original reports

Brentuximab Vedotin Plus AVD for First-Line Treatment of Early-Stage Unfavorable Hodgkin Lymphoma (BREACH): A Multicenter, Open-Label, Randomized, Phase II Trial

Luc-Matthieu Fornecker, MD, PhD[1]; Julien Lazarovici, MD[2]; Igor Aurer, MD, PhD[3]; René-Olivier Casasnovas, MD[4]; Anne-Claire Gac, MD[5]; Christophe Bonnet, MD[6]; Krimo Bouabdallah, MD[7]; Pierre Feugier, MD[8]; Lena Specht, MD[9]; Lysiane Molina, MD[10]; Mohamed Touati, MD[11]; Cécile Borel, MD[12]; Aspasia Stamatoullas, MD[13]; Emmanuelle Nicolas-Virelizier, MD[14]; Laurent Pascal, MD[15]; Pieternella Lugtenburg, MD, PhD[16]; Nicola Di Renzo, MD[17]; Thierry Vander Borght, MD, PhD[18]; Alexandra Traverse-Glehen, MD[19]; Peggy Dartigues, MD[2]; Martin Hutchings, MD[20]; Annibale Versari, MD[21]; Michel Meignan, MD[22]; Massimo Federico, MD[23]; and Marc André, MD[18] for the LYSA-FIL-EORTC Intergroup

abstract

PURPOSE The prognosis of patients with early-stage unfavorable Hodgkin lymphoma remains unsatisfactory. We assessed the efficacy and safety of brentuximab vedotin plus doxorubicin, vinblastine, and dacarbazine (BV-AVD) in previously untreated, early-stage unfavorable Hodgkin lymphoma (ClinicalTrials.gov identifier: NCT02292979).

METHODS BREACH is a multicenter, randomized, open-label, phase II trial. Eligible patients were age 18-60 years with ≥ 1 unfavorable EORTC/LYSA criterion. Patients were randomly assigned (2:1) to four cycles of BV-AVD or standard doxorubicin, bleomycin, vincristine, and dacarbazine (ABVD), followed by 30 Gy involved node radiotherapy. The primary end point was the positron emission tomography (PET) response rate after two cycles by expert independent review using the Deauville score. The study was designed to test if the PET-negative rate after two cycles of BV-AVD was superior to 75%. We hypothesized a 10% increase in the PET-negative rate after two cycles of BV-AVD.

RESULTS Between March 2015 and October 2016, 170 patients were enrolled. After two cycles, the primary end point of the study was met: 93 (82.3%; 90% CI, 75.3 to 88.0) of 113 patients in the BV-AVD arm were PET-negative (Deauville score 1-3) compared with 43 (75.4%; 90% CI, 64.3% to 84.5%) of 57 in the ABVD arm. The 2-year progression-free survival (PFS) was 97.3% (95% CI, 91.9 to 99.1) and 92.6% (95% CI, 81.4% to 97.2%) in the BV-AVD and ABVD arms, respectively. High total metabolic tumor volume was associated with a significantly shorter PFS (hazard ratio, 17.9; 95% CI, 2.2 to 145.5; $P < .001$). For patients with high total metabolic tumor volume, the 2-year PFS rate was 90.9% (95% CI, 74.4 to 97.0) and 70.7% (95% CI, 39.4% to 87.9%) in the BV-AVD and ABVD arms, respectively.

CONCLUSION BV-AVD demonstrated an improvement in the PET-negative rate compared with ABVD after two cycles.

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ASSOCIATED CONTENT

Appendix

Data Sharing Statement

Protocol

Author affiliations and support information (if applicable) appear at the end of this article.

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INTRODUCTION

The outcome of patients with early-stage Hodgkin lymphoma and unfavorable prognostic factors remains inferior compared with favorable early-stage patients with a 5-year overall survival (OS) of 90% or less.[1,2] These results can be improved by a more intensified chemotherapy regimen as demonstrated in the HD14 trial from the German Hodgkin Study Group with a significant improvement in progression-free survival (PFS) after two cycles of increased dose of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone ($BEACOPP_{escalated}$) followed by two cycles of doxorubicin, bleomycin, vincristine, and dacarbazine (ABVD) compared with four cycles of ABVD followed by 30 Gy involved-field radiotherapy in both groups.[3]

Early interim [^{18}F]-fluorodeoxyglucose positron emission tomography (PET) performed after two cycles has emerged as a major prognostic tool, allowing early identification of patients at high risk of relapse.[4-6] In early-stage Hodgkin lymphoma, interim PET can also be used to guide treatment, as demonstrated by the RAPID and H10 trials.[7,8] PET is commonly interpreted according to the Deauville criteria, which are considered a standard for PET assessment in routine practice and clinical trials.[9] PET2 evaluation according to 2014 Lugano criteria was chosen as the primary end point of this phase II study because of the high

CONTEXT

Key Objective

The prognosis of patients with early-stage unfavorable Hodgkin lymphoma remains unsatisfactory with the use of the standard doxorubicin, bleomycin, vincristine, and dacarbazine (ABVD) regimen, followed by radiotherapy. Brentuximab vedotin (BV) has demonstrated high efficacy for relapsed/refractory Hodgkin lymphoma. For early-stage Hodgkin lymphoma, the brentuximab vedotin plus doxorubicin, vinblastine, and dacarbazine (BV-AVD) regimen demonstrated promising efficacy with a tolerable safety profile. We performed a randomized, phase II trial to assess the efficacy and safety of BV-AVD in the first-line treatment of early-stage unfavorable Hodgkin lymphoma.

Knowledge Generated

Our results demonstrated that BV-AVD improved the positron emission tomography–negative rate by centralized independent review after two cycles. Our findings also confirmed the negative prognostic impact of high total metabolic tumor volume at baseline.

Relevance (*J.W. Friedberg*)

This study demonstrates the efficacy of BV-AVD followed by radiotherapy as first-line treatment for patients with early-stage unfavorable Hodgkin lymphoma. Future randomized trials should compare this approach with current standards and explore which patients may be candidates to eliminate radiation therapy.*

*Relevance section written by *JCO* Editor-in-Chief Jonathan W. Friedberg, MD.

negative predictive value associated with early metabolic response that could ultimately translate into a better PFS. In early-stage Hodgkin lymphoma, total metabolic tumor volume (TMTV) measured on baseline PET has also demonstrated a high prognostic value, complementing interim PET in early-stage Hodgkin lymphoma.[10-12]

Brentuximab vedotin (BV) initially demonstrated high single-agent activity in relapsed/refractory Hodgkin lymphoma.[13-15] Its use in first-line in combination with chemotherapy was initially investigated in a phase I trial in patients with stage IIA bulky disease or stage III-IV disease. Long-term results of this study indicated excellent disease control using the BV plus doxorubicin, vinblastine, and dacarbazine (BV-AVD) regimen with a 5-year failure-free survival rate of 92% and a 5-year OS rate of 100%.[16,17] The ECHELON-1 trial, which evaluated the BV-AVD regimen in the first-line treatment of advanced-stage Hodgkin lymphoma, demonstrated better tumor control with a significant improvement in PFS in favor of the BV-AVD arm compared with ABVD.[18]

On the basis of these results, we performed a randomized, phase II intergroup trial to evaluate the efficacy of the BV-AVD as a first-line treatment of newly diagnosed, early-stage unfavorable Hodgkin lymphoma to improve the PET-negative rate after two cycles of therapy.

METHODS

Study Design and Participants

We performed a prospective, multicenter, randomized, open-label, phase II trial of patients with previously untreated, early-stage supradiaphragmatic unfavorable Hodgkin lymphoma age 18-60 years (registered with ClinicalTrials.gov identifier: NCT02292979). Patients were eligible if they had at least one unfavorable criterion according to EORTC/LYSA clinical prognostic factors: ≥ 4 involved nodal areas, age ≥ 50 years, bulky disease defined as a mediastinal/thoracic ratio ≥ 0.35, or elevated erythrocyte sedimentation rate ≥ 50 mm/hour without B symptoms or ≥ 30 mm/hour or higher with B symptoms. Complete eligibility and exclusion criteria are available in the Protocol (online only).

The study received the ethical committee approval (Est-III) and was conducted according to the Declaration of Helsinki and Good Clinical Practice guidelines. All patients provided informed written consent before study entry.

Random Assignment and Masking

Patients were randomly assigned (2:1) to receive BV-AVD or ABVD. Patients were stratified according to the presence or not of bulky disease. Investigators and patients were aware of treatment allocation. Nuclear physicians were blinded for PET-independent central review.

Procedures

In the experimental arm, each cycle of BV-AVD consisted of BV 1.2 mg/kg (but no > 120 mg), doxorubicin 25 mg/m^2, vinblastine 6 mg/m^2, and dacarbazine 375 mg/m^2 once per day on days 1 and 15. In the standard arm, each cycle of ABVD consisted of doxorubicin 25 mg/m^2, bleomycin 10 mg/m^2, vinblastine 6 mg/m^2, and dacarbazine 375 mg/m^2 once per day on days 1 and 15. All responding patients received consolidation radiotherapy carried out in accordance with involved node radiation therapy principles at a dose of 30 Gy delivered in fractions of 1.8-2 Gy 5 times per week.[19] No boost to residual masses was allowed.

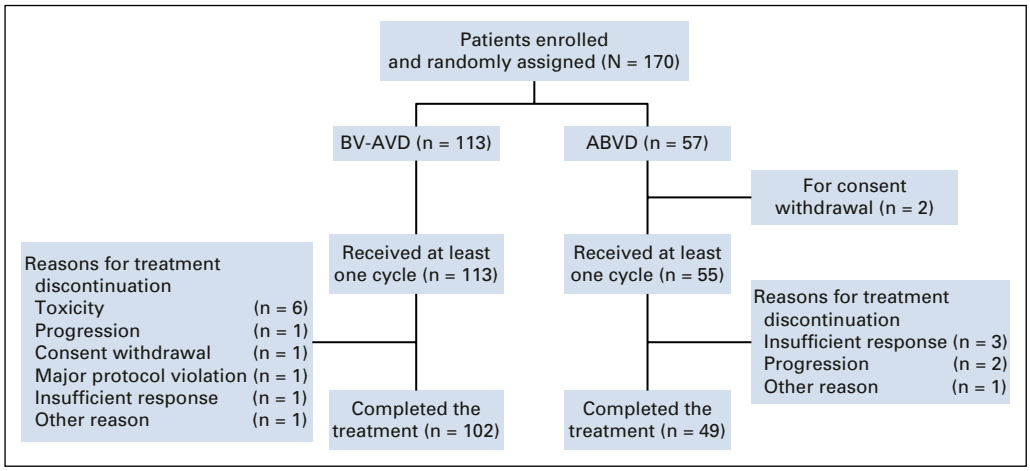

FIG 1. CONSORT diagram. ABVD, doxorubicin, bleomycin, vincristine, and dacarbazine; BV-AVD, brentuximab vedotin plus doxorubicin, vincristine, and dacarbazine.

Administration of granulocyte colony-stimulating factor was initially at the discretion of the investigator in both arms but was made mandatory for all patients randomly assigned to the experimental arm after protocol amendment in May 2015 on the basis of the first results of the ECHELON-1 trial showing high hematological toxicity in the BV-AVD arm.[18]

Adverse events (AEs) were assessed throughout the treatment period and graded according to the Common Terminology Criteria for Adverse Events, version 4.

Baseline PET (PET0) was performed in all patients. Interim PET (PET2) was performed on days 23-28 of the second cycle. PET0 and PET2 were centrally reviewed. A second interim PET after cycle 4 and before radiotherapy (PET4) could be performed at the physician's discretion for patients with a positive PET2. Final PET was performed at the end of treatment (EOT PET).

Outcomes

The primary end point was the PET response rate, categorized as positive or negative, after two cycles of treatment (PET2) according to central review results. Secondary end points included the complete response rate on the basis of the 2007 Cheson criteria[20] at EOT, PFS defined as the time from random assignment to first disease progression or death due to any cause, OS defined as the time from random assignment to death due to any cause, treatment duration, and safety end points (frequency and reasons for treatment discontinuation and AEs).

PET Analysis

Baseline PET and interim PET2 were transferred into the LYSA imaging platform (Imagys, Keosys, Herblay, France). A remote online central review of interim PET2 was performed by three independent experts (A.V., M.H., and M.M.) who were blind to treatment allocation. PET2 was reported using the Deauville score. Deauville scores of 1, 2, or 3 were considered as PET-negative and scores of 4 or 5 as positive. The final score (positive or negative) was obtained for most readings.

Response at EOT was locally reported according to 2007 Cheson criteria.[20] A post hoc evaluation of response at the EOT according to 2014 Lugano criteria was also performed. All the reports from EOT PET performed locally in each center were collected and centrally reviewed to assess the response according to 2014 Lugano criteria. In addition, for patients who did not achieve a complete response at EOT according to 2007 Cheson criteria, PET was centrally reviewed according to 2014 Lugano criteria by an independent and blinded nuclear medicine expert (T.V.B.).

For TMTV measurement, the baseline images were extracted from the platform. TMTV was computed by one expert in the field (M.M.) with the 41% maximum standardized uptake value threshold method as already published.[10,12,21-23] The free semiautomatic software Beth Israel Fiji20 was used.[10] Regional volumes automatically identified by the software were checked by visual assessment to confirm inclusion of only pathological lesions. PET images were scaled using a fixed display and color table scaled to the standardized uptake value as recommended. TMTV was obtained by summing the metabolic volumes of all lesions. The TMTV value of 147 cm^3, already published in early-stage Hodgkin lymphoma as the cutoff separating high-risk from low-risk patients,[10] was considered.

Statistical Analysis

According to our previous experience in the H10 study, we expected that 75% of the patients would be PET-negative after two cycles of ABVD (null hypothesis).[8] We hypothesized a 10% increase in the PET-negative rate after two cycles of BV-AVD, and the study was designed as a phase II randomized study. The randomized arm of ABVD patients was added to the study design to confirm this null assumption, not for any comparison against the BV-AVD arm.

TABLE 1. Baseline Characteristics

Characteristic	BV-AVD (n = 113)	ABVD (n = 57)
Median age, years (range)	29 (18-59)	28 (18-60)
Sex		
Male	53 (47)	31 (54)
Female	60 (53)	26 (46)
Weight ≥ 100 kg	6 (5)	6 (11)
Histology (expert pathology review)		
Nodular sclerosis	90 (87)	39 (80)
Mixed cellularity	2 (2)	1 (2)
Classic not otherwise specified	8 (8)	7 (14)
Others	3 (3)[a]	2 (4)[b]
Missing data	10	8
Ann Arbor stage		
I	8 (7)	3 (5)
II	104 (92)	53 (93)
III	1 (1)	1 (2)
Median No. of involved nodal areas (range)	3 (1-5)	3 (1-5)
B symptoms	42 (37)	25 (45)
Unfavorable risk factors		
Age ≥ 50 years	10 (9)	9 (16)
≥ 4 involved nodal areas	44 (39)	21 (37)
Mediastinal/thoracic ratio ≥ 0.35	66 (60)	28 (51)
Elevated ESR[c]	61 (54)	26 (46)
Total metabolic tumor volume		
≤ 147 cm^3	75 (69)	35 (71)
> 147 cm^3	33 (31)	14 (29)
Missing	5	8

NOTE. Data are presented as No. (%) unless otherwise indicated.

Abbreviations: ABVD, doxorubicin, bleomycin, vincristine, and dacarbazine; BV-AVD, brentuximab vedotin plus doxorubicin, vincristine, and dacarbazine; DLBCL, diffuse large B-cell lymphoma; ESR, erythrocyte sedimentation rate.

[a]B-cell lymphoma, unclassifiable, with features intermediate between classic Hodgkin lymphoma and DLBCL, mediastinal large B-cell lymphoma, and nontumoral lesion (each n = 1).

[b]B-cell lymphoma, unclassifiable, with features intermediate between classic Hodgkin lymphoma and DLBCL and interfollicular Hodgkin lymphoma with lacuna cells (each n = 1).

[c]Elevated ESR ≥ 50 mm/h without B symptoms or ≥ 30 mm/h with B symptoms.

On the basis of an exact single-stage phase II design, 113 patients treated with BV-AVD were needed to achieve 82.6% power to detect a 10% difference in the negative PET rate at a 5% significance level comparing the response rate of the BV-AVD arm to the hypothesized rate of 75%. A standard arm with ABVD was added to verify the hypotheses used in the sample size calculation. Random assignment was performed between the experimental arm (BV-AVD) and the standard arm (ABVD) with a 2:1 ratio, with 57 ABVD patients expected to be recruited.

The response rate was expressed with 90% CI to be consistent with one-sided 5% level of significance according to the Pearson-Clopper method. Survival estimates with 95% CIs were calculated using the Kaplan-Meier method. Survival distributions were compared using the log-rank test, and Cox proportional hazard regression models were used to estimate hazard ratios (HRs) and associated 95% CIs.

All enrolled patients were included in the efficacy analysis whether they received study treatment or not (intention-to-treat set). Those who received at least one dose of any study drug were included in the safety analyses (safety set).

RESULTS

Between March 2015 and October 2016, 170 patients were enrolled and randomly assigned to receive four cycles of BV-AVD (n = 113) or ABVD (n = 57), followed by 30 Gy involved node radiation therapy (Fig 1). Patient's characteristics are described in Table 1.

After two cycles, 7 (4%) patients were not evaluable by PET and were considered as nonresponders (three in the ABVD arm and four in the BV-AVD arm). On the basis of the central review, 93 (82.3%; 90% CI, 75.3% to 88.0%) of 113 patients had a negative PET2 (Deauville score 1-3) after two cycles of BV-AVD. In the ABVD arm, 43 (75.4%; 90% CI, 64.3 to 84.5) of 57 patients were PET-negative, as expected from the hypotheses used for sample size calculation (Table 2). Among the 16 patients who were PET2-positive after central review in the BV-AVD arm, all 16 completed four cycles of BV-AVD, and among the 11 patients who were PET2 positive after central review in the ABVD arm, nine completed four cycles of ABVD.

At the end of the treatment according to the investigator assessment using the 2007 Cheson criteria, 98 (86.7%; 90% CI, 80.3% to 91.6%) of 113 patients had a complete response in the BV-AVD arm and 45 (78.9%; 90% CI, 68.1% to 87.7%) of 57 patients in the ABVD arm. Three patients had progressive disease (1 of 113 [1%] in the BV-AVD arm and 2 of 57 [4%] in the ABVD arm). According to the 2014 Lugano criteria, 99 (87.6%; 90% CI, 81.3% to 92.4%) of 113 patients had a complete metabolic response (CMR) in the BV-AVD arm and 44 (77.2%; 90% CI, 66.2% to 85.9%) of 57 patients in the ABVD arm. One patient in the BV-AVD arm had a partial metabolic response, two patients (1 of 113 [1%] in the BV-AVD arm and 1 of 57 [2%] in the ABVD arm) had no metabolic response and four patients (3 of 113 [3%] in the BV-AVD arm and 1 of 57 [2%] in the ABVD arm) had a progressive metabolic disease (Table 2).

After a median follow-up of 45 months (range, 0.2-60.6 months), eight patients had disease progression (three in the BV-AVD arm and five in the ABVD arm). Among the 22 patients who did not achieve a CMR, only one had disease progression after 5 months in the BV-AVD arm and only two

TABLE 2. Response to Treatment

Response	BV-AVD (n = 113)	ABVD (n = 57)
PET response after two cycles[a]		
Deauville 1	4 (4)	4 (7)
Deauville 2	34 (30)	22 (39)
Deauville 3	55 (49)	17 (30)
Deauville 4	13 (12)	8 (14)
Deauville 5	3 (3)	3 (5)
Not evaluated	4 (4)	3 (5)
Response at EOT using 2007 Cheson criteria[b]		
Complete response	98 (87)	45 (79)
Partial response	5 (4)	1 (2)
Stable disease	1 (1)	1 (2)
Progressive disease	1 (1)	2 (4)
Missing	8 (7)	8 (14)
Response at EOT using 2014 Lugano criteria[c]		
CMR	99 (88)	44 (77)
Partial metabolic response	1 (1)	0 (0)
No metabolic response	1 (1)	1 (2)
Progressive metabolic disease	3 (3)	1 (2)
Missing	9 (8)	11 (19)

NOTE. Data are presented as No. (%).

Abbreviations: ABVD, doxorubicin, bleomycin, vincristine, and dacarbazine; BV-AVD, brentuximab vedotin plus doxorubicin, vincristine, and dacarbazine; CMR, complete metabolic response; EOT, end of treatment; PET, positron emission tomography.

[a]By independent expert centralized review.

[b]By local assessment using 2007 Cheson critieria.[19]

[c]After central review of all PET reports performed locally.

had disease progression after 4 months in the ABVD arm. The 2-year PFS was 97.3% (95% CI, 91.9% to 99.1%) and 92.6% (95% CI, 81.4% to 97.2%) in the BV-AVD and ABVD arms, respectively (Fig 2A). According to PET results after two cycles, PFS was significantly better for PET-negative patients compared with PET-positive patients with a 2-year PFS of 97.8% (95% CI, 93.3% to 99.3%) and 84.8% (95% CI, 64.5% to 94.0%), respectively (P = .006; Fig 2B). For patients with positive PET after two cycles, the 2-year PFS rate was 93.8% (95% CI, 63.2% to 99.1%) for BV-AVD and 71.6% (95% CI, 35.0% to 89.9%) for ABVD. For patients with negative PET after two cycles, the 2-year PFS rates were similar in both arms: 97.8% (95% CI, 91.6% to 99.5%) and 97.7% (95% CI, 84.6% to 99.7%) for BV-AVD and ABVD, respectively (Appendix Fig A1, online only). No deaths were recorded during the study.

TMTV was assessed in 157 (92%) of 170 patients at baseline. The median TMTV at baseline in the whole cohort was 92 cm^3 (interquartile range, 54-173). By using the threshold of 147 cm^3 previously defined from the H10 trial for early-stage Hodgkin lymphoma,[9] 47 (30%) of 157 patients had a high TMTV (> 147 cm^3) and 110 (70%) had a low TMTV (≤ 147 cm^3). The proportion with high TMTV was similar in both study arms: 33 (31%) of 108 patients in the BV-AVD arm and 14 (29%) of 49 patients in the ABVD arm (P = .853). The mediastinal/thoracic ratio was significantly correlated with TMTV. The proportion with mediastinal/thoracic ratio ≥ 0.35 was higher among patients with high TMTV: 37 (79%) of 47 patients with high TMTV and 53 (48%) of 110 patients with low TMTV. High TMTV was significantly associated with a shorter PFS (HR, 17.9; 95% CI, 2.2 to 145.5; P < .001). The 2-year PFS for patients with high TMTV was 84.9% (95% CI, 71% to 92.5%) and 100% for patients with low TMTV (Fig 2C). Among the eight patients who experienced disease progression, seven had a high TMTV at baseline, and according to PET results after two cycles, four were PET-positive, and four were PET-negative. Among the 47 patients with high TMTV, 14 were treated with ABVD and 33 with BV-AVD. Four events limiting PFS occurred in the ABVD arm (4 of 14, 28.6%) and three in the BV-AVD arm (3 of 33, 9.1%). For patients with high TMTV, the 2-year PFS rate was 90.9% (95% CI, 74.4% to 97.0%) for BV-AVD and 70.7% (95% CI, 39.4% to 87.9%) for ABVD. Among the 110 patients with low TMTV, 35 were treated with ABVD and 75 with BV-AVD. Only one event limiting PFS was recorded in the ABVD arm (Appendix Fig A2, online only).

In univariate analysis, four factors were significantly associated with PFS: presence of B symptoms (HR, 4.82; 95% CI, 1.0 to 23.9; P = .035), performance status 1-2 (16.63; 95% CI, 2.1 to 135.2; P < .001), TMTV > 147 cm^3 (17.89; 95% CI, 2.2 to 145.5; P < .001), and negative PET after two cycles (0.18; 95% CI, 0.1 to 0.7; P = .02; Table 3). Multivariate analysis could not be performed because of the small number of events.

Among the whole study population, 151 (89%) of 170 patients completed treatment: 102 (90%) of 113 patients in the BV-AVD arm and 49 (86%) of 57 patients in the ABVD arm (Fig 1). In the BV-AVD arm, 90 (80%) of 113 patients received the eight planned infusions of BV. During the study, 72 serious AEs (SAEs) were notified in 36 (21%) patients: 60 events in 29 (26%) of 113 patients in the BV-AVD arm and 12 events in seven (13%) of 55 patients in the ABVD arm. In the BV-AVD arm, 28 (47%) of 60 SAEs were considered at least possibly related to BV and nine (15%) led to permanent discontinuation of BV with seven considered as related to BV (febrile neutropenia [n = 3 cases] and epileptic seizure, peripheral neuropathy, hyponatremia, and cutaneous rash [each n = 1]) and two considered as unrelated to BV (amnesia and loss of weight [each n = 1]). Two SAEs were recorded during radiotherapy (one case of deep venous thrombosis in the BV-AVD arm and 1 case of infection in the ABVD arm). Grade 3-4 AEs occurred in 97 (86%) of 113 patients in the BV-AVD arm and 38 (69%) of 55 patients in

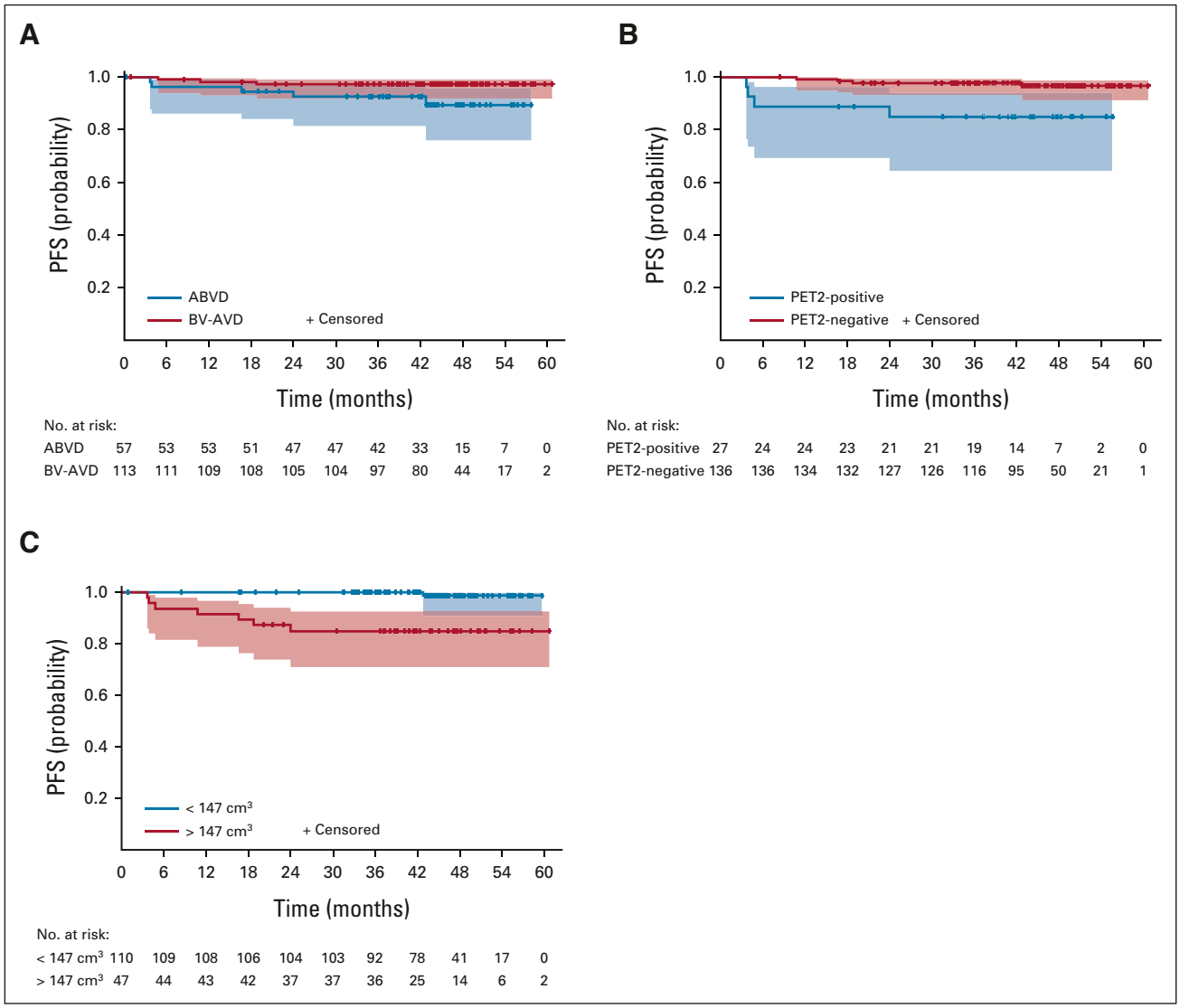

FIG 2. Kaplan-Meier curves of progression-free survival (A) by treatment arm, (B) by PET status after two cycles, and (C) by baseline TMTV. ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; BV-AVD, brentuximab vedotin plus doxorubicin, vincristine, and dacarbazine; FAS, full analysis set; PET, positron emission tomography; TMTV, total metabolic tumor volume.

the ABVD arm. The most frequent grade 3-4 AEs were hematological toxicities. Grade 3 or higher peripheral neuropathy occurred in three (3%) of 113 patients in the BV-AVD arm and one (2%) of 55 patients in the ABVD arm (Table 4). Three secondary primary malignancies were recorded during the study, two in the ABVD arm (renal cell carcinoma and basal cell carcinoma) and one in the BV-AVD arm (renal cell carcinoma).

DISCUSSION

We evaluated the efficacy of the BV-AVD regimen in the first-line treatment of early-stage unfavorable Hodgkin lymphoma. The PET-negative rate after two cycles on the basis of the central review, the primary end point, proved positive with BV-AVD (82.3%, 90% CI, 75.3% to 88.0%). These results are similar to those obtained in a pilot study in which 116 patients with early-stage unfavorable Hodgkin lymphoma were treated in four cohorts to evaluate various consolidation radiotherapy modalities after four cycles of BV-AVD: among all patients, the PET-negative rate (Deauville score of 1-3) after two cycles was 87%.[24] However, response rates after two cycles are inferior in our study compared with the results obtained in a previous phase II study evaluating BV-AVD in 34 patients with stage I/II Hodgkin lymphoma.[25] In that study, the PET-negative rate (Deauville score 1-3) after two cycles was 97.1%. Of note, patients with bulky disease were excluded, and unfavorable patients represented only 38% of the whole population in that study. Moreover, all patients had a first cycle with BV monotherapy before proceeding to combination BV-AVD therapy.

TABLE 3. Univariate Analysis of Factors Associated With Progression-Free Survival

Variable	HR (95% CI)	P
ECOG performance status 1-2	16.63 (2.1 to 135.2)	.0006
Total metabolic tumor volume (quantitative)	1.006 (1.0 to 1.0)	< .0001
Total metabolic tumor volume > 147 cm^3	17.89 (2.2 to 145.5)	< .001
PET-negative after 2 cycles	0.18 (0.1 to 0.7)	.02
Presence of B symptoms	4.82 (1.0 to 23.9)	.035
Treatment arm (BV-AVD)	0.28 (0.1 to 1.2)	.075
No. of involved nodal areas > 3	1.72 (0.4 to 6.9)	.45
Mediastinal/thoracic ratio ≥ 0.35	0.73 (0.2 to 2.9)	.66
Age > 29 years	0.42 (0.1 to 2.1)	.26
Male	1.70 (0.4 to 7.1)	.46

Abbreviations: BV-AVD, brentuximab vedotin plus doxorubicin, vincristine, and dacarbazine; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; PET, positron emission tomography.

Our study demonstrated that the BV-AVD regimen is feasible in combination with radiotherapy. We observed a higher incidence of hematological toxicities with grade 3-4 neutropenia and febrile neutropenia in patients treated with BV-AVD, but the incidence of infections was only slightly higher compared with ABVD. Peripheral neuropathy was reported more frequently in patients treated with BV-AVD, but the incidence of grade 3-4 peripheral neuropathy remained low. This toxicity profile is similar to that observed in other trials evaluating the BV-AVD regimen.[19,24,25]

Our study confirmed in an independent series the prognostic value of TMTV with a threshold of 147 cm^3, previously defined from the H10 trial, to discriminate outcomes between patients with high or low TMTV.[9] Among the eight patients who experienced disease progression, seven had a high TMTV and only one had a low TMTV. The proportion of patients with high TMTV who relapsed was lower in the BV-AVD arm compared with the ABVD arm (9.1% *v* 28.6%). These results suggest that patients with high TMTV may benefit more from the addition of BV compared with patients with low TMTV. Despite its strong prognostic value on the outcome, the use of TMTV in a real-world setting is still limited by potential sources of bias because of the lack of standardization among the many methods available for TMTV determination.[26,27] In our study, all TMTV were determined by a single expert, but it is also well known that operator dependence is another obstacle that needs to be taken into consideration for a routine usage of TMTV. Therefore, TMTV determination needs to be standardized before it can be fully integrated into routine practice.

In our study, all patients received four cycles of chemotherapy regardless of PET2 response. However, the 2-year PFS rate of 93.8% (95% CI, 63.2 to 99.1) for PET2-positive patients treated with BV-AVD in the present BREACH study compares favorably to the 5-year PFS rate of 90.6% (95% CI, 84.7 to 94.3) for PET2-positive patients in the H10 study.[8] A PET-adapted strategy in early-stage Hodgkin lymphoma was also evaluated in the RAPID trial, which demonstrated that radiotherapy can be omitted in patients with early-stage Hodgkin lymphoma who achieved a CMR after three cycles of ABVD.[7] More recently, the HD17 trial also demonstrated that radiotherapy can be safely omitted for patients with a negative PET after two cycles of $BEACOPP_{escalated}$ and two cycles of ABVD.[28] The BV-AVD regimen could also represent a backbone chemotherapy regimen to avoid consolidative radiotherapy. This strategy was evaluated in a cohort of 29 patients with early-stage Hodgkin lymphoma and bulky disease. In this cohort, 93% of the patients had a negative PET after two cycles of BV-AVD, and the CR rate at EOT was 97%. With a median follow-up of 2.2 years, the 2-year PFS was 96.6% (95% CI, 89.9 to 1.0).[24] The randomized phase III RADAR trial (ClinicalTrials.gov identifier: NCT04685616) will evaluate the BV-AVD regimen compared with ABVD in a PET-adapted strategy in early-stage Hodgkin lymphoma to reduce the number of patients receiving radiotherapy.

TABLE 4. Treatment-emergent Adverse Events

	BV-AVD (n = 113)			ABVD (n = 55)		
Adverse Event	Grade 1	Grade 2	Grade 3-4	Grade 1	Grade 2	Grade 3-4
Neutropenia	20 (18)	36 (32)	85 (75)	10 (18)	29 (53)	34 (62)
Leukopenia	45 (40)	46 (41)	40 (35)	27 (49)	25 (46)	15 (27)
Febrile neutropenia	0	0	9 (8)	0	0	3 (6)
Gastrointestinal tract	95 (84)	69 (61)	14 (12)	44 (80)	34 (62)	0
ALT and/or AST increase	52 (46)	18 (16)	7 (6)	20 (36)	3 (6)	1 (2)
Peripheral neuropathy	45 (40)	22 (20)	3 (3)	8 (15)	1 (2)	1 (2)
Infections	11 (10)	32 (28)	9 (8)	7 (12)	16 (29)	2 (4)
Skin and subcutaneous tissue disorders	52 (46)	15 (13)	5 (4)	26 (47)	7 (13)	0

NOTE. Data are presented as No. (%).

Abbreviations: ABVD, doxorubicin, bleomycin, vincristine, and dacarbazine; BV-AVD, brentuximab vedotin plus doxorubicin, vincristine, and dacarbazine.

In summary, incorporation of BV in the first-line treatment of early-stage unfavorable Hodgkin lymphoma improves early disease control with a significant improvement in the PET-negative rate after two cycles. Of note, our study was designed as a randomized phase II study that did not allow by design a direct comparison of the two arms. Our results suggest that BV-AVD could be considered sufficiently effective to further investigations. On the basis of our results, we can hypothesize that the BV-AVD combination might benefit the subgroup of patients with high TMTV at baseline. Alternative approaches to incorporate BV in first-line treatment have also been evaluated such as a sequential strategy of BV monotherapy, followed by chemotherapy in elderly patients.[29] Finally, the use of first-line BV in combination with chemotherapy is now challenged with promising results of studies evaluating a similar strategy with nivolumab as demonstrated in a recently published phase II trial in patients with early-stage unfavorable Hodgkin lymphoma.[30]

AFFILIATIONS

[1]Institut de Cancérologie Strasbourg Europe (ICANS) and University of Strasbourg, Strasbourg, France
[2]Gustave Roussy, Villejuif, France
[3]University Hospital Centre Zagreb, Zagreb, Croatia
[4]University Hospital F Mitterrand, Dijon, France
[5]Institut d'hématologie de Basse-Normandie, Caen, France
[6]CHU Liège, Liège, Belgium
[7]University Hospital of Bordeaux, Bordeaux, France
[8]University Hospital of Nancy and University of Lorraine, Vandoeuvre les Nancy, France
[9]Rigshospitalet, University of Copenhagen, Copenhagen, Denmark
[10]University Hospital Grenoble Alpes, Grenoble, France
[11]CHU Limoges, Limoges, France
[12]IUCT-Oncopole, CHU Toulouse, Toulouse, France
[13]Centre H Becquerel, Rouen, France
[14]Centre L Bérard, Lyon, France
[15]Hôpital Saint Vincent de Paul, Lille, France
[16]Erasmus MC Cancer Institute, University Medical Center Rotterdam, Rotterdam, the Netherlands
[17]Presidio Ospedaliero Vito Fazzi, Lecce, Italy
[18]CHU UCL Namur, Yvoir, Belgium
[19]Hospices Civils de Lyon and Université Lyon 1, Lyon, France
[20]Rigshospitalet, Copenhagen, Denmark
[21]Azienda USL-IRCCS di Reggio Emilia, Reggio Emilia, Italy
[22]LYSA Imaging and University Paris Est Créteil, Créteil, France
[23]University of Modena and Reggio Emilia, Modena, Italy

CORRESPONDING AUTHOR

Luc-Matthieu Fornecker, MD, PhD, Department of Hematology, Institut de Cancérologie Strasbourg Europe (ICANS), 17 rue Albert Calmette, BP 23025, 67033 Strasbourg Cedex, France; e-mail: lm.fornecker@icans.eu.

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CLINICAL TRIAL INFORMATION

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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DATA SHARING STATEMENT

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AUTHOR CONTRIBUTIONS

Conception and design: Luc-Matthieu Fornecker, Massimo Federico, Marc André
Administrative support: Lena Specht, Marc André
Provision of study materials or patients: All authors
Collection and assembly of data: All authors
Data analysis and interpretation: Luc-Matthieu Fornecker, Marc André
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Brentuximab Vedotin Plus AVD for First-Line Treatment of Early-Stage Unfavorable Hodgkin Lymphoma (BREACH): A Multicenter, Open-Label, Randomized, Phase II Trial

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APPENDIX

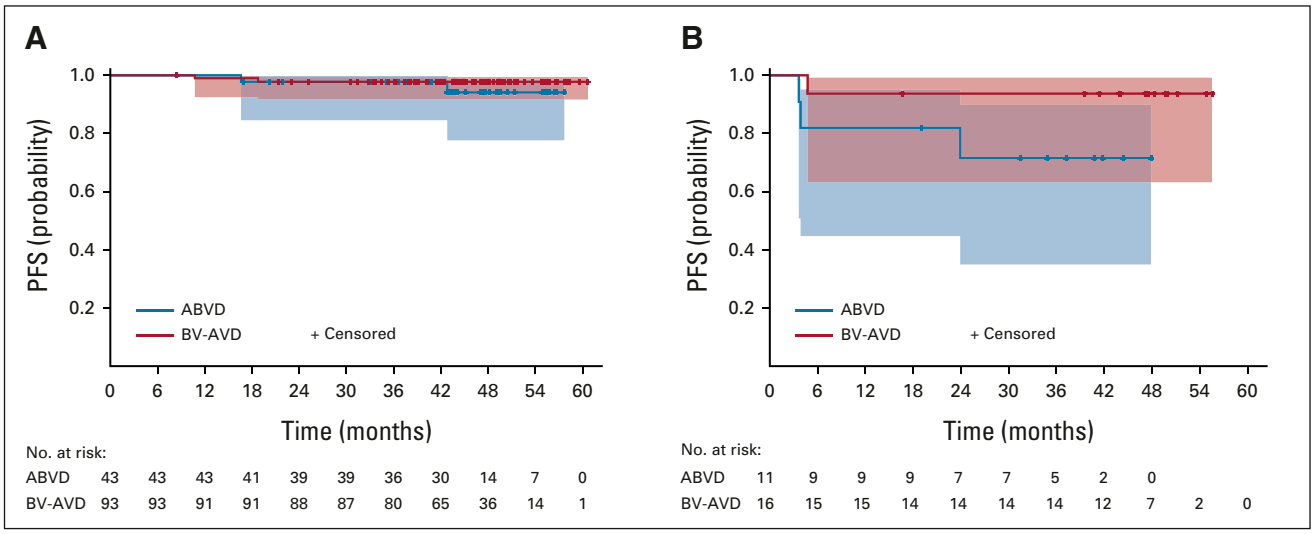

FIG A1. PFS according to the treatment arm and PET2 results. Patients with (A) negative PET2 and (B) positive PET2. ABVD, doxorubicin, bleomycin, vincristine, and dacarbazine; BV-AVD, brentuximab plus doxorubicin, vincristine, and dacarbazine; FAS, full analysis set; PET2, positron emission tomography after 2 cycles; PFS, progression-free survival.

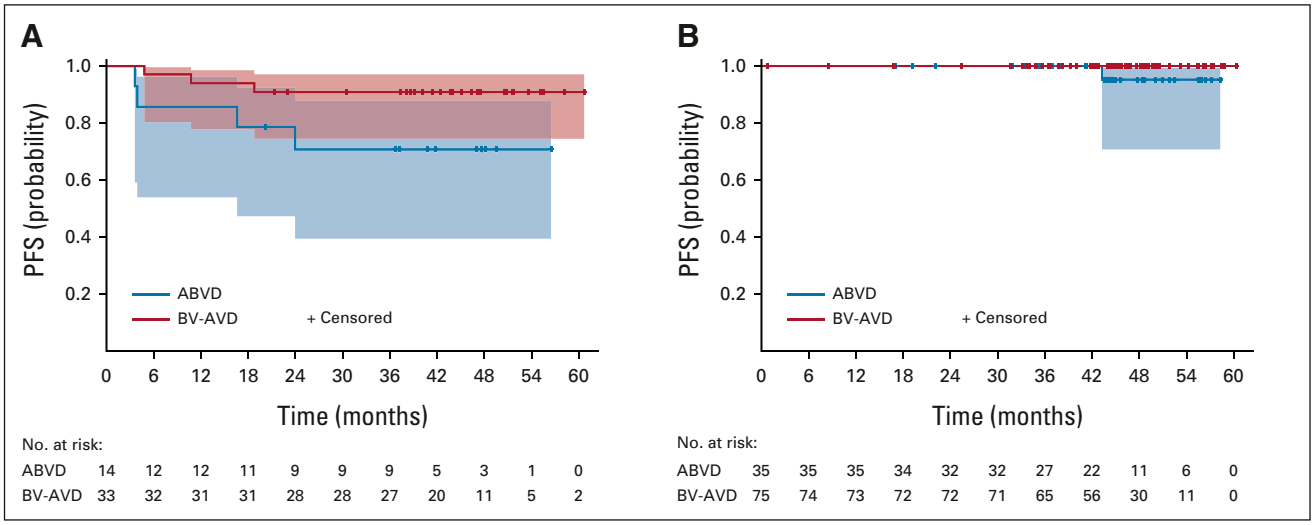

FIG A2. PFS according to the treatment arm and TMTV. Patients with (A) TMTV > 147 cm^3 and (B) TMTV ≤ 147 cm^3. ABVD, doxorubicin, bleomycin, vincristine, and dacarbazine; BV-AVD, brentuximab plus doxorubicin, vincristine, and dacarbazine; FAS, full analysis set; PFS, progression-free survival; TMTV, total metabolic tumor volume.