline Brice, Hussein Khaled, Olivier Casasnovas, Denis Caillot, Isabelle Gaillard, Serge Bologna, Christophe Ferme, Pietermella Johanna Lugtenburg, Frank Morschhauser, Igor Aurer, Bertrand Coiffier, Ralph Meyer, Matthew Seftel, Max Wolf, Bengt Glimelius, Anna Sureda, and Nicolas Mounier

ABSTRACT

Purpose
To compare patients with high-risk stage III to IV Hodgkin lymphoma (HL) in the phase III European Organisation for Research and Treatment of Cancer 20012 intergroup trial (Comparison of Two Combination Chemotherapy Regimens in Treating Patients With Stage III or Stage IV Hodgkin’s Lymphoma) who were randomly assigned to either doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) or to bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPP).

Patients and Methods
Patients with clinical stage III or IV HL, International Prognostic Score of 3 or higher, and age 60 years or younger received ABVD for eight cycles (ABVD8) or escalated-dose BEACOPP (BEACOPP<sub>escalated</sub>) for four cycles followed by baseline BEACOPP (BEACOPP<sub>baseline</sub>) for four cycles (BEACOPP<sub>4+4</sub>) without radiotherapy. Primary end points were event-free survival (EFS), treatment discontinuation, no complete response (CR) or unconﬁrmed complete response (CRu) after eight cycles, progression, relapse, or death. Secondary end points were CR rate, overall survival (OS), quality of life, secondary malignancies, and disease-free survival in CR/CRu patients.

Results
Between 2002 and 2010, 549 patients were randomly assigned to ABVD8 (n = 275) or BEACOPP<sub>4+4</sub> (n = 274). Other characteristics included median age, 35 years; male, 75%; stage IV, 74%; “B” symptoms, 81%; and International Prognostic Score ≥ 4, 59%. WHO performance status was 0 (34%), 1 (48%), or 2 (17%). Median follow-up was 3.6 years. CR/CRu was 82.5% in both arms. At 4 years, EFS was 63.7% for ABVD8 versus 69.3% for BEACOPP4+4 (hazard ratio [HR], 0.71; 95% CI, 0.42 to 1.21; P = .312); disease-free survival was 85.8% versus 91.0% (HR, 0.59; 95% CI, 0.33 to 1.06; P = .076), and OS was 86.7% versus 90.3% (HR, 0.71; 95% CI, 0.42 to 1.21; P = .208). Death as a result of toxicity occurred in six and five patients, early discontinuation (before cycle 5) in 12 and 26 patients, treatment crossovers in five and 10 patients, and secondary malignancies in eight and 10 patients in the ABVD8 and BEACOPP4+4 arms, respectively.

Conclusion
ABVD8 and BEACOPP4+4 resulted in similar EFS and OS in patients with high-risk advanced-stage HL. Because BEACOPP4+4 did not demonstrate a favorable effectiveness or toxicity ratio compared with ABVD8, treatment burden, immediate and late toxicities, and associated costs must be considered before selecting one of these regimens on which to build future treatment strategies.

J Clin Oncol 34. © 2016 by American Society of Clinical Oncology

INTRODUCTION

Doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) is standard for advanced Hodgkin lymphoma (HL),<sup>1,2</sup> ABVD proved to be superior to or less toxic than non-cross-resistant alternating regimens (mechlorethamine, vincristine, procarbazine, and prednisone/doxorubicin, bleomycin, vinblastine, and dacarbazine [MOPP/ABVD] and MOPP/ABV), multidrug regimens (MOPP/epirubicin, bleomycin, and vinblastine/cyclophosphamide, doxorubicin,
dacarbazine, cytarabine, and daunorubicin [MOPP/EBV/CAD];
methotrexate, etoposide, and lomustine [MEC]; chlorambucil,
vindabamide, procarbazine, and prednisone/prednisolone, doxorubicin,
bleoymycin, vincristine, and etoposide [ChlVPP/PABIOE]; hybrid
ChlVPP/etoposide, vindalastine, and doxorubicin [ChlVPP/EVA]),
and chemoradiotherapy (mechlorethamine, doxorubicin, vinblastine,
vincristine, bleomycin, etoposide, and prednisone [Stanford V]).

Increased cumulative and intensity-dosing have improved complete response (CR) rates and event-free survival (EFS) in HL.
This relationship with the response warranted dose escalation from standard cyclophosphamide, vincristine, procarbazine, and prednisone [COPP/ABVD to bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPP) at baseline (BEACOPPbaseline) and escalated BEACOPP (BEACOPPescalated) HD9 trial).11-13 BEACOPPescalated compared with BEACOPPbaseline provided fewer early progressions and higher 3-year freedom from treatment failure (FFTF) and EFS at 40 months (89% vs 79%) and 70% with standard COPP/ABVD (P < .05 each comparison). This higher FFTF translated into a higher overall survival (OS): 92% for BEACOPPescalated and 91% for BEACOPPbaseline Versus 86% for COPP/ABVD. Deaths were 32 of 463 versus 41 of 457 versus 46 of 263, respectively.14 However, no FFTF advantage was observed in patients older than age 60 years. Immediate toxicity was severe: grade 3 to 4 anemia occurred in 25% of the cycles and 69% of the patients. More occurrences of therapy-related acute myeloid leukemia and myelodysplastic syndromes were observed in the BEACOPPescalated arm (1.8% [SE, 0.8%] after 3 years).

The HD12 trial confirmed the HD9 results: it compared eight cycles of BEACOPPescalated with BEACOPP4+4 (with or without involved field radiotherapy), which was meant to reduce late hematologic and gonadal toxicity in young patients while maintaining disease control, mainly through a 25% reduction of the cumulative dose of etoposide (4.8 g/m2 reduced to 3.6 g/m2).15 This reinforced the hypothesis that a dose increment was important primarily during the first part of the treatment. Indeed, in accordance with the effective dose model, similar results were observed in the HD12 trial: FFTF was 86.4% and 84.8% (difference, –1.6%; 95% CI, –5.2% to 1.9%), progression-free survival (PFS) was 87.5% and 85% (difference, –2.5%; 95% CI, –6% to 1%), and 5-year OS was 92% versus 90.3% (difference, –1.7%; 95% CI, –4.6% to 1.1%), respectively.15,15 Similarly, eight cycles of BEACOPPescalated was tested against six cycles of BEACOPPescalated in the HD15 trial: the 5-year FFTF rates were 84.4% for eight cycles of BEACOPPescalated versus 89.3% for six cycles of BEACOPPescalated (97.5% CI, 0.5% to 9.3% for difference), thus promoting the standard of care. OS was 91.9% versus 95.3%, respectively (97.5% CI, 0.36 to 0.98).17 The cumulative drug doses in the BEACOPPescalated regimen and in six cycles of BEACOPPescalated are almost identical, a relevant criterion in the effective dose model (doxorubicin, 240 v 210 mg/m2; cyclophosphamide, 7,600 v 7,500 mg/m2; etoposide, 3,600 v 3,600 mg/m2; and procarbazine, 560 v 420 mg/m2, respectively).

The contribution of radiotherapy was unclear in the HD9 trial; it was marginal and restricted to the 10% of the patients with residual disease of 2.5 cm or more who were still positive by positron emission tomography after chemotherapy in the HD12 trial.14,15,17 Conversely, a large randomized trial showed that consolidation radiotherapy was detrimental for OS in CR and CR unconfirmed (CRu) patients after chemotherapy.18 First-line irradiation was not allowed in the EORTC 20012 Intergroup protocol.

Considering that standard dose regimens are suboptimal in poor-prognosis advanced-stage HL, we selected the patients with International Prognostic Score (IPS) ≥ 3 as the most likely to benefit from increased chemotherapy dosing.19 We aimed to clarify whether BEACOPPescalated provides a better EFS and leads to a longer OS than ABVD, especially because COPP/ABVD was not a standard therapy regimen.20-23 Meanwhile, two trials compared ABVD and BEACOPP4+4 and failed to show a survival difference.24,25 These randomized trials contradict the results of a recent and contested German Hodgkin Study Group meta-analysis that addressed the effect of initial treatment strategy on the survival of patients with advanced-stage HL, which increased interest in the EORTC 20012 Intergroup study, the largest one to target patients with high-risk stage III or IV HL.26,27

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The European Organisation for Research and Treatment of Cancer Lymphoma Group led this phase III intergroup trial, in collaboration with the Lymphoma Study Association, Groupe d’Etude des Lymphomes de l’Adulte, the Australasian Leukaemia and Lymphoma Group, the National Cancer Research Institute Lymphoma Group, Grup per l’Estudi dels Limfomes de Catalunya i Balears, the National Cancer Institute of Canada Clinical Trials Group, and the Nordic Lymphoma Group.

Patients
Inclusion criteria included untreated histologic classic HL, age 16 to 60 years, clinical stage III or IV, at least one bidimensionally measurable target lesion, performance status (PS) of 0 to 2, IPS ≥ 3, and no other malignancies except basal cell skin and in situ uterine cervix carcinomas. Exclusion criteria included no measurable disease; fertile patients who were not using contraception; pregnant or lactating patients; active infection; severe cardiopulmonary, neurologic, or metabolic disease; inadequate liver function (bilirubin ≥ 2.5 times upper limit of normal) or renal function (creatinine ≥ 150 μmol/L or ≥ 2.0 mg/dL) unless they were a result of HL. Written informed consent per the local ethics committee was mandatory before enrollment. The study was conducted according to the Declaration of Helsinki.

Treatment
Random assignments were stratified by institution and IPS (3 v 4). The standard treatment was eight cycles of ABVD (ABVD8) given every 4 weeks. The experimental treatment was four cycles of BEACOPPescalated followed by four cycles of BEACOPPbaseline (BEACOPP4+4) given every 3 weeks. Prophylactic granulocyte colony-stimulating factor was mandatory with BEACOPPescalated. Planned regimens are listed in Appendix Table A1 (online only).

Assessments and End Points
Disease assessment was planned after cycles 4, 6, and 8 by using clinical and computed tomography examinations according to the Response Evaluation Criteria in Solid Tumors (RECIST) for HL.28 The central study coordinators (CSCs) blindly reviewed the responses of the local investigator (II). An extension of the definition for CRu (as defined in the HD12 trial) was used for central review: patients who, on the basis of disease status evaluation at 4 to 6 weeks after treatment completion, were in...
partial response without additional treatment and progression of disease within 6 months. EFS was the primary end point, defined as the time from random assignment to early discontinuation of protocol treatment and no CR or CRu after eight cycles of chemotherapy, relapse, progression, or death. Secondary end points were CR or CRu, disease-free survival (DFS) in patients with CR, OS, quality of life, second malignancies, and cost effectiveness. As a result of the composite nature of the primary end point (including both treatment efficacy and feasibility), PFS was defined as time from random assignment to progression, relapse, or death and was also analyzed after the study was closed. Toxicities were graded according to Common Toxicity Criteria version 2.0.

### Statistical Design and Planned Analysis

The study was designed to detect a 10% increase in the 3-year EFS rate from 70% (ABVD8) to 80% (BEACOPP4+4; hazard ratio [HR], 0.62) by using a two-sided log-rank test with type I error of 0.05. With one interim analysis, 152 events were required to yield a power of 80% with 550 patients randomly assigned over 5.5 years and observed for 8 months after last random assignment. An interim analysis of EFS was planned after 50 events to stop the trial in case of superiority of the experimental arm. An alpha-spending function with a boundary parameter equal to 0.2 based on the Wang-Tsiatis method was used as a compromise between the O'Brien-Fleming and the Pocock approaches. The Independent Data Monitoring Committee was to be consulted if the lower limit of the 95% CI for the death-as-a-result-of-toxicity rate was ≥ 3% in any arm. All randomly assigned patients were to be included in the analysis of efficacy end points per intention to treat. The Kaplan-Meier method was used to analyze time-to-event end points, and the log-rank test was used to compare the two arms. All inferential tests were performed at the two-sided α = .05 level, and estimates were provided with their 95% CIs. Adverse events (AEs) were analyzed for all patients who started protocol therapy. The worst grade for each Common Toxicity Criteria toxicity item recorded during the entire treatment period was tabulated. For the most frequent events, the proportions of grade 4 hematologic toxicities and of grade 3 or 4 nonhematologic toxicities were computed with 95% CIs. Relative dose intensity (RDI) was the ratio (% of the average 1-day dose administered or planned during the treatment period. This article is based on data for 549 patients with 233 events for the primary end point up to the clinical cutoff date of November 19, 2010, 2 months after all patients stopped protocol treatment (Fig 1, CONSORT diagram). Median follow-up was 3.6 years.

### RESULTS

Between October 2002 and January 2010, 550 patients were randomly assigned. One patient who lacked informed consent was not included, leaving 275 (ABVD8) and 274 (BEACOPP4+4) intention-to-treat patients. Three (ABVD8) and five (BEACOPP4+4) patients who did not start treatment were excluded from safety analyses (Fig 1). Eighteen patients (3%), nine in each arm, among whom 15 started treatment, were ineligible because of the absence of...
bidimensionally measurable target lesion (3), concomitant active diseases (2), IPS < 3 (2), age older than 60 years (1), inappropriate stage (4), histology (4), prior treatment (1), and inadequate organ function (1). There were 531 eligible patients, 266 in the ABVD8 arm and 265 in the BEACOPP4+4 arm (per protocol population). No data were available at the time of database lock for two BEACOPP4+4 patients (Fig 1).

**Patient Characteristics**

Baseline characteristics are provided in Table 1 and include stage IV disease, 74%; WHO PS 0 to 1, 82%; and "B" symptoms, 81%. Median age was 35 years, 75% were males, and IPS was ≥ 4 in 9% of patients. Baseline characteristics were balanced across the two groups.

**Flow of Patients and Adherence to Protocol Treatment**

In the ABVD8 arm, three patients did not start treatment, 229 (84%) completed treatment, and 43 discontinued treatment, compared with the BEACOPP4+4 arm in which five patients did not start treatment, 218 (81%) completed treatment, and 49 discontinued treatment. Reasons for treatment discontinuation in the ABVD8 and BEACOPP4+4 arms were progressive disease (eight vs one), inability to achieve partial response after cycle 4 or CRu after cycle 6 (nine vs 11), toxicity (seven vs 24), patient refusal (seven vs six), and death not as a result of HL (two vs two), respectively (Fig 1).

Main protocol treatment violations were the absence of fully documented restaging at cycle 6 contrary to protocol requirements: 54% (ABVD8) and 48% (BEACOPP4+4) of the patients continued chemotherapy beyond cycle 6 without restaging. Incorrect response assessment was observed for 5.1% and 3.6% of the patients in the ABVD8 and BEACOPP4+4 arms, respectively.

RDI for ABVD8 was 97.5% for doxorubicin, 92.6% for bleomycin, 95.7% for vinblastine, and 97.0% for dacarbazine. RDI for the four cycles of BEACOPPescalated was 100.9% for doxorubicin, 99.7% for cyclophosphamide, 96.3% for etoposide, and 99.6% for procarbazine; vincristine was the only drug with an RDI below 90%. Treatment was delayed, reduced, or both less often in the ABVD8 arm than in the BEACOPP4+4 arm (16.7% vs 30.6% of cycles), usually from hematologic toxicity.

**Response**

A total of 227 patients (83%; 95% CI, 78% to 87%) achieved a CR or CRu, which was the same in both arms after centralized review, a higher number than that from the LI. According to the LI, CR was achieved by 202 patients (73.5%; 95% CI, 68.2% to 78.7%) in the ABVD8 arm and by 189 patients (69.0%; 95% CI, 63.5% to 74.5%) in the BEACOPP4+4 arm.

**EFS (primary end point)**

EFS at 4 years was 63.7% in the ABVD8 arm and 69.3% in the BEACOPP4+4 arm (HR, 0.86; 95% CI, 0.64 to 1.15; \(P = .313\) by
centralized review; Table 2 and Fig 2). The events that defined EFS were premature discontinuation (10.5% v 13.9%), no CR or CRu at cycle 8 (9.1% v 4.7%), progression or relapse (12.7% v 7.7%), and death (3.3% v 3.3%), respectively. In the BEACOPP4+4 arm, more patients ended protocol treatment prematurely as a result of immediate hematologic and infectious complications, including septic shock (one [ABVD8] v 18 [BEACOPP4+4]). Indeed, compared with the ABVD8 arm, grade 4 hematologic toxicity was more frequent in the BEACOPP4+4 arm for neutropenia (31.6% v 64.7%), febrile neutropenia (5.9% v 33.8%), severe AEs, and severe adverse reactions, which were sevenfold more frequent (101 v 708). Respiratory-related treatment discontinuations were more frequent and severe in the ABVD8 arm (7 v 5), including two deaths as a result of toxicity. An amendment for additional lung function tests prevented additional respiratory severe AEs. No difference for EFS was observed per LI in either arm (Appendix Table A2 [online only] and Appendix Fig A1 [online only]).

**DFS in CR and CRu Patients**

DFS rates in CR and CRu patients at 4 years were 85.8% in the ABVD8 arm and 91.0% in the BEACOPP4+4 arm (HR, 0.59; 95% CI, 0.33 to 1.06; P = .076; by centralized review: Table 2 and Fig 3).

**PFS**

PFS rates at 4 years were 72.8% in the ABVD8 arm and 83.4% in the BEACOPP4+4 arm (HR, 0.58; 95% CI, 0.39 to 0.85; P = .005 by centralized review [Table 2 and Appendix Fig A2, online only] and by LI [Appendix Table A2 and Appendix Fig A2]).

**OS and Causes of Death**

OS rates at 4 years were 86.7% in the ABVD8 arm and 90.3% in the BEACOPP4+4 arm (HR, 0.71; 95% CI, 0.42 to 1.21; P = .208; Table 2 and Fig 4). We observed 56 deaths (Tables 2 and 3): 33 (12.0%) in the ABVD8 arm and 23 (8.4%) in the BEACOPP4+4 arm. The main causes were HL (15 and seven patients) and toxicity (nine and six patients), respectively (Table 3). Only one death as a result of HL (BEACOPP4+4) occurred early (ie, within 3 months of the end of treatment). There were 11 early deaths as a result of toxicity (six in the ABVD8 arm and five in the BEACOPP4+4 arm), including five (two and three) as a result of bleomycin-induced acute respiratory distress syndrome, acute hepatitis (ABVD8 [one in each arm]), septic shock during aplasia, including one case of enterocolitis (BEACOPP4+4 [three]). Death as a result of a secondary malignancy occurred in two and four patients, respectively.

**AEs and Toxicity During Treatment**

Grade 4 hematologic toxicities in the ABVD8 and BEACOPP4+4 arms were a result of febrile neutropenia in 0.0% and 6.3%, leukopenia in 4.8% and 70.6%, granulocytopenia in 31.6% and 64.7%, and thrombocytopenia in 0% and 7.8% of the patients, respectively. Main nonhematologic toxicities (grade 3 to 4 in ≥5% of patients) were cardiovascular other than edema, hypertension, or hypotension (4.8% and 7.4%); fatigue (2.6% and 10.4%); GI other than anorexia, constipation, diarrhea, nausea, or vomiting (1.8% and 9.7%); infection in non-neutropenic patients (4.4% and 9.7%); neurologic other than dizziness or neuropathy (2.6% and 5.2%); and pulmonary other than cough, dyspnea, or pleural effusion (4.0% and 7.1%).
Deaths in the ABVD₈ and BEACOPP₄+₄ arms that were not a result of HL were, respectively, bleomycin-induced pulmonary toxicity (six and zero), septic shock or severe intercurrent infection (four and eight), liver failure (one and two), cardiomyopathy (two and one), and death after a second tumor (two and four), including non-Hodgkin lymphoma (NHL; two and one), bronchogenic and unknown primary carcinoma (zero and two), and acute monoblastic leukemia (zero and one).

Late AEs and Second Malignancies

Second malignancies were observed in eight patients in the ABVD₈ arm (two lung, three NHL, two myeloproliferative diseases, one other) and in 10 patients in the BEACOPP₄+₄ arm (one lung, two NHL, four myeloproliferative disease, three other). Cumulative incidence rates (Appendix Fig A3, online only) did not differ significantly (3.4% and 4.7% at 4 years, respectively).

This randomized phase III trial compared ABVD₈ and BEACOPP₄+₄ to assess chemotherapy dose density and dose intensity in the highest-risk patients (IPS ≥ 3) with stage III or IV HL (n = 550). Patients with poor-prognosis stage II disease (13% of the advanced-stage HL series) who were potentially curable with less advanced-stage HL population of the initial IPS project, HD9, EORTC 20012 Intergroup, and Groupe d’Etude des Lymphomes de l’Adulte H89 studies, respectively. The corresponding FFTF rates were 55%, 64%, and 84% at 3 years and 72% at 5 years, respectively, although OS rates were 78%, 86%, and 89% at 3 years and 80% at 5 years, a suboptimal result. The EORTC 20012 Intergroup study investigated whether patients age 60 years or younger with stages III to IV HL at the highest-risk IPS (≥ 3) would most benefit from dose-dense and dose-intense treatment, in keeping with the Kairos hypothesis.

EFS was chosen as the main end point to account for treatment efficacy and feasibility. Positron emission tomography imaging, not standard when the trial started, was excluded from the initial response assessment plan. To secure patient management, response evaluations were scheduled after cycles 4 and 6 in both arms. However, protocol time point evaluations were often omitted by the LI (primary analysis), particularly after cycle 6. Nevertheless, a retrospective central evaluation of responses (sensitivity analysis) was performed in all cases by the CSC (M.D., N.M., P.C.). No statistically significant difference was observed in EFS between the ABVD₈ and BEACOPP₄+₄ arms by either local or central assessment.

Central reviewers noted that many deaths as a result of toxicity could have been avoided considering the poor initial condition of patients: indeed, numbers were similar in both arms (six v five patients; 2% overall), in keeping with observations of the German Hodgkin Study Group.

OS rate was similarly high. Remarkably, OS in the BEACOPP₄+₄ arm of the EORTC 20012 Intergroup trial was the same (90.3%).

DISCUSSION
as in the BEACOPP+4 arm of the HD12 trial for patients with standard-risk stages II, III, or IV disease who received radiotherapy.15

Some questions were not answered. Late morbidity will be reported later, hopefully decreased by the omission of irradiation.35,36 However, BEACOPP+4 induced 3.5-fold more secondary hematologic malignancies than other regimens.37 Furthermore, in the HD2000 randomized trial, second malignancy risk—mostly solid tumors—at 10 years was 6.7 for BEACOPP+4 versus 0.9 for ABVD (P = .027).38 Although ABVD is known to preserve fertility, BEACOPP is associated with testicular and ovarian damage.39-43 This is a significant drawback in a young population (median age, 35 years; 67% of patients were younger than age 44 years). Feasibility and the results of stem-cell harvest for salvage therapy for our progressing or relapsing patients after ABVD and BEACOPP will be reported.

The large EORTC 20012 Intergroup trial compared ABVD and BEACOPP+4, administered with excellent compliance in patients in the highest-risk group of advanced-stage HL. As compared with ABVD, BEACOPP+4 produced an identical CR/CRu rate (82%) and no significant increase in 4-year EFS and OS. The marginal effect seen on DFS in favor of BEACOPP+4 (P = .001 [per LII]; P = .076 [per CSC]) did not translate into a difference in OS. A higher PFS for BEACOPP+4 (centralized review) also did not translate into higher OS, contrary to the result of the companion Lymphoma Study Association trial in patients with IPS 0 to 2.44 One explanation may be a better efficacy of salvage therapy after ABVD. Another explanation might be a poorer tolerance of BEACOPP+4 in the population of patients with more severe initial characteristics than in the other studies: age 35 versus 28 years; sex ratio of males to females, 3:1 versus 1:1; WHO PS of 1 or higher, 66% versus 36%; stage IV, 74% versus 57%; and B symptoms, 81% versus 54%.45,46 Our results confirm the results of two studies that randomly assigned patients with advanced-stage HL to ABVD or BEACOPP+4, which resulted in identical OS, with fewer BEACOPP+4 patients requiring salvage therapy.47,48 The disappointing yield from dose increment in the high-risk group, the severe early and late morbidities, and associated costs, all raise questions about the benefits of BEACOPP. Pooling the results of the three randomized studies that compared ABVD and BEACOPP+4 (manuscript in preparation) should reinforce their similar conclusions, assess potential differences, and may identify a group of patients that benefit from initial increment of dose intensity and dose density while minimizing immediate and late toxicities. Meanwhile, new agents should be tested with both regimens.

Table 3. Causes of Death

<table>
<thead>
<tr>
<th>Cause of Death</th>
<th>ABVD8 (n = 275)</th>
<th>%</th>
<th>BEACOPP+4 (n = 274)</th>
<th>%</th>
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<tr>
<td>Hodgkin lymphoma</td>
<td>15</td>
<td>5.5</td>
<td>7</td>
<td>2.6</td>
</tr>
<tr>
<td>Secondary hematologic or solid tumor</td>
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<td>0.7</td>
<td>4</td>
<td>1.5</td>
</tr>
<tr>
<td>Toxicity including death as a result of toxicity</td>
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<td>3.3</td>
<td>6</td>
<td>2.2</td>
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<td>Intercurrent infectious disease</td>
<td>2</td>
<td>0.7</td>
<td>3</td>
<td>1.1</td>
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Abbreviations: ABVD8, doxorubicin, bleomycin, vinblastine, and dacarbazine (eight cycles); BEACOPP+4, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (four cycles of BEACOPPescalated followed by four cycles of BEACOPPbaseline.

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Affiliations
Patrice Carde and Christophe Ferme, Gustave Roussy Cancer Campus, Villejuif; Pauline Brice, Hopital St. Louis, Paris; Olivier Casasnovas and Denis Caillot, Centre Hospitalier Universitaire (CHU) de Dijon, Dijon; Isabelle Gaillard, CHU Henri Mondor, Creteil; Serge Bolognese, Centre Hospitalier Regional Universitaire (CHR) de Nancy; Nancy; Frank Mochel and Agnes Merli, CHR de Lille, Lille; Bertrand Coffier, CHU de Lyon, Lyon; Nicolas Mounier, Hopital de L’Arche, Nice, France; Matthias Karrasch and Catherine Fortpied, European Organisation for Research and Treatment of Cancer Headquarters, Brussels, Belgium; Hussein Khaled, National Cancer Institute, Cairo,
Egypt; Piernella Johanna Lugtenburg, Erasmus Medical Center Cancer Institute, Rotterdam, the Netherlands; Igor Aurer, University Hospital Centre Zagreb, Zagreb, Croatia; Ralph Meyer, Juravinski Cancer Centre, Hamilton, Ontario; Matthew Seftel, Cancer Care Manitoba, Winnipeg, Manitoba, Canada; Max Wolf, Peter MacCallum Cancer Institute, East Melbourne, Victoria, Australia; Bengt Glimelius, Uppsala University, Uppsala, Sweden; and Anna Sureda, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain.
AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Eight Cycles of ABVD Versus Four Cycles of BEACOPP_{escalated} Plus Four Cycles of BEACOPP_{baseline} in Stage III to IV, High-Risk Hodgkin Lymphoma: First Results of the Phase III EORTC 20012 Intergroup Trial

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Patrice Carde
No relationship to disclose

Matthias Karrasch
Travel, Accommodations, Expenses: Abbott, MSD, Seegene

Catherine Fortpied
No relationship to disclose

Pauline Brice
No relationship to disclose

Hussein Khaled
No relationship to disclose

Olivier Casasnovas
Honoraria: Genentech, Takeda Pharmaceuticals, Gilead Sciences, Sanofi
Consulting or Advisory Role: Genentech, Takeda Pharmaceuticals, Gilead Sciences
Research Funding: Genentech (Inst)
Travel, Accommodations, Expenses: Genentech, Takeda Pharmaceuticals, Gilead Sciences

Denis Caillot
No relationship to disclose

Isabelle Gaillard
Employment: Amgen
Honoraria: Amgen
Research Funding: Amgen
Travel, Accommodations, Expenses: Amgen

Serge Bologna
No relationship to disclose

Christophe Ferme
No relationship to disclose

Pietermela Johanna Lugtenburg
Consulting or Advisory Role: Takeda Pharmaceuticals

Frank Morschhauser
Consulting or Advisory Role: Gilead Sciences, Servier
Expert Testimony: Genentech, Janssen Oncology
Travel, Accommodations, Expenses: Sanofi Pasteur, Celgene, Gilead Sciences

Igor Aurer
No relationship to disclose

Bertrand Coiffier
No relationship to disclose

Ralph Meyer
No relationship to disclose

Matthew Seftel
Consulting or Advisory Role: Lundbeck
Research Funding: Lundbeck

Max Wolf
No relationship to disclose

Bengt Glimelius
No relationship to disclose

Anna Sureda
No relationship to disclose

Nicolas Mounier
No relationship to disclose
Acknowledgment

We thank Marine Divine, MD, our previous co-coordinator, and the European Organisation for Research and Treatment of Cancer Headquarters team, in particular Bart Meulemans, Livia Giurgea, Tiana Raveloarivahy, Steven Mortier, Niels Goetschalcks, Hilde Bressens, Emad Shash, Safaa Ramadan, Sarah Nuyens, and Alice Preumont.

Appendix

Table A1. Treatment Regimen

<table>
<thead>
<tr>
<th>Drug</th>
<th>ABVD8</th>
<th>BEACOPPescalated</th>
<th>BEACOPPbaseline</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Daily Dose</td>
<td>Days Given</td>
<td>Daily Dose</td>
</tr>
<tr>
<td>Bleomycin</td>
<td>10 mg/m²</td>
<td>1, 15</td>
<td>10 mg/m²</td>
</tr>
<tr>
<td>Etoposide*</td>
<td>200 mg/m²/d</td>
<td>1-3</td>
<td>100 mg/m²/d</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>25 mg/m²</td>
<td>1, 15</td>
<td>35 mg/m²</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>1,250 mg/m²</td>
<td>1</td>
<td>650 mg/m²</td>
</tr>
<tr>
<td>Vincristine</td>
<td>1.4 mg/m²</td>
<td>8</td>
<td>1.4 mg/m²</td>
</tr>
<tr>
<td>(maximum, 2 mg)</td>
<td></td>
<td></td>
<td>(maximum, 2 mg)</td>
</tr>
<tr>
<td>Procarbazine</td>
<td>100 mg/m²/d</td>
<td>1-7</td>
<td>100 mg/m²/d</td>
</tr>
<tr>
<td>Prednisone†</td>
<td>40 mg/m²/d</td>
<td>1-14</td>
<td>40 mg/m²/d</td>
</tr>
<tr>
<td>Vinblastine</td>
<td>6 mg/m²</td>
<td>1, 15</td>
<td></td>
</tr>
<tr>
<td>Dacarbazine</td>
<td>375 mg/m²</td>
<td>1, 15</td>
<td></td>
</tr>
</tbody>
</table>

NOTE. Protocol treatment was to be discontinued in case of insufficient response (ie, less than partial response after four cycles, less than unconfirmed complete response after six cycles, progression, or relapse), excessive toxicity, patient refusal, or investigator’s decision. Radiotherapy was not part of the protocol treatment.

Abbreviations: ABVD8, doxorubicin, bleomycin, vinblastine, and dacarbazine (eight cycles); BEACOPP, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone.

*A dose of etoposide phosphate 113 mg is equivalent to etoposide 100 mg.
†Prednisone could be replaced by an equivalent dose of dexamethasone (5 mg/m²/d).
Table A2. EFS, DFS in CR Patients, and PFS

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No. of Patients</th>
<th>OEs</th>
<th>HR</th>
<th>95% CI</th>
<th>P</th>
<th>Median (years)</th>
<th>% (at 4 years)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>EFS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ABVD₈</td>
<td>275</td>
<td>121</td>
<td>1.00</td>
<td></td>
<td>.8980*</td>
<td>NR</td>
<td>54.01</td>
<td>47.57 to 60.01</td>
</tr>
<tr>
<td>BEACOPP₄+₄</td>
<td>274</td>
<td>112</td>
<td>1.02</td>
<td>0.79 to 1.32</td>
<td>NR</td>
<td>58.08</td>
<td>51.78 to 63.86</td>
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</tr>
<tr>
<td>DFS (LI, CSC)†</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ABVD₈</td>
<td>202</td>
<td>35</td>
<td>1.00</td>
<td></td>
<td>.001*</td>
<td>NR</td>
<td>79.7</td>
<td>72.7 to 85.1</td>
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<td>BEACOPP₄+₄</td>
<td>189</td>
<td>13</td>
<td>0.36</td>
<td>0.19 to 0.68</td>
<td>.001*</td>
<td>NR</td>
<td>92.0</td>
<td>86.4 to 95.3</td>
</tr>
<tr>
<td>PFS (LI)‡§</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ABVD₈</td>
<td>275</td>
<td>75</td>
<td>1.00</td>
<td></td>
<td>&lt; .001</td>
<td>NR</td>
<td>69.36</td>
<td>62.88 to 74.93</td>
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<tr>
<td>BEACOPP₄+₄</td>
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<td>39</td>
<td>0.50</td>
<td>0.34 to 0.73</td>
<td>&lt; .001</td>
<td>NR</td>
<td>84.02</td>
<td>78.56 to 88.20</td>
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</tbody>
</table>

Abbreviations: ABVD₈, doxorubicin, bleomycin, vinblastine, and dacarbazine (eight cycles); BEACOPP₄+₄, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (four cycles of BEACOPPescalated followed by four cycles of BEACOPPbaseline; CR, complete response; CSC, central study coordinator; DFS, disease-free survival; EFS, event-free survival; HR, hazard ratio; LI, local investigator; NR, not reached; OE, observed events; PFS, progression-free survival.

*Log-rank P value.
†For DFS, HR, 95% CI, and P values were determined according to the Cox model; median, percent (at 4 years), and 95% CI were determined according to a nonparametric model.
‡Score test P value.
§From initial Case Report Form.

Fig A1. Event-free survival according to local assessment. ABVD₈, doxorubicin, bleomycin, vinblastine, and dacarbazine (eight cycles); BEACOPP₄+₄, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (four cycles of BEACOPPescalated followed by four cycles of BEACOPPbaseline; N, No. at risk; O, observed events.
Fig A2. Progression-free survival according to data from (A) a centralized review and (B) local assessment. ABVD8, doxorubicin, bleomycin, vinblastine, and dacarbazine (eight cycles); BEACOPP4+4, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (four cycles of BEACOPP escalated followed by four cycles of BEACOPP baseline); N, No. at risk; O, observed events.
<table>
<thead>
<tr>
<th>Time (years)</th>
<th>No. at risk</th>
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<tbody>
<tr>
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<td>10</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>30</td>
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</tr>
<tr>
<td></td>
<td>50</td>
<td>60</td>
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</tr>
<tr>
<td></td>
<td>90</td>
<td>100</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment</th>
<th>ABVD8 (N = 275; O = 8)</th>
<th>BEACOPP4+4 (N = 274; O = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cumulative Incidence (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>10</td>
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</tr>
<tr>
<td>1</td>
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</tr>
<tr>
<td>2</td>
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<tr>
<td>8</td>
<td>90</td>
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</table>

**Fig A3.** Cumulative incidence for second malignancies with death as a competing event. ABVD8, doxorubicin, bleomycin, vinblastine, and dacarbazine (eight cycles); BEACOPP4+4, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (four cycles of BEACOPP escalated followed by four cycles of BEACOPP baseline); N, No. at risk; O, observed events.