

6 Long-Term Follow-Up of the Response-Adapted Intergroup EORTC/LYSA/FIL H10 Trial for Localized Hodgkin Lymphoma

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ABSTRACT

Clinical trials frequently include multiple end points that mature at different times. The initial report, typically based on the primary end point, may be published when key planned co-primary or secondary analyses are not yet available. Clinical Trial Updates provide an opportunity to disseminate additional results from studies, published in JCO or elsewhere, for which the primary end point has already been reported.

The primary analysis of the Early positron emission tomography (ePET) Response-Adapted Treatment in localized Hodgkin Lymphoma H10 Trial demonstrated that in ePET-negative patients, the risk of relapse increased when involved-node radiotherapy (INRT) was omitted and that in ePET-positive patients, switching from doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) to bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPPesc) significantly improved 5-year progression-free survival (PFS). Here, we report the final results of a preplanned analysis at a 10-year follow-up. In the favorable (F) ePET-negative group, the 10-year PFS rates were 98.8% versus 85.4% (hazard ratio [HR], 13.2; 95% CI, 3.1 to 55.8; *P* value for noninferiority = .9735; difference test *P* < .0001) in favor of ABVD + INRT; in the unfavorable (U) ePET-negative group, the 10-year PFS rates were 91.4% and 86.5% (HR, 1.52; 95% CI, 0.84 to 2.75; *P* value for noninferiority = .8577; difference test *P* = .1628). In ePET-positive patients, the difference in terms of PFS between standard ABVD and intensified BEACOPPesc was no longer statistically significant (HR, 0.67; 95% CI, 0.37 to 1.20; *P* = .1777). In conclusion, the present long-term analysis confirms that in ePET-negative patients, the omission of INRT is associated with lower 10-year PFS. Instead, in ePET-positive patients, no significant difference between standard and experimental arms emerged although intensification with BEACOPPesc was safe, with no increase in late adverse events, namely, second malignancies.

ACCOMPANYING CONTENT

- Appendix
- Data Supplement
- Protocol

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INTRODUCTION

Efforts to improve outcomes of patients with early-stage Hodgkin lymphoma (HL) and minimize the risk of short- and long-term toxicities have been made. In particular, different positron emission tomography (PET)-adapted strategies have been explored.¹⁻³

Our EORTC/LYSA/FIL H10 trial incorporated an early PET (ePET) response-adapted treatment strategy for both ePET-negative and ePET-positive patients with stage I and II HL. After a median follow-up of 4.5 years, the study showed that when ePET was positive after two cycles of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD), switching to bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPPesc) + involved-node

radiotherapy (INRT) significantly improved 5-year progression-free survival (PFS). In ePET-negative patients, noninferiority of ABVD alone could not be demonstrated: the risk of relapse increased when INRT was omitted, especially in patients in the favorable (F) group.^{4,5} Here, we present the results of the preplanned 10-year follow-up analysis.

PATIENTS AND METHODS

Details of the study design have been published previously.⁴ The study was conducted in compliance with the Declaration of Helsinki and approved by the scientific and ethical committees, and all patients gave written informed consent (ClinicalTrials.gov identifier: [NCT00433433](https://clinicaltrials.gov/ct2/show/study/NCT00433433)). This preplanned analysis focused on late adverse events, overall survival (OS), and PFS. The analyses were conducted on

ePET-positive patients, ePET-negative patients with F and U prognosis treated per the initial protocol, and ePET-negative patients treated per safety amendment. Statistical analysis methodology is reported in the Data Supplement (online only).

RESULTS

From November 2006 to June 2011, 1,925 patients completed the two ABVD cycles and performed an ePET scan; of these patients, details of 1,419 patients have been updated (Fig 1). Patient characteristics are listed in Table 1.

After a median follow-up of 9.5 years, 106 progressions or recurrences and 57 deaths were recorded, resulting in 136 events for PFS.

Standard Versus Experimental Arm

Survival analyses were performed in the intention-to-treat population randomly assigned up to the safety amendment (n = 969). The 10-year PFS rates were 91.4% (95% CI, 88.5 to 93.7) and 85.6% (95% CI, 82.0 to 88.5) in the standard versus experimental arm, respectively, with a hazard ratio (HR) of 1.67 (95% CI, 1.13 to 2.44; raw $P = .0085$; Data Supplement, Fig 1A; adjusted $P = .0255$). The 10-year OS rates were 95.2% (95% CI, 92.7 to 96.9) and 95.5% (95% CI, 93.0 to 97.1) in the

standard versus experimental arm, respectively ($P = .6717$; Data Supplement, Fig 1B).

ePET-Negative Patients

In the F group, a total of 28 events occurred: two patients experienced relapse in the ABVD + INRT arm versus 24 patients who experienced relapse and two patients who died from a cause not related to HL in the ABVD-only arm. Nineteen of 24 relapses (79%) in the ABVD-only arm occurred in previously involved nonirradiated locations. The 10-year PFS rates were 98.8% (95% CI, 95.4 to 99.7) and 85.4% (95% CI, 79.3 to 89.8) in the ABVD + INRT and ABVD-only arms, respectively, with a HR of 13.2 (95% CI, 3.1 to 55.8; noninferiority test [with noninferiority margin HR, 3.2]; $P = .9735$; difference test $P < .0001$, Fig 2A).

There were a total of four deaths in the F group: one in the ABVD + INRT arm and three in the ABVD-only arm. The 10-year OS rates were 100.0% versus 98.0% for the ABVD + INRT and ABVD-only arms, respectively, with a HR of 2.80 (95% CI, 0.29 to 26.9; difference test $P = .3522$; Fig 2B).

In the U group, a total of 46 events occurred: 11 and 22 patients experienced relapse and seven and six patients died from a cause not related to HL in the standard and experimental arms, respectively. Twenty of the 22 relapses (91%)

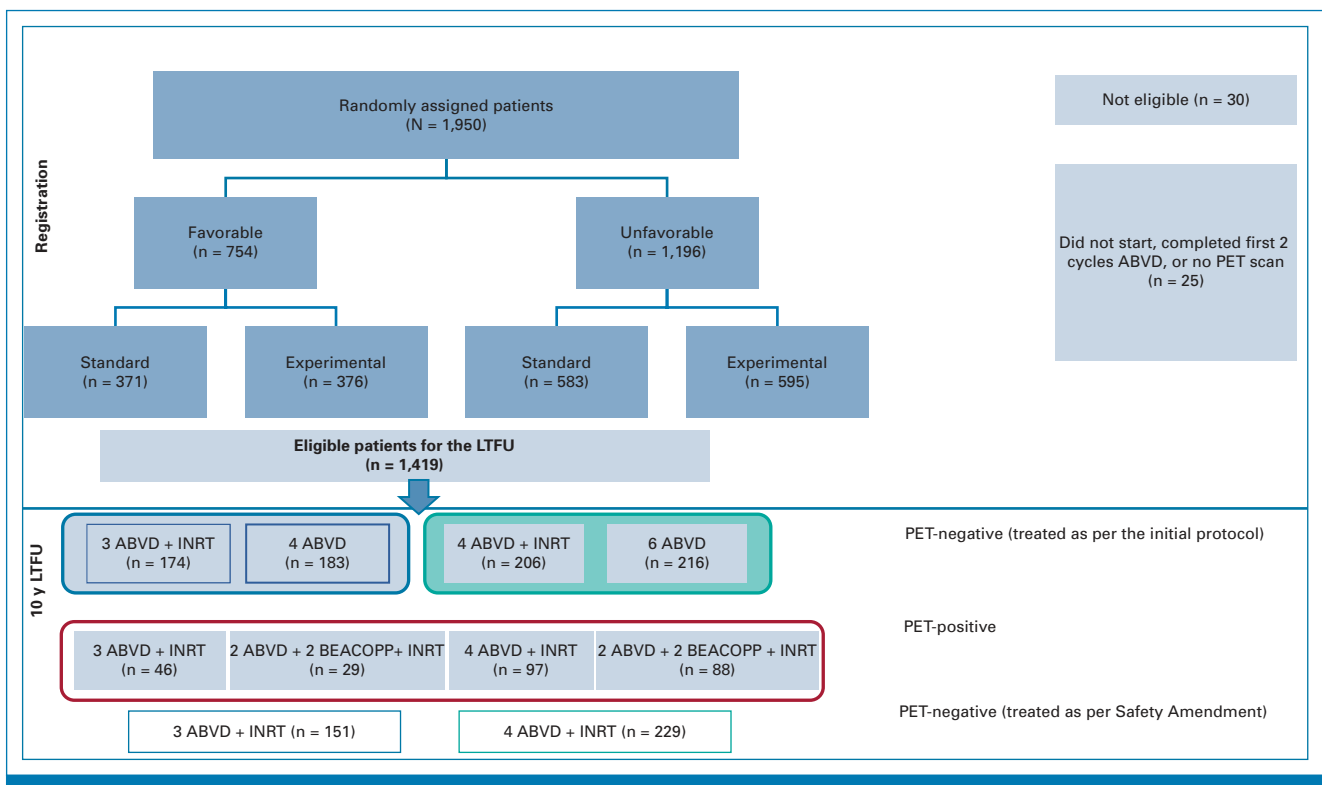


FIG 1. CONSORT diagram. ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; BEACOPPesc, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone; INRT, involved-node radiotherapy; LTFU, long-term follow-up; PET, positron emission tomography.

TABLE 1. Patient Characteristics

Characteristic	Treatment Arm								
	ePET-Negative			ePET-Positive			Treated per Safety Amendment		
	Favorable, Standard (3 ABVD + INRT; n = 174)	Favorable, Experimental (4 ABVD; n = 183)	Unfavorable, Standard (4 ABVD + INRT; n = 206)	Unfavorable, Experimental (6 ABVD; n = 216)	Standard (3 or 4 ABVD + INRT; n = 143)	Experimental (2 AVBD + 2 BEACOPPesc + INRT; n = 117)	Favorable (3 ABVD + INRT; n = 151)	Unfavorable (4 ABVD + INRT; n = 229)	Total (N = 1,419)
Age, years									
Median	31.5	30.5	33.5	32.1	31.4	30.3	28.6	32.3	31.5
Range	15.6-49.9	16.3-49.8	16.8-70.8	16.8-69.2	16.3-66.9	15.5-68.8	16.6-49.3	16.2-68.0	15.5-70.8
Sex, No. (%)									
Male	106 (60.9)	82 (44.8)	97 (47.1)	100 (46.3)	75 (52.4)	66 (56.4)	72 (47.7)	102 (44.5)	700 (49.3)
Female	68 (39.1)	101 (55.2)	109 (52.9)	116 (53.7)	68 (47.6)	51 (43.6)	79 (52.3)	127 (55.5)	719 (50.7)
Stage, No. (%)									
I	50 (28.7)	59 (32.2)	42 (20.4)	42 (19.4)	30 (21.0)	20 (17.1)	41 (27.2)	34 (14.8)	318 (22.4)
II	123 (70.7)	124 (67.8)	161 (78.2)	174 (80.6)	112 (78.3)	95 (81.2)	109 (72.2)	195 (85.2)	1,093 (77.0)
Histology, No. (%)									
NS	131 (75.3)	130 (71.0)	180 (87.4)	177 (81.9)	108 (75.5)	93 (79.5)	122 (80.8)	204 (89.1)	1,145 (80.7)
WHO performance status, No. (%)									
0	161 (92.5)	176 (96.2)	170 (82.5)	170 (78.7)	110 (76.9)	92 (78.6)	140 (92.7)	188 (82.1)	1,207 (85.1)
1	13 (7.5)	7 (3.8)	35 (17.0)	45 (20.8)	33 (23.1)	23 (19.7)	11 (7.3)	38 (16.6)	205 (14.4)
2	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.5)	0 (0.0)	2 (1.7)	0 (0.0)	3 (1.3)	7 (0.5)
B symptoms, No. (%)									
No	159 (91.4)	169 (92.3)	134 (65.0)	140 (64.8)	97 (67.8)	75 (64.1)	139 (92.1)	144 (62.9)	1,057 (74.5)
Yes	15 (8.6)	14 (7.7)	72 (35.0)	76 (35.2)	46 (32.2)	42 (35.9)	12 (7.9)	85 (37.1)	362 (25.5)
Bulky disease, No. (%)									
No	173 (99.4)	182 (99.5)	117 (56.8)	127 (58.8)	99 (69.2)	75 (64.1)	150 (99.3)	127 (55.5)	1,050 (74.0)
Yes	1 (0.6)	1 (0.5)	89 (43.2)	88 (40.7)	44 (30.8)	42 (35.9)	0 (0.0)	102 (44.5)	367 (25.9)

NOTE. Unfavorable: at least one of the following criteria: age $\geq$ 50 years or >3 nodal areas or mediastinal-thoracic ratios of ≥ 0.35 or no B symptoms and an ESR of ≥ 50 or B symptoms and an ESR of ≥ 30 . Favorable: all others. All early PET-negative patients who were included after the safety amendment received treatment with ABVD + INRT, as the independent data monitoring committee recommended to close the ABVD-only arm. Bulky mediastinum is defined as a mediastinal-thoracic ratio of ≥ 0.35 .

Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; BEACOPPesc, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone; ePET, early positron emission tomography; ESR, erythrocyte sedimentation rate; INRT, involved-node radiotherapy; NS, nodular sclerosis.

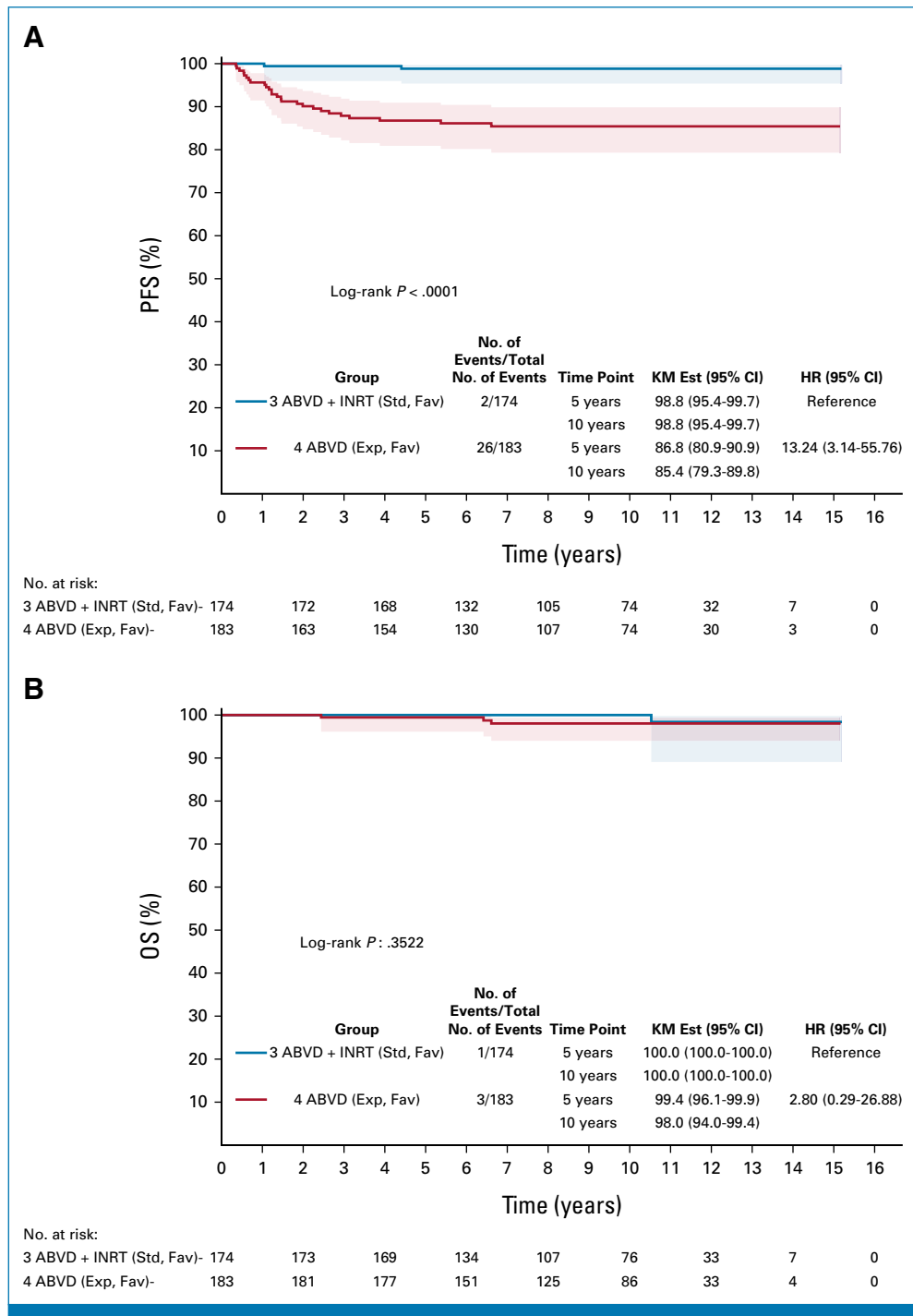


FIG 2. (A) Ten-year PFS in the ABVD + INRT and ABVD-only arms; HR, 13.2 (95% CI, 3.1 to 55.8 [noninferiority test with noninferiority margin HR, 3.2; $P = .9735$]); difference test $P < .0001$. (B) Ten-year OS; HR, 2.80 (95% CI, 0.29 to 26.9); difference test $P = .3522$. ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; Exp, Fav, experimental favorable; HR, hazard ratio; INRT, involved-node radiotherapy; KM Est, Kaplan-Meier estimate; OS, overall survival; PFS, progression-free survival; Std, Fav, standard favorable.

in the ABVD-only arm occurred in previously involved nonirradiated locations. The 10-year PFS rates were 91.4% (95% CI, 86.4 to 94.5) and 86.5% (95% CI, 81.0 to 90.5) in the standard and experimental arms, respectively, with a HR of 1.52 (95% CI, 0.84 to 2.75; P value for the noninferiority test

[with noninferiority margin HR, 2.1; $P = .8577$; difference test $P = .1628$; Data Supplement, Fig 2A).

There were 21 deaths in the U group: 11 in the ABVD + INRT arm and 10 in the ABVD-only arm. The 10-year OS rates were

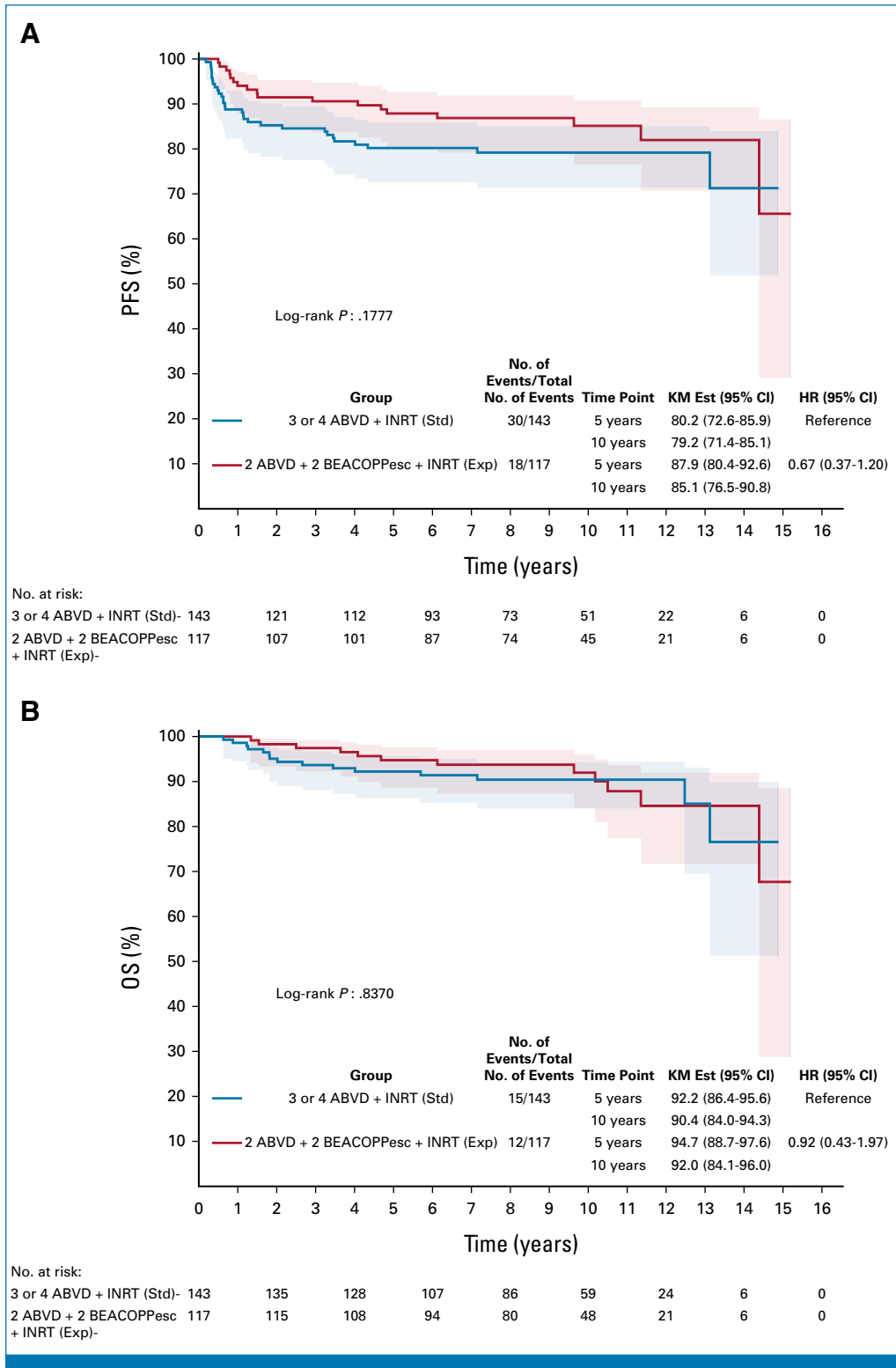


FIG 3. (A) Ten-year PFS of early positron emission tomography-positive patients, according to treatment arms: ABVD + INRT versus BEACOPPesc + INRT; $P = .1777$. (B) Ten-year OS; $P = .8370$. ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; BEACOPPesc, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone; Exp, experimental; HR, hazard ratio; INRT, involved-node radiotherapy; KM Est, Kaplan-Meier estimate; OS, overall survival; PFS, progression-free survival; Std, standard.

94.3% versus 94.8%, respectively, with a HR of 0.84 (95% CI, 0.36 to 1.98; difference test $P = .6908$; Data Supplement, Fig 2B).

ePET-Positive Patients

In the ePET-positive group, a total of 48 events occurred for PFS: 24 relapses and 6 deaths not related to HL in the ABVD + INRT arm and 12 relapses and 6 deaths not related to HL in the BEACOPPesc + INRT arm. The 10-year PFS rates were 79.2% (95% CI, 71.4 to 85.1) and 85.1% (95% CI, 76.5 to 90.8) in the ABVD + INRT and BEACOPPesc + INRT arms, respectively, with a HR of 0.67 (95% CI, 0.37 to 1.20; $P = .1777$; Fig 3A). The 10-year OS rates were 90.4% versus 92.0% for the ABVD + INRT and BEACOPPesc + INRT arms, respectively, with a HR of 0.92 (95% CI, 0.43 to 1.97; $P = .8370$; Fig 3B).

Prognostic Value of PET

In the subset of patients randomly assigned to standard treatment, ePET positivity resulted in a worse outcome in terms of PFS (HR, 4.9; 95% CI, 2.9 to 8.2; $P < .0001$; Data Supplement, Fig 3A) and OS (HR, 4.1; 95% CI, 2.0 to 8.4; $P < .0001$; Data Supplement, Fig 3B).

Late Adverse Events

A total of 420 patients (30%) experienced late adverse events (Data Supplement, Table 1). In ePET-negative patients, the cumulative incidence rate of late adverse events was similar in the standard and the experimental arms in the F ($P = .7077$; Data Supplement, Fig 4A) and U ($P = .4734$; Data Supplement, Fig 4B) groups.

In the ePET-positive group, the incidence rate of late adverse events was 30.7% (95% CI, 22.6 to 39.1) and 33.9% (95% CI, 24.3 to 43.8) in the ABVD + INRT and BEACOPPesc + INRT arms, respectively ($P = .7578$); 15.9% (95% CI, 9.7 to 23.3) and 14.1% (95% CI, 7.9 to 22.1) for late pulmonary adverse events ($P = .6634$); 7.7% (95% CI, 3.5 to 14.3) and 9.3% (95% CI, 4.3 to 16.6) for late cardiovascular adverse events ($P = .6089$); and 4.6% (95% CI, 1.7 to 10.0) and 4.7% (95% CI,

1.5 to 10.7), respectively, for late second malignancies ($P = .7375$; Data Supplement, Fig 5).

DISCUSSION

The H10 trial was designed to assess the role of PET-adapted treatment in patients with stage I and II HL, offering early intensification of chemotherapy in PET-positive patients and sparing radiotherapy (RT) in PET-negative patients.

At the time of primary analysis, after a median follow-up of 4.5 years, a significant improvement (13.2%) in 5-year PFS was observed in the BEACOPPesc + INRT arm compared with continuation with ABVD + INRT. This finding was considered of immediate clinical relevance.⁴ Now, with a longer follow-up (9.5 years), it has emerged that switching from ABVD to BEACOPPesc was not associated with a statistically significant better outcome, suggesting that exploring an earlier use of brentuximab vedotin⁶⁻⁸ or nivolumab⁹-containing regimens is opportune. However, escalation to two courses of BEACOPPesc resulted safe: the 10-year cumulative incidence of late adverse events, namely, second malignancies, was similar in the ABVD and BEACOPPesc arms.

Our results confirm the excellent overall outcome of ePET-negative patients, either after combined modality treatment (CMT) or after chemotherapy alone. However, CMT resulted in better disease control because omitting RT resulted in more early relapses, mainly affecting the originally involved areas. Fortunately, the low tumor burden at the time of relapse and the efficacy of the timely adoption salvage therapy allowed patients with relapse to achieve a second and durable remission in almost all cases. Instead, the achievement of a negative ePET, as assessed in the H10 trial, seems not to be the ideal tool for identifying those patients who could be spared RT.

In conclusion, this long-term analysis confirmed the previous findings that PET positivity after two cycles of ABVD is associated with a worse outcome, unfortunately not corrected completely by intensification with two cycles of BEACOPPesc.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at DOI <https://doi.org/10.1200/JCO.23.01745>.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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