original reports

Positron Emission Tomography–Driven Strategy in Advanced Hodgkin Lymphoma: Prolonged Follow-Up of the AHL2011 Phase III Lymphoma Study Association Study

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abstract

PURPOSE The AHL2011 study (ClinicalTrials.gov identifier: NCT01358747) demonstrated that a positron emission tomography (PET)-driven de-escalation strategy after two cycles of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPP) provides similar progression-free survival (PFS) and overall survival (OS) and reduces early toxicity compared with a nonmonitored standard treatment. Here, we report, with a prolonged follow-up, the final study results.

METHODS Patients with advanced Hodgkin lymphoma (stage III, IV, or IIB with mediastinum/thorax ratio > 0.33 or extranodal involvement) age 16-60 years were prospectively randomly assigned between 6 × BEACOPP and a PET-driven arm after 2 × BEACOPP delivering 4 × ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) in PET2– and 4 × BEACOPP in PET2+ patients. PET performed after four cycles of chemotherapy had to be negative to complete the planned treatment.

RESULTS In total, 823 patients were enrolled including 413 in the standard arm and 410 in the PET-driven arm. With a 67.2-month median follow-up, 5-year PFS (87.5% *v* 86.7%; hazard ratio [HR] = 1.07; 95% CI, 0.74 to 1.57; $P = .67$) and OS (97.7% in both arms; HR = 1.012; 95% CI, 0.50 to 2.10; $P = .53$) were similar in both randomization arms. In the whole cohort, full interim PET assessment predicted patients' 5-year PFS (92.3% in PET2–/PET4–, 75.4% [HR = 3.26; 95% CI, 18.3 to 5.77] in PET2+/PET4– and 46.5% [HR = 12.4; 95% CI, 7.31 to 19.51] in PET4+ patients, respectively; $P < .0001$) independent of international prognosis score. Five-year OS was also affected by interim PET results, and PET2+/PET4– patients (93.5%; HR = 3.3; 95% CI, 1.07 to 10.1; $P = .036$) and PET4+ patients (91.9%; HR = 3.756; 95% CI, 1.07 to 13.18; $P = .038$) had a significant lower OS than PET2–/PET4– patients (98.2%). Twenty-two patients (2.7%) developed a second primary malignancy, 13 (3.2%) and 9 (2.2%) in the standard and experimental arms, respectively.

CONCLUSION The extended follow-up confirms the continued efficacy and favorable safety of AHL2011 PET-driven strategy, which is noninferior to standard six cycles of BEACOPP. PET4 provides additional prognostic information to PET2 and allows identifying patients with particularly poor prognosis.

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ASSOCIATED CONTENT

Data Sharing Statement

Data Supplement

Protocol

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

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INTRODUCTION

Escalated bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPP) was developed in the mid-90s to improve disease control in patients with advanced Hodgkin lymphoma (HL). Several studies showed that BEACOPP provides better progression-free survival (PFS) estimates but not significant overall survival (OS) gain when compared with doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) and was associated with a manageable higher risk of immediate hematologic toxicity and a greater concern related to a higher risk of myelodysplasia, leukemia, and gonadal toxicity. To limit patient's exposure to BEACOPP without compromising the disease control, positron emission tomography (PET)–guided strategies were developed to either restrict BEACOPP to patients with positive PET after two cycles of ABVD[1-3] or use only two to four cycles of BEACOPP instead of six cycles in PET2-negative patients after upfront BEACOPP.[4] AHL2011 is a phase III randomized study that compared in patients with advanced Hodgkin lymphoma a

CONTEXT

Key Objective

The better disease control and progression-free survival in young patients with advanced Hodgkin lymphoma is obtained with 6 × escalated bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPP). However, BEACOPP is associated to safety concerns including high risk of early hematologic toxicity, myelodysplasia/acute myeloid leukemia events, and gonadal toxicity. We designed the phase III AHL2011 study to investigate whether a positron emission tomography (PET)–driven de-escalation strategy after 2 × BEACOPP delivering 4 × doxorubicin, bleomycin, vinblastine, and dacarbazine in PET2-negative patients provides similar outcome and reduces toxicity compared with a nonmonitored standard 6 × BEACOPP treatment.

Knowledge Generated

With a prolonged median follow-up of 67.2 months, the PET-driven approach provides similar progression-free survival and overall survival compared with the standard treatment with a reduced early and late toxicity. With the current follow-up, the risk of secondary primary malignancy is low, estimated to be 2.2%.

Relevance

This study establishes a new PET-guided strategy of standard of care for patients with advanced Hodgkin lymphoma.

standard non–PET-driven arm delivering 6 × BEACOPP and a PET-driven arm after 2 × BEACOPP to decide the subsequent treatment with a switch to 4 × ABVD in PET2-negative patients and four additional cycles of BEACOPP in PET2-positive patients.

At the primary analysis with a median follow-up of 50.4 months, 5-year PFS estimates were similar in the standard care arm and the PET-driven arm in the intention to treat (ITT) (86.2% *v* 85.7%; hazard ratio [HR] = 1.084; 95% CI, 0.737 to 1.596; $P = .65$) and per-protocol (86.7% *v* 85.4%; HR = 1.144; 95% CI, 0.758 to 1.726; $P = .74$) populations.[5] Interestingly, the PET-driven arm was associated with less frequent hematologic toxicity, febrile neutropenia, infection, gastrointestinal disorders, and less frequent treatment related death were reported compared with the standard care arm. We present here an update of the patient's outcome with a 67.2-month median follow-up, prognostic risk scores, second-line treatment in relapsing patients by randomization arm, and a late safety overview.

METHODS

Study Design, Patients, and Treatments

This open-label, multicenter randomized phase III study was designed by the Lymphoma Study Association scientific committee and conducted in 90 centers from Belgium and France.

Eligible patients were age 16-60 years with an Eastern Cooperative Oncology Group performance status < 3, a minimum life expectancy of 3 months and previously untreated, histologically proven, classical HL according to WHO 2008 criteria, and an Ann Arbor stage III, IV, or IIB with a mediastinum/thorax ratio ≥ 0.33 or extranodal localization. Patients were required to have negative HIV, hepatitis C virus, and human T-lymphotropic virus serology, and normal liver (bilirubin < 2.5 normal level), renal (creatinine ≤ 150 μmol/L) and hematologic functions (leukocyte count ≥ 2,000/μL, platelet count ≥ 100,000/μL) unless abnormalities were related to HL. Patients with severe cardiopulmonary (left ejection ventricular fraction < 50% or respiratory insufficiency prohibiting bleomycin use) or metabolic disease (uncontrolled diabetes mellitus) interfering with normal application of protocol treatment were not eligible for inclusion. All patients provided written informed consent before enrollment. The study was approved by the French and Belgium Health authorities, the Dijon Hospital ethics committee for French centers and by the institutional review boards of each participating site in Belgium, and was done in accordance with the Declaration of Helsinki and the International Conference on Harmonisation Guidelines for Good Clinical Practice.

Patients were randomly assigned to receive in 1:1 ratio a PET-driven strategy or a standard treatment not monitored by PET. The random assignment of patients was done centrally and stratified according to Ann Arbor stage (IIB *v* III-IV) and international prognosis score (IPS: 0-2 *v* ≥ 3) using a random assignment procedure previously reported.[5]

Patients received two cycles of upfront BEACOPP (delivered every 21 days; bleomycin on day 8, etoposide on days 1-3, doxorubicin on day 1, cyclophosphamide on day 1, vincristine on day 8, procarbazine on days 1-7, and prednisone on days 1-14). In the PET-driven arm, on the basis of the blinded central PET review results, patients with positive PET2 received four additional cycles of BEACOPP and those with negative PET2 received 4 × ABVD (delivered every 28 days; doxorubicin, bleomycin, vinblastine, and dacarbazine all on days 1 and 15). In the standard arm, patients received four additional cycles of BEACOPP regardless of the PET2 result. PET was implemented in both arms to evaluate response after four cycles of chemotherapy and secure the de-escalation strategy. PET4-positive patients were considered

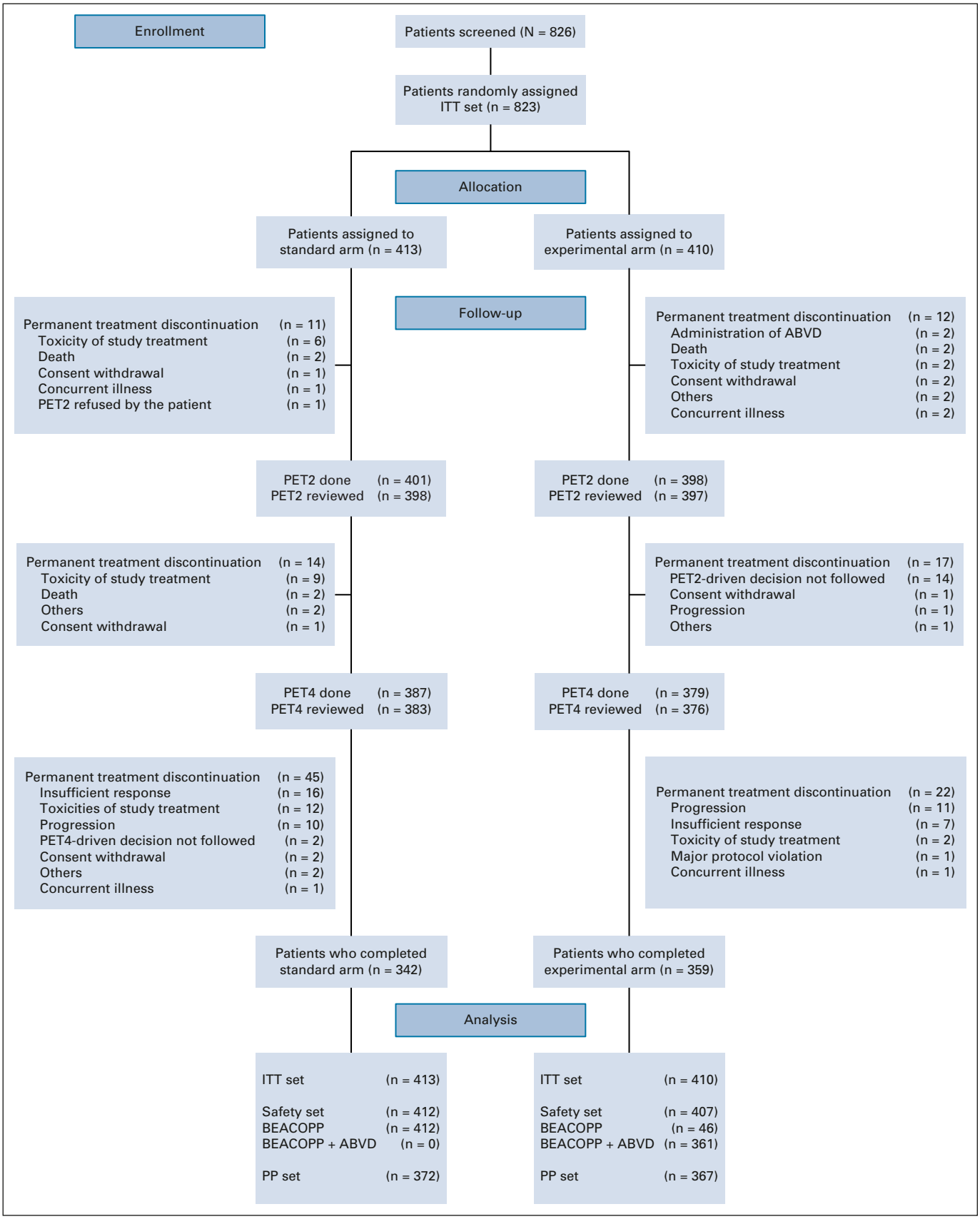

FIG 1. CONSORT diagram. ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; BEACOPP, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone; ITT, intention to treat; PET, positron emission tomography; PP, per protocol.

as treatment failure and treated at the discretion of the investigator.

Assessments

For patients with no disease progression, follow-up assessments were scheduled every 3 months for the first 2 years, then every 6 months for an additional 3 years, and then annually. Patients with disease progression were followed annually for the initiation of new treatment until data cutoff.

Safety outcome measures were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3, and included adverse events (AEs), serious AEs, and grade 3 or higher AEs.

Efficacy and Safety Analyses

PFS was the primary end point of the study. Key secondary end points included response to treatment and OS. PFS2 was estimated in patients with progressive or relapse disease.

Statistical Analysis

PFS was defined as the time from randomization assignment to first progression or relapse or death of any cause or last follow-up. PFS2 was calculated in patients with progressive disease from time to first progression or relapse to second progression or relapse or death of any cause. OS was defined as the time from random assignment to death of any cause or last follow-up. Response to treatment was assessed with Cheson et al[6] criteria.

Survival end points were estimated by Kaplan-Meier methodology and compared using a two-sided log-rank test stratified by Ann Arbor stage and IPS. We aimed at excluding inferiority of the PET-driven arm of at least 10% PFS compared with the standard arm. Noninferiority was also tested using the Com-Nougue et al[7] test. Response rates were compared using a χ^2 test.

Sensitivity analyses of PFS and OS according to interim PET results using landmark timepoints either at PET2 or PET4 were performed to assess the outcome of patients who had actually interim PET evaluation.

To compare the relative impact of the full PET-driven strategy on PFS and OS by baseline characteristics influencing outcome in univariate analysis, a Cox proportional hazard regression was performed including PET profile, IPS, and bulk as explanatory variables.

The data cutoff of the analyses presented here was April 29, 2019.

RESULTS

Patients

Overall, a total of 823 patients at 90 sites were randomly assigned (ITT set) to 6 × BEACOPP (n = 413) or to the PET-driven arm (n = 410; Fig 1). Baseline patient demographics and disease characteristics for the ITT population and by PET2 and PET4 status were well balanced between groups (Table 1) and have been previously described.[5] Key data are detailed in Table 1 and showed a similar PET2-negativity rate in both arms, which allowed to switch 346 patients (84% of the ITT set and 87% of those assessed for PET2) to ABVD in the PET-driven arm.

Efficacy

With a 5.6-year median follow-up (95% CI, 5.5 to 5.7 years), well balanced between arms (6 × BEACOPP: 5.7 years [95% CI, 5.5 to 5.8]; PET-driven arm: 5.6 years [95% CI, 5.5 to 5.7; $P = .99$), the PET-driven arm continues to provide PFS and OS estimates similar to that observed with the standard arm, which delivered 6 × BEACOPP in the ITT

TABLE 1. Key Baseline Patients Characteristics and Interim PET Response According to Central Review

Patient Characteristic	Standard Arm (n = 413)	PET-Driven Arm (n = 410)
Median age, years (range)	31 (16-60)	29 (16-60)
Male, No. (%)	263 (64)	253 (62)
ECOG, No. (%)		
0	203 (49)	193 (47)
1	181 (44)	184 (45)
2	27 (7)	31 (8)
Missing	2	2
B symptoms, No. (%)	282 (68)	278 (68)
Ann Arbor stage, No. (%)		
I or II A	2 (< 1)	9 (2)
IIB	42 (10)	45 (11)
III	114 (28)	115 (28)
IV	255 (62)	241 (59)
Bulky mass, No. (%), cm		
≥ 10	143 (38)	134 (37)
< 10	233 (62)	229 (63)
Missing	37	47
IPS group, No. (%)		
0-2	160 (39)	183 (45)
≥ 3	250 (61)	225 (55)
Missing	3	2
PET2 central review, No. (%)		
Positive	49 (12)	51 (13)
Negative	349 (88)	346 (87)
Missing	15	13
PET4 central review, No. (%)		
Positive	27 (7)	16 (4)
Negative	356 (93)	360 (96)
Missing	30	34

Abbreviations: ECOG, Eastern Cooperative Oncology Group; IPS, international prognosis score; PET, positron emission tomography.

TABLE 2. Key Efficacy Results After 50- and 67-Month Follow-Up in the ITT and Per-Protocol Populations After Random Assignment

	50-Month Follow-Up		67-Month Follow-Up	
Outcome	**Standard Arm**	**PET-Driven Arm**	**Standard Arm**	**PET-Driven Arm**
PFS				
ITT population	n = 413	n = 410	n = 413	n = 410
5-year PFS, %	86.2	85.7	87.5	86.7
HR (95% CI), *P*	1.04 (0.73 to 1.59), .65		1.07 (0.73 to 1.55), .64	
PP population	n = 372	n = 367	n = 372	n = 367
5-year PFS, %	86.7	85.4	88.1	86.5
HR (95% CI), *P*	1.14 (0.75 to 1.72), .74		1.01 (0.75 to 1.66), .75	
OS				
ITT population	n = 413	n = 410	n = 413	n = 410
5-year OS, %	95.2	96.4	96.7	96.7
HR (95% CI), *P*	0.93 (0.42 to 2.05), .43		0.93 (0.49 to 2.06), .51	
PP population	n = 372	n = 367	n = 372	n = 367
5-year OS, %	95.6	95.9	97.1	96.3
HR (95% CI), *P*	1.24 (0.53 to 2.88), .69		1.20 (0.55 to 2.60), .69	

Abbreviations: HR, hazard ratio; ITT, intention to treat; OS, overall survival; PET, positron emission tomography; PFS, progression-free survival; PP, per-protocol.

population (5-year PFS were 86.7% *v* 87.5%, respectively [HR = 1.07; 95% CI, 0.74 to 1.57; *P* = .67], and 5-year OS was 97.7% in both arms [HR = 1.012; 95% CI, 0.50 to 2.10; *P* = .53]). A similar picture was observed in the per protocol (PP) population (5-year PFS were 86.5% *v* 88.1%, respectively [HR = 1.01; 95% CI, 0.75 to 1.66; *P* = .75], and 5-year OS were 96.3% and 97.1%, respectively [HR = 1.20; 95% CI, 0.55 to 2.60; *P* = .69]; Table 2 and Fig 2). The Com-Nougue noninferiority test for PFS provided a similar conclusion in the ITT and PP populations by rejecting the null hypothesis (*P* = .0037 and *P* = .015, respectively).

The outcome of PET2-negative patients in the standard arm treated with 6 × BEACOPP and those in the experimental arm treated with 2 × BEACOPP plus 4 × ABVD is similar from random assignment or PET2 time analysis (Data Supplement, online only): 5-year PFS and 5-year OS from random assignment were, respectively, 89.9% (95% CI, 86.2 to 92.7) versus 90.5% (95% CI, 86.9 to 93.2) and 97.6% (95% CI, 95.2 to 98.8) versus 97.8% (95% CI, 95.5 to 99.0). The outcome of PET2-positive patients who received 6 × BEACOPP in both randomization arms was unsurprisingly also similar: 5-year PFS and 5-year OS from random assignment were, respectively, 73.5% (95% CI, 58.7 to 83.6) versus 68.2% (95% CI, 53.4 to 79.2) and 93.7% (95% CI, 81.7 to 97.9) versus 92.0% (95% CI, 80.0 to 96.9).

Prognosis Factors

In the whole cohort, among the prespecified subgroups, male sex, bulky mass > 10 cm, IPS ≥ 3, and interim PET positivity were associated with reduced PFS estimates in univariate analysis (Fig 3A). In multivariable analysis, full interim PET assessment predicted patients' PFS (5-year PFS = 92.3% in PET2–/PET4–, 75.4% [HR = 3.26; 95% CI, 18.3 to 5.77] in PET2+/PET4– and 46.5% [HR = 12.4; 95% CI, 7.31 to 19.51] in PET4+ patients respectively; *P* < .0001; Data Supplement) independent of IPS (Table 3). OS was also affected by interim PET results in both univariate analysis (Data Supplement) and multivariable analysis (Table 3), and PET2+/PET4– patients (5-year OS: 93.5%; HR = 3.3; 95% CI, 1.07 to 10.1; *P* = .036) and PET4+ patients (5-year OS: 91.9%; HR = 3.756; 95% CI, 1.07 to 13.18; *P* = .038) had a significant lower OS than PET2–/PET4– patients (98.2%). No other prespecified subgroup was associated with OS prediction (Fig 3B). Landmark analysis with a timepoint at PET4 provides consistent results for both PFS and OS (Data Supplement).

Second-Line Treatments

Ninety-two patients experienced disease progression including 43 and 49 patients in the standard and experimental arms, respectively. Median time to progression was 10.5 months (range: 2.3-76.8 months) since random assignment and similar in the standard and experimental arms (10.28 months, range: 2.6-76.8 months; *v* 9.92 months, range: 2.3-74.8 months). Within the standard arm, 30 of 349 (8.5%) with negative PET2 and 13 of 49 (26.5%) with positive PET2, all receiving BEACOPP, progressed. Within the experimental arm, 34 of 346 (9.8%) negative PET2 patients who had been allocated to further ABVD and 15 of 51 (29.4%) positive PET2 patients treated only with BEACOPP developed a disease progression or relapse. At the time of progression, 19 patients (20.7%) had B

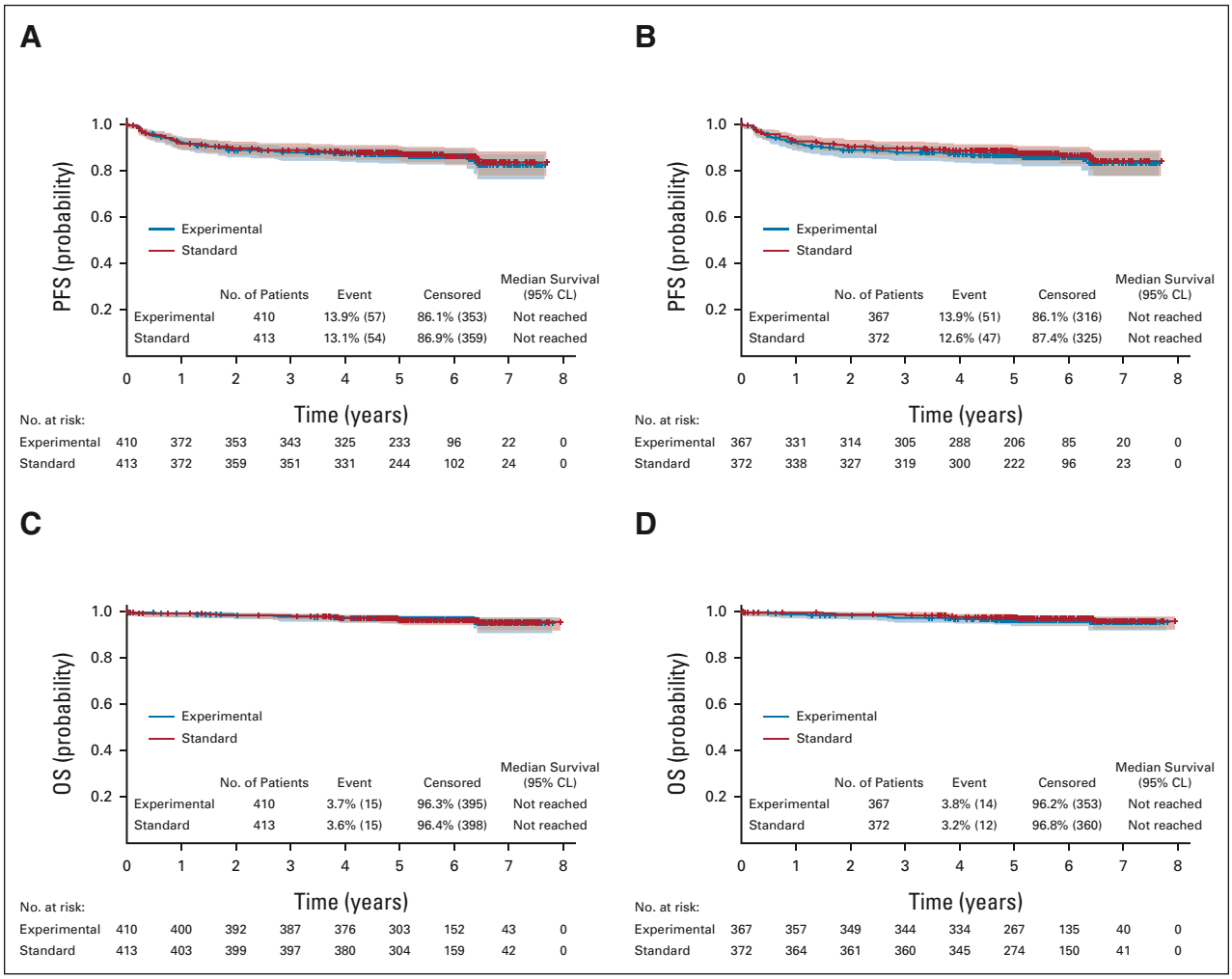

FIG 2. Kaplan-Meier estimates of survival from random assignment. (A) PFS in the ITT set, (B) PFS in the PP set, (C) OS in the ITT set, and (D) OS in the PP set, with number of patients at risk and 95% CLs. CL, confidence limit; ITT, intention to treat; OS, overall survival; PFS, progression-free survival; PP, per protocol. Long-term efficacy and tolerability of AHL2001 PET-guided treatment in advanced Hodgkin lymphoma.

symptoms and 54 (60%) patients had an advanced disease with an Ann Arbor stage III-IV. Patients' characteristics at progression were similar in both randomization arms (Data Supplement), and a tumor biopsy documented progression in 52 patients (56.5%). Eighty-eight patients received a documented second-line therapy, the most common subsequent chemotherapy regimens being dexamethasone, cisplatin, and cytarabine (DHAP; n = 52; 56.5%), ifosphamide, carboplatin, and etoposide (n = 14; 15%), gemcitabine, vinorelbine, and pegylated liposomal doxorubine (n = 5; 5%), or other chemotherapy (n = 10; 11%). Brentuximab vedotin (BV) was used as part of salvage induction therapy either as single-agent second-line treatment in five cases (5%) or associated with salvage chemotherapy in 17 cases (18%; Data Supplement). Salvage induction treatments were well balanced in patients treated in the standard and experimental arms. Forty-one out of 92 patients (45%), including 17 (39.5%) and 24 (48.9%) from the standard and experimental arms, respectively, proceeded to high-dose therapy plus autologous hematopoietic stem-cell transplantation (ASCT) and 16 patients received additional radiotherapy. Among the 41 patients who proceeded to ASCT, five patients received a second ASCT (three in the standard arm and two in the experimental arm) and two patients a BV maintenance (one in each arm). The outcome of salvage therapy is detailed in Table 4 and was associated with 65% overall response rate and 55% complete response with a 5-year PFS2 estimate of 54% (95% CI, 42 to 64.5). Second-line treatment allowed complete response to more frequently reach in patients who had progressive disease in the experimental arm than those previously treated in the standard arm (67% *v* 42%, $P = .021$) but it does not translate to significant PFS2 difference (Table 4).

Safety

Since the primary AHL2011 study analysis, a patient developed a grade 2 peripheral neuropathy in the standard arm and no additional immediate or late toxicity event of grade 3 or higher was reported. At the 5.6-year analysis, 22 patients (2.7%) had developed a second primary

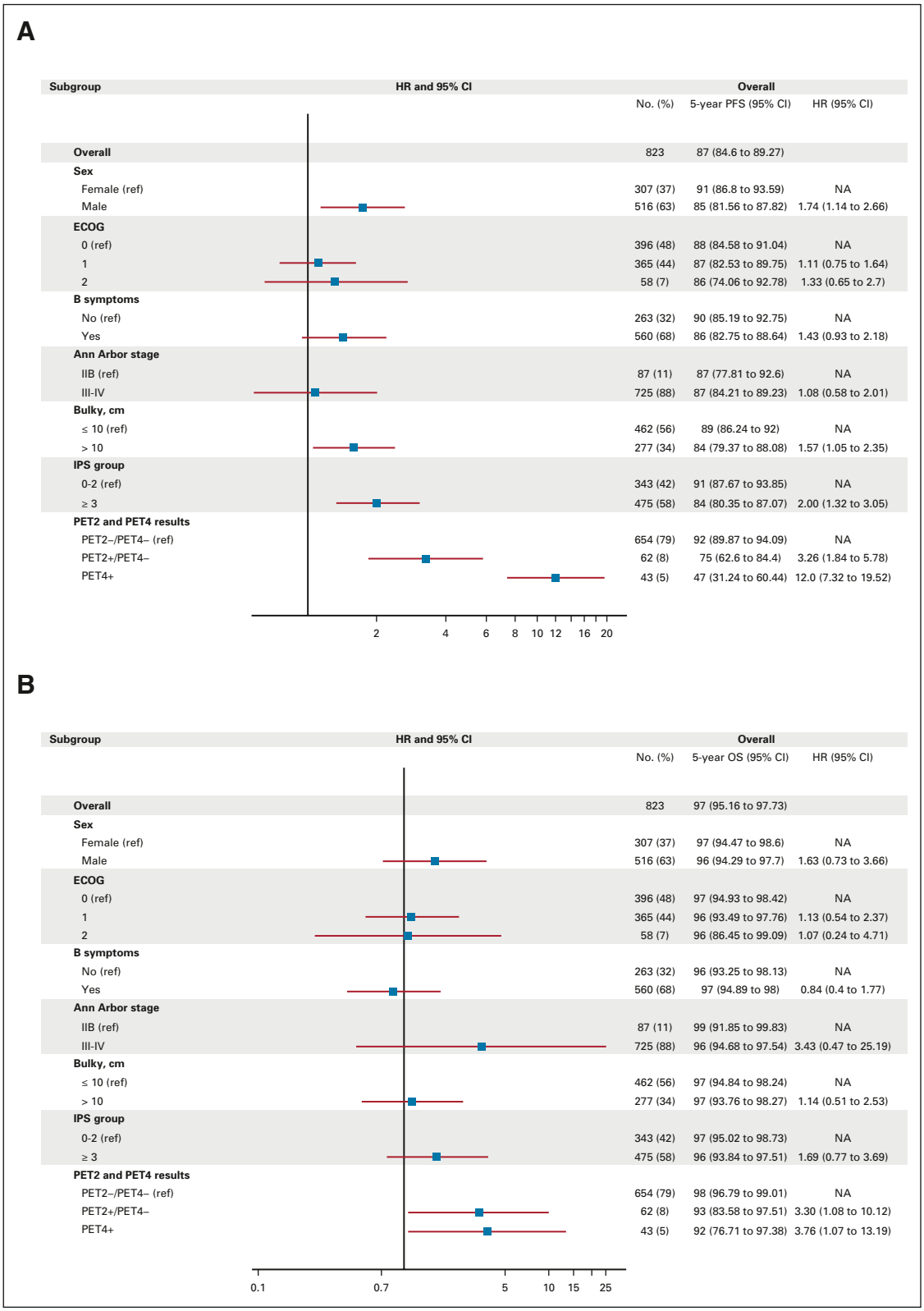

FIG 3. Forest plot of 5-year (A) PFS and (B) OS in the whole cohort according to prespecified subsets of patients. ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; IPS, international prognosis score; NA, not applicable; OS, overall survival; PET, positron emission tomography; PFS, progression-free survival.

TABLE 3. Risk Factors Influencing PFS and OS

		PFS					OS				
			Univariate Analysis		Multivariate Analysis			Univariate Analysis		Multivariate Analysis	
Risk Factors	No. (%)	5-Year PFS, % (95% CI)	HR	*P*	HR	*P*	5-Year OS, % (95% CI)	HR	*P*	HR	*P*
PET2/PET4											
PET2–/PET4–	654 (79)	92.3 (89.9 to 94.1)	1.0		1.0		98.2 (96.8 to 99.0)	1.0		1.0	
PET2+/PET4–	62 (7.5)	75.4 (62.5 to 84.4)	3.588	< .0001	3.316	< .0001	93.5 (83.6 to 97.5)	3.3	.036	3.3	.036
PET4+	43 (5.2)	46.5 (31.2 to 60.4)	13.14	< .0001	12.968	< .0001	91.9 (76.7 to 97.4)	3.7	.038	3.7	.038
IPS											
0-2	343 (42)	90.3 (85.8 to 93.4)	1.0		1.0		97.5 (95.0 to 98.7)	1.0			
≥ 3	475 (58)	82.8 (78.5 to 86.3)	1.915	.0025	1.6	.044	96.1 (93.8 to 97.5)	1.6	.18	0.86	.78

Abbreviations: HR, hazard ratio; IPS, international prognosis score; OS, overall survival; PET, positron emission tomography; PFS, progression-free survival.

malignancy (SPM), 13 (3.2%) and 9 (2.2%) in the standard and experimental arms, respectively (Data Supplement). A total of 86 patients (10.5%), 35 (8.5%) in the standard arm and 51 (12.5%) in the PET-driven arm, reported 109 pregnancies, 44 in the standard arm and 65 in the PET-driven arm, which required assisted reproductive technology treatment more frequently in the standard arm (9 of 44 [20.5%] *v* 7 of 65 pregnancies [10.8%]).

DISCUSSION

The AHL2011 study updated analysis shows that with a 67.2-month median follow-up, the PET-driven strategy after 2 × BEACOPP switching to ABVD PET2-negative patients provides a robust and sustained noninferior PFS compared with non-PET monitored arm delivering 6 × BEACOPP. In the ITT population, 5-year PFS were 86.7% versus 87.5% (difference of –0.8%; HR = 1.07; 95% CI, 0.74 to 1.57; *P* = .67) in the standard and the PET-driven arms, respectively, and consistent results were observed in the PP population.

These results compare favorably with other PET-driven strategies using either upfront BEACOPP reducing the number of BEACOPP to four cycles[4] in PET2-negative patients or upfront ABVD escalating PET2-positive patients to BEACOPP,[1-3] in terms of disease control, safety, and cost-effectiveness.[8]

Indeed, in the PET-driven arms, PET2-negative patients age < 60 years receiving 6 × ABVD have an 82.1% (95% CI, 76.5 to 86.5) 3-year PFS in the RATHL study[2] and 87% (95% CI, 84 to 89) in the GITIL/FIL study,[3] those receiving 4 × BEACOPP in HD18 a 5-year PFS of 93% (95% CI, 90.6 to 95.4),[9] and those included in AHL2011 receiving 2 × BEACOPP plus 4 × ABVD 90.5% (95% CI, 86.9 to 93.2). In the PET2-positive group, the 3-year PFS were 63.9% (95% CI, 52.9 to 72.9) and 60% (95% CI, 51 to 68) in RATHL and GITIL/FIL studies, respectively, and the 5-year PFS were 90.1% (95% CI, 87.2 to 92.9) and 68.2% (95% CI, 53.4 to 79.2) in patients who received 6 × BEACOPP in HD18 and AHL2011, respectively. The apparent better outcome of PET2-positive patients in HD18 was related to the PP PET positivity definition which includes patients with a Deauville score of 3, who share similar prognosis with DS1-2 patients.[10] Indeed, the HD18 PET2-positive group included a majority (> 50%) of early-responding patients (Deauville

TABLE 4. Outcome of Salvage Therapy According to Randomization Arm

Response	All (N = 92), No. (%)	Standard Arm (n = 43), No. (%)	Experimental Arm, (n = 49), No. (%)	*P*
ORR	60 (65)	24 (56)	36 (73)	.084
CR	51 (55)	18 (42)	33 (67)	.021
PR	9 (10)	6 (14)	3 (6)	.3
Stable disease	3 (3)	3 (7)	0 (0)	.098
Progressive disease	26 (28)	14 (33)	12 (24)	.48
Not evaluated	3 (3)	2 (5)	1 (2)	
PFS2				**HR**
5-year PFS, % (95 CI)	54 (42.0 to 64.5)	52.1 (36.0 to 66.0)	56.3 (39.2 to 70.4)	0.716 (0.38 to 1.34)

Abbreviations: CR, complete response; HR, hazard ratio; ORR, overall response rate; PFS, progression-free survival; PR, partial response.

score = 3), and has an unexpected good outcome, making this group noncomparable with the PET2-positive groups of other studies including AHL2011.

AHL2001 PET-driven strategy compares also favorably to the AVD-BV arm of the ECHELON1 study, which provides, in patients age < 60 years, an overall 3-year PFS of 84.9% (95% CI, 81.6 to 87.9), with 87.2% 3-year PFS (95% CI, 83.9 to 89.9) in PET2-negative and 69.2% (95% CI, 54.1 to 80.1) in PET2-positive patients.

The excellent disease control achieved in most patients with the present PET-driven strategy is associated as previously reported[5] to reduced myelosuppression and subsequent febrile neutropenia and infections events when compared with the standard arm. As well, gonadotoxicity in both male and female was also lowered in the experimental arm in terms of either premature ovarian insufficiency, low ovarian reserve, or severe testicular damage[11] and patients had a better chance of infertility recovery. Indeed, it translates to more pregnancies reported in the PET-driven arm. With the current follow-up, the risk of SPM remains low (2.7%), particularly in the PET-driven arm and similar in both treatment groups (2.2% *v* 3.2%). SPM frequency in the PET-driven arm was significantly lower than that reported in both the phase II SWOG S0816 study with a 5.9-year median follow-up, which reached 14% of 49 patients who received BEACOPP,[12] and in the phase III HD9 and HD12 studies (8.8%)[13] in patients treated with 6 × BEACOPP but with a longer median follow-up, which reached 10 years. Inversely, the AHL2011 SPM rate is similar to those reported either in the HD18 study[4] in patients receiving 4 × BEACOPP (3%), the RATHL study[2] (29 patients [2.4%] in the whole cohort and 3 [1.7%] in those treated with BEACOPP), or the ECHELON1 study[14] (14 patients, 2.3% in patients receiving AVD-BV). So, even if longer follow-up is required to better estimate the long-term risk of SPM, the AHL2011 PET-driven strategy appears to be safe in patients with advanced Hodgkin lymphoma while based on upfront BEACOPP with, to date, a particularly low risk of SPM occurrence.

This updated analysis confirms that interim PET results significantly affect patient's outcome in terms of PFS and OS. High risk of unfavorable outcome of PET2-positive patients was highlighted in many previous reports analyzing PET-driven[1,3,5,10] and non–PET-driven[14-17] studies in advanced Hodgkin lymphoma. However, the group of PET2-positive patients remains heterogenous and those who achieve PET4 negativity have an intermediate prognosis when continuing BEACOPP while those with a positive PET4 have an extremely poor outcome. Indeed, PET4 adds statistically significant prognosis information to PET2 allowing diseases refractory to BEACOPP be identified early and capture the rare negative PET2 patients with progressive disease at PET4 (13 patients in our series). PET4 prognosis value was also recently demonstrated in unfavorable early-stage HL patients treated with two cycles of BEACOPP plus two cycles of ABVD followed by radiotherapy.[18] Consequently, the original approach of tandem interim PET implemented in the AHL2011 trial allows to refine the PET-driven strategy on the basis of only PET2 or PET4 assessment and to better stratify patients with advanced Hodgkin lymphoma as it was already shown in patients with diffuse large B-cell lymphoma.[19,20]

The risk of disease progression was well balanced in both randomization arms, and treatment failure occurred early in the disease course of most patients with a consistent 10.5-median time from random assignment to progression or relapse in this study as reported in other series.[21]

Although the salvage therapy proposed to patients with progressive disease was chosen according to the investigator decision, the strategy of second-line treatment was similar in both randomization arms using in most cases DHAP regimen (56%) and a combination of BV plus chemotherapy in 18% of patients. Forty-five percent of patients were consolidated with high-dose therapy plus ASCT including 5% with tandem ASCT[22] and 16% received radiotherapy. Few patients received BV after ASCT as AETHERA study[23] was not or just recently published and BV maintenance post-ASCT not still approved when most of the patients were treated. Thirty-one percent of patients failed to respond to salvage therapy in line with the treatment failure rates observed either with ifosphamide, carboplatin, and etoposide plus ASCT in patients refractory or relapsing after upfront ABVD[24] or DHAP plus ASCT in patients who received prior BEACOPP.[25] The CR rate achieved with the salvage therapy was superior in patients previously included in the experimental arm compared with those included in the standard arm, whereas overall response rates and PFS2 estimates were similar in both randomization arms, suggesting that patients treated in the PET-driven arm could expect at least similar chance of disease control in case of disease progression compared with patients treated with a non-PET monitored approach.

In conclusion, the extended follow-up of a median 67.2 months revealed a continued efficacy and favorable safety of the PET-driven strategy delivering 4 × ABVD in PET-negative patients after two upfront cycles of BEACOPP. This valuable approach compares favorably with other PET-driven strategies and BV-AVD treatments and could be considered as standard of care in young patients with advanced Hodgkin lymphoma.

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Positron Emission Tomography–Driven Strategy in Advanced Hodgkin Lymphoma: Prolonged Follow-Up of the AHL2011 Phase III Lymphoma Study Association Study

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