original reports

Positron Emission Tomography–Guided Treatment in Early-Stage Favorable Hodgkin Lymphoma: Final Results of the International, Randomized Phase III HD16 Trial by the German Hodgkin Study Group

Michael Fuchs, MD[1]; Helen Goergen[1]; Carsten Kobe, MD[2]; Georg Kuhnert, MD[2]; Andreas Lohri, MD[3,4]; Richard Greil, MD[5,6]; Stephanie Sasse, MD[1]; Max S. Topp, MD[7]; Erhardt Schäfer, MD[8]; Bernd Hertenstein, MD[9]; Martin Soekler, MD[10]; Martin Vogelhuber, MD[11]; Josée M. Zijlstra, MD, PhD[12]; Ulrich Bernd Keller, MD[13]; Stefan W. Krause, MD[14]; Martin Wilhelm, MD[15]; Georg Maschmeyer, MD[16]; Julia Thiemer, MD[17]; Ulrich Dührsen, MD[18]; Julia Meissner, MD[19]; Andreas Viardot, MD[20]; Hans Eich, MD[21]; Christian Baues, MD[22]; Volker Diehl, MD[1]; Andreas Rosenwald, MD[23]; Bastian von Tresckow, MD[1]; Markus Dietlein, MD[2]; Peter Borchmann, MD, PhD[1]; and Andreas Engert, MD[1]

abstract

PURPOSE Combined-modality treatment (CMT) with 2× ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) and small-field radiotherapy is standard of care for patients with early-stage favorable Hodgkin lymphoma (HL). However, the role of radiotherapy has been challenged. Positron emission tomography (PET) after 2× ABVD (PET-2) might help to predict individual outcomes and guide treatment.

METHODS Between November 2009 and December 2015, we recruited patients age 18 to 75 years with newly diagnosed, early-stage favorable HL for this international randomized phase III trial. Patients were assigned to standard CMT of 2× ABVD and 20-Gy involved-field radiotherapy or PET-guided treatment, omitting involved-field radiotherapy after negative PET-2 (Deauville score < 3). Primary objectives were to exclude inferiority of 10% or more in 5-year progression-free survival (PFS) of ABVD alone compared with CMT in a per-protocol analysis among PET-2–negative patients (noninferiority margin for hazard ratio, 3.01) and to confirm PET-2 positivity (Deauville score ≥ 3) as a risk factor for PFS among CMT-treated patients.

RESULTS We enrolled 1,150 patients. Median follow-up was 45 months. Among 628 PET-2–negative, per-protocol–treated patients, 5-year PFS was 93.4% (95% CI, 90.4% to 96.5%) with CMT and 86.1% (95% CI, 81.4% to 90.9%) with ABVD (difference 7.3% [95% CI, 1.6% to 13.0%]; hazard ratio, 1.78 [95% CI, 1.02 to 3.12]). Five-year overall survival was 98.1% (95% CI, 96.5% to 99.8%) with CMT and 98.4% (95% CI, 96.5% to 100.0%) with ABVD. Among 693 patients who were assigned to CMT, 5-year PFS was 93.2% (95% CI, 90.2% to 96.2%) among PET-2–negative patients and 88.4% (95% CI, 84.2% to 92.6%) in PET-2–positive patients ($P = .047$). When using the more common liver cutoff (Deauville score, 4) for PET-2 positivity, the difference was more pronounced (5-year PFS, 93.1% [95% CI, 90.7% to 95.5%] *v* 80.9% [95% CI, 72.2% to 89.7%]; $P = .0011$).

CONCLUSION In early-stage favorable HL, a positive PET after two cycles ABVD indicates a high risk for treatment failure, particularly when a Deauville score of 4 is used as a cutoff for positivity. In PET-2–negative patients, radiotherapy cannot be omitted from CMT without clinically relevant loss of tumor control.

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ASSOCIATED CONTENT

Data Supplements

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

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INTRODUCTION

Hodgkin lymphoma (HL) is one of the best-curable cancers in adults today. This is especially true for patients with early-stage favorable disease for which more than 90% of all patients achieve long-term remission with first-line therapy.[1-3] Treatment intensity for these patients has been substantially reduced over the last decades in terms of both chemotherapy and radiotherapy. To date, two cycles of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD), followed by 20-Gy involved-site radiotherapy, are considered the standard of care.

Despite the limited amount of therapy needed to achieve these high cure rates, there is still concern over late adverse effects, including second malignant neoplasms (SMNs)[4,5] and organ toxicity.[6-8] Assuming

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that the combination of chemotherapy and radiotherapy is more harmful than chemotherapy alone, several trials addressed the impact of omitting radiotherapy with the use of positron emission tomography (PET), which is considered a useful tool for identifying patients who are at low risk for disease recurrence.[9,10] HD16 is a randomized trial comparing combined-modality therapy (CMT) with chemotherapy alone in terms of progression-free survival (PFS) for those patients who have a negative PET scan after two cycles of ABVD. The second goal of our trial was to analyze whether a positive PET scan after two cycles of ABVD is a risk factor for PFS among patients who are treated with both modalities. Here, we describe the results of the German Hodgkin Study Group (GHSG) HD16 trial.

METHODS

Study Design and Patients

This multicenter, international, randomized phase III trial was conducted across 250 sites in Germany, Switzerland, Austria, and the Netherlands. The trial was designed by the GHSG steering committee and approved by the responsible ethics committees. We recruited patients age 18 to 75 years with newly diagnosed, histology-proven classic HL in clinical stages I or II, or nodular lymphocyte-predominant HL in Ann Arbor stage IB, IIA, or IIB, without any of the following risk factors: large mediastinal mass (one third or more of the maximal thoracic diameter), extranodal lesions, elevated erythrocyte sedimentation rate (≥ 50 mm/h without B symptoms, ≥ 30 mm/h with B symptoms), or three or more involved nodal areas. Diagnostic histology samples were reassessed by at least one of a panel of six lymphoma expert pathologists. Other inclusion criteria are provided in the Data Supplement. All patients provided written informed consent before study entry according to the Good Clinical Practice guidelines of the International Conference on Harmonization.

Random Assignment

Before starting treatment, patients were centrally randomly assigned (1:1) between two parallel treatment groups: CMT that consisted of two cycles of ABVD and involved-field radiotherapy (IFRT) at 20 Gy, or PET-guided treatment that consisted of two cycles of ABVD for all patients and IFRT 20 Gy only for those patients with positive PET after two chemotherapy cycles (PET-2) by central review. Randomization was stratified according to center, age (< 45 *v* ≥ 45 years), sex, B symptoms, disease localization (supradiaphragmatic *v* infradiaphragmatic), albumin level (< 4 g/dL *v* ≥ 4 g/dL), and presence versus absence of initial bulk (< 5 cm *v* ≥ 5 cm in largest diameter). Patients and investigators were masked to treatment allocation until central review of PET-2 was completed.

Procedures

Procedures are described in the Data Supplement. ABVD was administered as previously described.[11] PET-2 was performed between day 22 and day 35 of the second ABVD cycle and centrally reviewed by a multidisciplinary panel of experts masked to treatment group allocation. PET-2 was rated according to the Deauville score (DS) using the mediastinal blood pool as cutoff for PET positivity (DS ≥ 3).[12] Patients with progressive disease were taken off study treatment. IFRT was centrally planned on the basis of initial staging imaging, and initial staging was revised if necessary. An independent data-monitoring board reviewed data on a regular basis and agreed with the timing and content of this analysis.

Outcomes

Primary end point was PFS, which was defined as the time from completion of staging until disease progression (within 3 months after the end of treatment), relapse, or death from any cause. If none of these events occurred, PFS was censored at the date of last information on disease status. Secondary end points were overall survival (OS), which was defined as the time from completion of staging until death from any cause or censored at the date of last information on the patient being alive, the proportion of patients with a negative PET-2, as well as the occurrence of SMNs.

Statistical Analysis

The current study had two independent objectives. The primary objective was to show noninferiority of treatment with ABVD alone compared with standard CMT in terms of PFS among PET-2–negative patients. Clinically relevant inferiority was defined as a hazard ratio (HR) of 3.01 or more on the basis of an absolute difference of 10% in 5-year PFS rates while assuming a 5-year PFS of 94.6% in the PET-2–negative CMT group (Data Supplement).

The second objective of the study was to assess the prognostic impact of PET-2 among patients who were assigned to CMT. Only patients with a valid PET-2 result who were assigned to receive CMT were to be analyzed—that is, PET-2–positive patients from both arms and PET-2–negative patients from the CMT arm.

We compared time-to-event end points using the Kaplan-Meier method, including HRs and 95% CIs. To assess whether the prognostic impact of PET-2 is independent from baseline factors, we performed sensitivity analyses for the comparison of PET-2–negative and PET-2–positive patients that included all stratification factors (except for center) in the Cox proportional hazards regression model. Cumulative SMN incidence was estimated according to the Kaplan-Meier method, accounting for death as a competing risk, and compared between treatment groups using subdistribution HRs. Other secondary end points were analyzed by means of descriptive statistics, with *P* values resulting from Fisher's exact test where applicable. Noninferiority test was primarily performed in the per-protocol population, excluding all patients with severe protocol

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deviations, as this was considered the most conservative analysis for noninferiority objectives in the trial protocol. Sensitivity analyses and all other analyses were performed according to the intention-to-treat (ITT) principle; however, all patients who dropped out before central review of PET-2 were excluded from all analyses regarding the main objectives of the trial (ITT_{PET} population). We used SAS (SAS/STAT User's Guide, Version 9.4; SAS Institute, Cary, NC) for all analyses.

RESULTS

We enrolled 1,150 patients—575 per arm—between November 25, 2009, and December 29, 2015. A total of

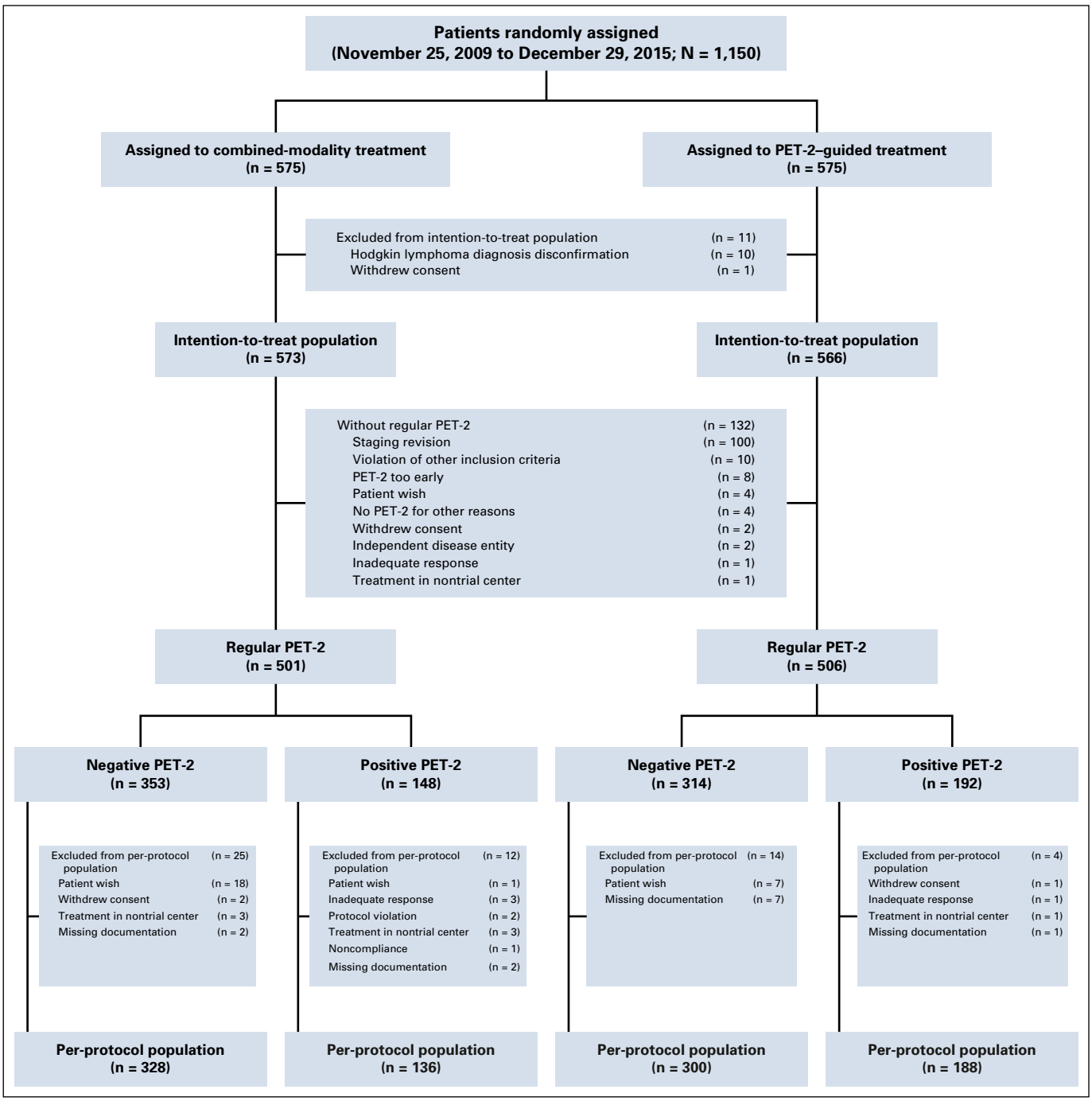

FIG 1. CONSORT diagram. Intention-to-treat population is defined as the set of all randomly assigned patients, except for those with disconfirmed diagnosis of Hodgkin lymphoma or withdrawal of trial consent, including anonymization of all study documents. Per-protocol population contains all intention-to-treat patients without severe protocol deviation, having a regular PET-2 (positron emission tomography after two cycles of chemotherapy) result and complete therapy documentation or progressive disease or death during therapy.

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11 patients were excluded from the ITT population as a result of disconfirmation of their HL diagnosis by pathology review (n = 10) or withdrawal of consent before starting treatment (n = 1; Fig 1). Another 132 patients (12%) dropped out before central review of PET-2, mainly because of a revision of the initial stage (n = 100). Thus, centrally reviewed PET-2 was available for 1,007 patients and was positive in 340 (34%), with DS 3 in 218 (22%) and DS 4 in 122 patients (12%). There was no documented case of DS 5.

Another 43 patients—4% of those with PET-2—dropped out after central PET review. The main reason for this was patients' wishes: 18 (5%) of 353 PET-2–negative patients in the CMT group refused to receive IFRT, whereas seven (2%) of 314 PET-2–negative patients in the PET-stratified group requested IFRT. Excluding another 12 patients with insufficient documentation, the per-protocol population was composed of 952 patients (83%; Fig 1).

Patient characteristics for the ITT population were similar between randomized treatment groups (Data Supplement). Median age was 39 years (range, 18 to 75 years), 120 patients (11%) were age 60 years or older, and 654 patients (57%) were male.

Protocol adherence for ABVD was good with a mean relative dose delivery of 98% (± 10%) and a mean delay of 3 days (± 5 days). Acute toxicity of Common Terminology Criteria for Adverse Events grades 3 or 4 was documented for 282 (26%) of 1,083 patients with available documentation. Most frequent toxicities were leukopenia (n = 203 [19%]) and nausea/vomiting (n = 47 [4%]). Respiratory tract disorders occurred in 22 patients (2%). IFRT was administered with a mean dose of 20 Gy (± 1 Gy). Acute

TABLE 1. Baseline Characteristics of the PET-2–Negative Per-Protocol Population

Characteristic	2× ABVD + 20 Gy IFRT (n = 328)	2× ABVD (n = 300)	Total (N = 628)
Age, years			
Median (range)	39 (18-75)	39 (18-75)	39 (18-75)
18-59	294 (90)	261 (87)	555 (88)
60-75	34 (10)	39 (13)	73 (12)
Sex			
Female	138 (42)	132 (44)	270 (43)
Male	190 (58)	168 (56)	358 (57)
Ann Arbor stage			
IA	105 (32)	94 (31)	199 (32)
IB	16 (5)	16 (5)	32 (5)
IIA	191 (58)	175 (58)	366 (58)
IIB	16 (5)	15 (5)	31 (5)
ECOG performance status			
0	307 (94)	276 (92)	583 (93)
1	20 (6)	24 (8)	44 (7)
2	1 (< 1)	0	1 (< 1)
Disease characteristics			
Albumin < 4 g/dL	57 (17)	58 (19)	115 (18)
Infradiaphragmatic disease	39 (12)	36 (12)	75 (12)
Bulky disease	59 (18)	54 (18)	113 (18)
Histologic subtype			
Nodular sclerosis cHL	88/237 (37)	64/206 (31)	152/443 (34)
Mixed cellularity cHL	74/237 (31)	75/206 (36)	149/443 (34)
Lymphocyte-rich cHL	35/237 (15)	31/206 (15)	66/443 (15)
Lymphocyte-depleted cHL	2/237 (1)	0/206	2/443 (< 1)
cHL, not otherwise specified	19/237 (8)	15/206 (7)	34/443 (8)
Nodular lymphocyte-predominant HL	19/237 (8)	21/206 (10)	40/443 (9)

NOTE. Data are presented as No. (%) or n/total (%), unless otherwise indicated.

Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; cHL, classic Hodgkin lymphoma; ECOG, Eastern Cooperative Oncology Group; HL, Hodgkin lymphoma; IFRT, involved-field radiotherapy; PET-2, positron emission tomography after two cycles of chemotherapy.

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radiotherapy toxicity of Common Terminology Criteria for Adverse Events grade 3 was reported for 19 (3%) of 659 patients with available documentation. Most frequently observed toxicities were dysphagia (n = 9 [1%]) and mucositis (n = 5 [1%]). No grade 4 toxicities occurred.

A total of 628 PET-2–negative patients were eligible for the per-protocol noninferiority analysis—328 received CMT and 300 had ABVD alone. Patient characteristics were similar between groups (Table 1). With a median follow-up of 47 months, one patient experienced disease progression, 43 cases of relapse, and eight deaths without prior disease recurrence occurred. Four patients died after experiencing progression or relapse (Table 2). SMNs were reported for 24 patients. Corresponding 5-year cumulative incidences did not differ between the CMT and ABVD groups (subdistribution HR, 0.78 [95% CI, 0.35 to 1.75]; $P = .54$; Table 2). PFS at 5 years was 93.4% (95% CI, 90.4% to 96.5%) in the CMT group and 86.1% (95% CI, 81.4% to 90.9%) in the ABVD group (Fig 2A). The 95% CI for the HR of 1.78 ranged from 1.02 to 3.12 and included the predefined noninferiority margin of 3.01. PFS difference primarily resulted from a significant increase in disease

TABLE 2. Outcomes of the PET-2–Negative Per-Protocol Population

Outcome	2× ABVD + 20 Gy IFRT (n = 328)	2× ABVD (n = 300)
Median observation time, months (IQR)		
For disease status	47 (30-65)	46 (30-63)
For survival status	51 (34-66)	48 (32-64)
Tumor event		
Progression	0	1 (< 1)
Early relapse (within 1 year after treatment)	2 (1)	9 (3)
Late relapse	13 (4)	19 (6)
Any tumor event	15 (5)	29 (10)
Second-line therapy		
HDCT and ASCT	7 (2)	12 (4)
DHAP or ICE without HDCT/ASCT	2 (1)	0
Other chemotherapy with or without radiotherapy	3 (1)	6 (2)
Radiotherapy only	1 (< 1)	6 (2)
Antibody therapy	0	1 (< 1)
Relapse, but no second-line therapy	1 (< 1)	0
Unknown second-line therapy	1 (< 1)	4 (1)
Cause of death		
Hodgkin lymphoma	1 (< 1)	0
SMN	4 (1)	0
Other disease*	1 (< 1)	2 (1)
Accident	0	1 (< 1)
Unclear	3 (1)	0
Any event	9 (3)	3 (1)
SMN		
Acute myeloid leukemia or myelodysplastic syndrome	0	1 (< 1)
Non-Hodgkin lymphoma	2 (1)	0
Solid tumor	12 (4)	9 (3)
Any event	14 (4)	10 (3)
5-year cumulative incidence estimate, % (95% CI)†	5.6 (2.3 to 9.0)	4.6 (1.4 to 7.9)

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

Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; ASCT, autologous stem-cell transplantation; DHAP, dexamethasone, cytarabine, and cisplatin; HDCT, high-dose chemotherapy; ICE, ifosfamide, carboplatin, and etoposide; IFRT, involved-field radiotherapy; PET-2, positron emission tomography after two cycles of chemotherapy; SMN, second malignant neoplasm.

*Including cardiovascular disease (n = 2), and other, nonspecified disease (n = 1).

†Accounting for death as a competing risk.

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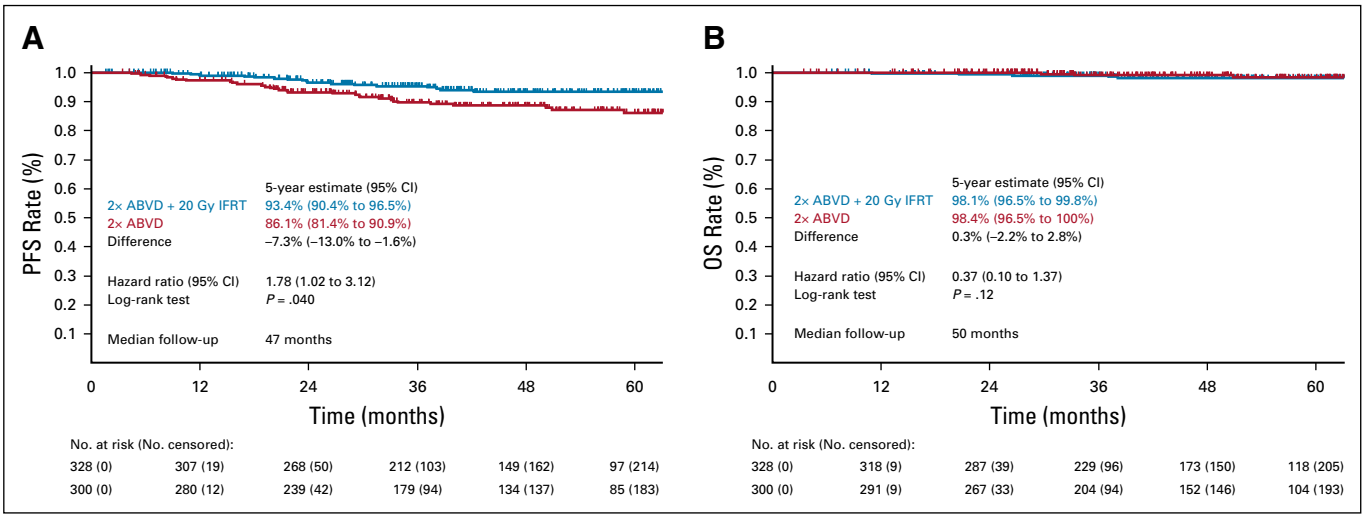

FIG 2. Kaplan-Meier estimates for the PET-2 (positron emission tomography after two cycles of chemotherapy) –negative per-protocol population. (A) Progression-free survival (PFS). (B) Overall survival (OS). ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; IFRT, involved-field radiotherapy.

recurrences within the hypothetical radiation field without IFRT (in-field recurrence rate, 2% *v* 9%; $P = .0003$), whereas there was no relevant difference regarding out-field recurrences (4% *v* 5%; $P = .55$). Most patients received high-dose chemotherapy and autologous stem-cell transplantation for treatment of progression or relapse (Table 2). Results for the ITT_{PET} population were largely similar (HR, 1.69 [95% CI, 0.98 to 2.90]; Data Supplement), but 95% CI for HR excluded the noninferiority margin. This divergence is based on two additional PFS events in the ITT_{PET} population, which were both in-field relapses in patients from the CMT group who dropped out of the per-protocol population as a result of IFRT refusal. Another sensitivity analysis was performed in the subgroup of patients with nonbulky stage IA or IIA disease with concordant results (HR, 2.88 [95% CI, 1.38 to 6.00]; Data Supplement).

OS was 98.1% (95% CI, 96.5% to 99.8%) with CMT and 98.4% (95% CI, 96.5% to 100.0%) with ABVD at 5 years (Fig 2B). PFS and OS comparisons between randomized treatment groups in the full ITT population (N = 1,139) are provided in the Data Supplement.

A total of 693 patients were assigned to receive IFRT after a negative (n = 353) or positive (n = 340) PET-2 and were thus eligible for analysis of the PET objective. Initial stage II and bulky disease were more frequent among patients with positive PET-2 ($P < .001$ each; Table 3). With median follow-up of 46 months, six patients experienced disease progression. There were 41 relapses and nine deaths without prior disease recurrence, and eight patients died after experiencing progression or relapse (Table 4). PFS at 5 years was 93.2% (95% CI, 90.2% to 96.2%) in the PET-2–negative subgroup and 88.4% (95% CI, 84.2% to 92.6%) in the PET-2–positive subgroup (HR, 1.71 [95% CI, 1.00 to 2.93]; $P = .047$). Sensitivity analysis adjusting for stratification factors led to similar, but nonsignificant results (HR, 1.73 [95% CI, 0.99% to 3.02%]; $P = .055$; Fig 3A). OS was 98.2% (95% CI, 96.7% to 99.8%) in the PET-2–negative subgroup and 97.9% (95% CI, 95.6% to 100.0%) in the PET-2–positive subgroup at 5 years ($P = .55$ adjusted for stratification factors; Fig 3B). To assess whether the prognostic impact of PET-2 would have increased with a different cutoff, we repeated the analysis using the more common cutoff of DS 4 for positivity. Of note, all six primary progressions observed among CMT-treated patients occurred in the DS 4 subgroup. PFS at 5 years was 93.1% (95% CI, 90.7% to 95.5%) in the DS 1 to 3 and 80.9% (95% CI, 72.2% to 89.7%) in the DS 4 subgroup (HR adjusted for stratification factors, 2.94 [95% CI, 1.63 to 5.31]; $P < .001$; Fig 3C). Still, there was no difference in OS (Fig 3D).

DISCUSSION

Two major findings emerge from the GHSG HD16 trial for patients with newly diagnosed early-stage favorable HL. First, radiotherapy cannot be omitted from standard CMT without a relevant loss of tumor control in patients with negative PET-2. Second, a positive PET scan after two cycles of ABVD represents a risk factor for PFS among patients who are treated with standard CMT, particularly when DS 4 is considered the cutoff for positivity.

For decades, radiotherapy had been the mainstay of treatment for patients with early-stage HL.[1-3] Over time, controversial discussions have led to smaller radiation fields and lower doses.[1,2,13,14] With the advent of multiagent chemotherapy, such as mechlorethamine, vincristine, procarbazine, and prednisone, and ABVD,[15] large radiation fields were replaced by combinations of chemotherapy and radiotherapy. The GHSG HD7 and EORTC-GELA H8 trials

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TABLE 3. Baseline Characteristics of PET-2–Negative and PET-2–Positive Patients Assigned to Receive Radiotherapy

Characteristic	Negative PET-2 (DS 1-2; n = 353)	Positive PET-2 (DS 3-4; n = 340)	*P*	DS 1-3 (n = 571)	DS 4 (n = 122)	*P*
Age, years						
Median (range)	39 (18-75)	37 (18-75)	.031	38 (18-75)	37 (18-74)	.25
18-59	319 (90)	311 (91)		515 (90)	115 (94)	
60-75	34 (10)	29 (9)		56 (10)	7 (6)	
Sex						
Female	150 (42)	124 (36)	.12	227 (40)	47 (39)	.84
Male	203 (58)	216 (64)		344 (60)	75 (61)	
Ann Arbor stage						
IA	116 (33)	71 (21)	.0002 (I *v* II)	166 (29)	21 (17)	.0012 (I *v* II)
IB	17 (5)	11 (3)		26 (5)	2 (2)	
IIA	204 (58)	241 (71)	.69 (A *v* B)	356 (62)	89 (73)	.60 (A *v* B)
IIB	16 (5)	17 (5)		23 (4)	10 (8)	
ECOG performance status						
0	332 (94)	308 (91)	.12	532 (93)	108 (89)	.091
1	20 (6)	32 (9)		38 (7)	14 (11)	
2	1 (< 1)	0		1 (< 1)	0	
Disease characteristics						
Albumin < 4 g/dL	59 (17)	62 (18)	.62	104 (18)	17 (14)	.39
Infradiaphragmatic disease	41 (12)	33 (10)	.46	63 (11)	11 (9)	.63
Bulky disease	65 (18)	115 (34)	< .001	135 (24)	45 (37)	.0031
Histologic subtype						
Classic Hodgkin lymphoma	237/256 (93)	204/237 (86)	.027	369/405 (91)	72/88 (82)	.020
Nodular lymphocyte-predominant Hodgkin lymphoma	19/256 (7)	33/237 (14)		36/405 (9)	16/88 (18)	

NOTE. Data are No. (%) or n/total (%), unless otherwise indicated.

Abbreviations: DS, Deauville score; ECOG, Eastern Cooperative Oncology Group; PET-2, positron emission tomography after two cycles of chemotherapy.

compared total-lymphoid radiation or extended-field radiation alone with a combined-modality approach including additional chemotherapy.[16,17] Both trials demonstrated significantly better outcomes with CMT, which subsequently became standard of care in early-stage HL.

The GHSG follow-up phase III trial, HD10, addressed the question of dose de-escalation for both chemotherapy and radiotherapy, comparing four cycles of ABVD with two cycles and IFRT 30 Gy with 20 Gy, respectively.[11] HD10 demonstrated noninferiority for efficacy for both objectives, whereas there was clearly less toxicity with reduced-intensity treatment. As a consequence, only two cycles of ABVD followed by 20 Gy of small-field radiotherapy are being considered the standard of care for early-stage favorable HL. However, additional de-escalation of these genotoxic and thus potentially harmful treatment modalities remains an important goal. This might be achieved by using a more individualized treatment approach that requires reliable identification of patients who are at low risk for treatment failure. As response assessment during treatment using metabolic imaging with PET has proven its prognostic impact in HL, we aimed at an additional reduction of treatment intensity in early-stage favorable HL using a PET-guided approach. In contrast to other trials with similar objectives, we examined a true reduction of treatment burden by omitting radiotherapy rather than replacing it with more chemotherapy.

The HD16 trial reported herein enrolled a total of 1,150 patients, of whom 628 were PET negative after two cycles of ABVD and treated per protocol. Among these, 5-year PFS was 93.4% (95% CI, 90.4% to 96.5%) in the standard group treated with CMT compared with 86.1% (95% CI, 81.4% to 90.9%) for the experimental group receiving ABVD alone. We thus clearly missed our primary goal of showing noninferiority of the PET-2–guided omission of radiotherapy.

This finding is in line with previously reported trials for PET-guided treatment in early-stage HL. In the United Kingdom RAPID trial (ClinicalTrials.gov identifier: NCT00943423), 571 patients underwent PET with 75% becoming PET-negative

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TABLE 4. Outcomes of PET-2–Negative and PET-2–Positive Patients Assigned to Receive Radiotherapy

	Negative PET-2	Positive PET-2	
Outcome	**DS 1-2 (n = 353)**	**DS 3 (n = 218)**	**DS 4 (n = 122)**
Median observation time, months (IQR)			
For disease status	47 (30-64)	45 (33-61)	48 (34-61)
For survival status	49 (33-66)	46 (34-62)	50 (34-63)
Tumor event			
Progression	0	0	6 (5)
Early relapse (within 1 year after end of treatment)	3 (1)	4 (2)	2 (2)
Late relapse	14 (4)	9 (4)	9 (7)
Any tumor event	17 (5)	13 (6)	17 (14)
Causes of death			
Hodgkin lymphoma	1 (< 1)	0	1 (1)
Toxicity of second-line therapy	0	1 (< 1)	0
Second malignant neoplasm	4 (1)	2 (1)	1 (1)
Cardiovascular disease	1 (< 1)	1 (< 1)	0
Unclear	3 (1)	1 (< 1)	1 (1)
Any event	9 (3)	5 (2)	3 (2)

NOTE. Data are presented as No. (%), unless otherwise indicated.
Abbreviations: DS, Deauville score; PET-2, positron emission tomography after two cycles of chemotherapy.

after three cycles of ABVD. Three-year PFS was 97.1% in patients who received additional radiotherapy (per-protocol analysis), but only 90.8% among those who received no additional treatment.[18] A larger trial was performed by the European Organisation for Research and Treatment of Cancer, Groupe d'Etude des Lymphomes de l'Adulte, and Fondazione Italiana Linfomi. Their standard consisted of three cycles of ABVD followed by involved-node radiotherapy, whereas in the experimental arm PET-2–negative patients received four cycles of ABVD alone. Five-year PFS rates among 465 randomized favorable-risk patients with negative PET were 99% in the standard arm and 87% in the experimental arm, respectively, with a corresponding HR of 15.8 (95% CI, 3.8 to 66.1).[19]

Taken together, all three large international randomized trials in early-stage HL failed to demonstrate noninferiority of PET-guided omission of radiotherapy in terms of PFS. However, these trials did not show poorer OS for interim-PET–negative patients who were treated without radiotherapy. Effects on OS should be judged with caution, as follow-up periods in clinical trials usually do not exceed 5 years. Registry data suggest a negative impact of the chemotherapy-alone treatment strategy in early-stage HL,[20,21] which indicates a meaningful effect of the loss in PFS observed in our trial. Of importance, patients do not want to experience relapse or disease progression, as these are associated with the need for additional, more toxic treatment as well as social and psychological burdens.[22,23] PFS is the most important end point from the patients' perspective and is thus highly relevant for the interpretation of trial results.

The fear of using radiotherapy emerged from reports of late toxicities of radiotherapy techniques used decades ago.[4] We assume that the small radiation fields and doses used in our HD16 trial will induce fewer late adverse events than those reported in the literature.[24,25] However, we cannot exclude an increased risk for certain late effects, such as breast cancer in very young women, as the risk for this specific second malignancy increases with younger age.[26] Uncertainty around the risk-to-benefit ratio of the CMT strategy for individual patients must be addressed in a shared decision-making process. With regard to the entire patient population enrolled in the HD16 trial, however, we feel safe to conclude that the hypothetical benefit of the chemotherapy-alone treatment strategy does not outweigh the immediate loss of tumor control with all its consequences.

Metabolic response assessment with PET-2 has proven predictive power in our trial. With standard CMT, 5-year PFS was 93.1% in the subgroup of patients having DS 1 to 3, but only 80.9% in patients having DS 4. Our study design did not include treatment intensification in the case of PET-2 positivity; however, in the EORTC H10 trial, the unsatisfactory failure rate of PET-2–positive patients could be reduced significantly by switching to a more intensive chemotherapy regimen. This observation supports the use of PET-guided treatment intensification.

There are a number of limitations in HD16 to be addressed. First, the definition of PET negativity was conservative, with

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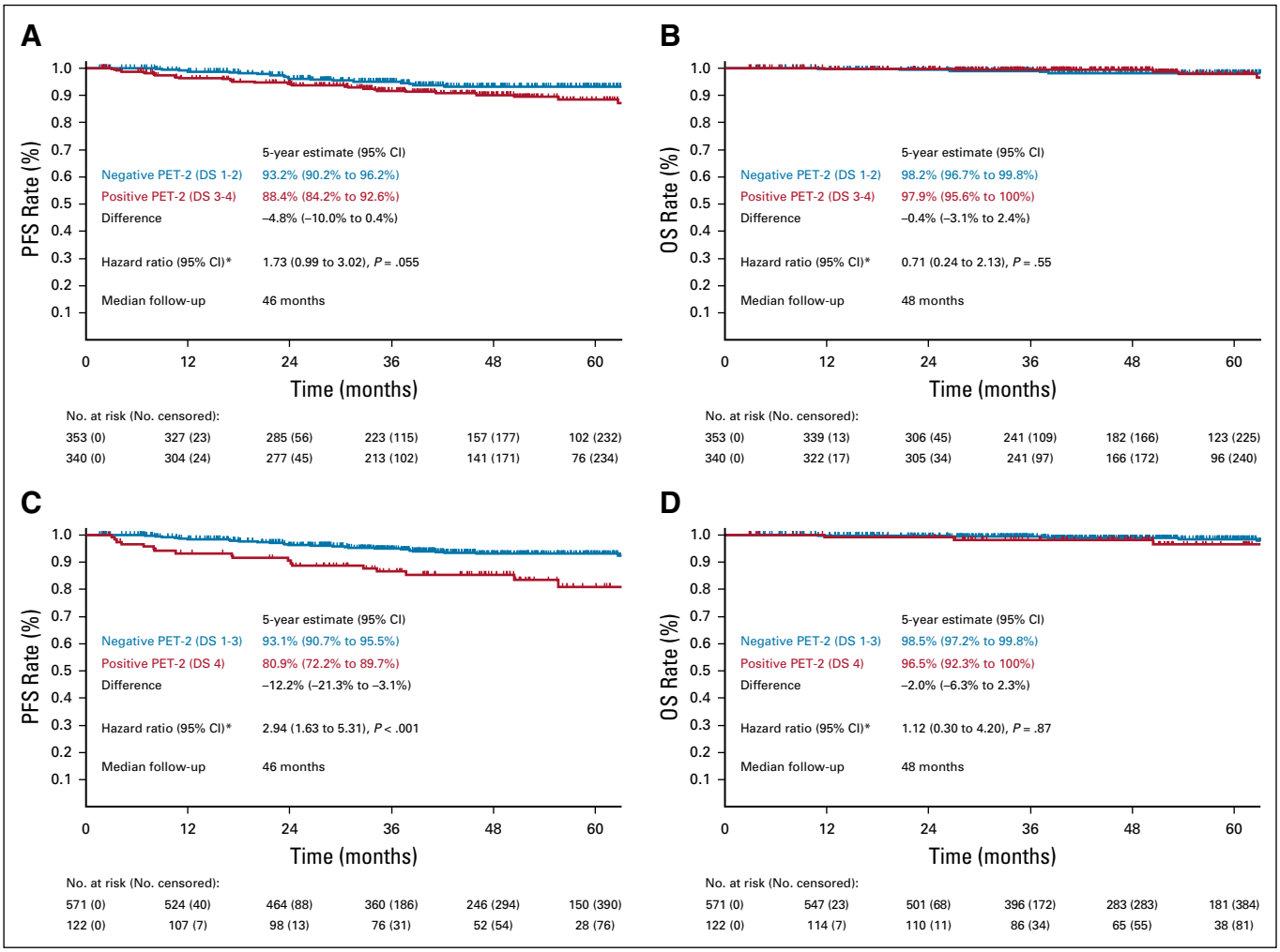

FIG 3. Kaplan-Meier estimates for PET-2 (positron emission tomography after two cycles of chemotherapy) –negative and PET-2–positive patients assigned to receive radiotherapy. (A) Progression-free survival (PFS), Deauville score (DS) 1-2 versus DS 3-4. (B) Overall survival (OS), DS 1-2 versus DS 3-4. (C) PFS, DS 1-3 versus DS 4. (D) OS, DS 1-3 versus DS 4. (*) Cox model adjusted for stratification factors age (< 45 years *v* ≥ 45 years), sex, B symptoms, disease localization (supradiaphragmatic *v* infradiaphragmatic), albumin level (< 4 g/dL *v* ≥ 4 g/dL), and bulky disease (< 5 cm *v* ≥ 5 cm in largest diameter).

DS 3 already being considered positive; however, this definition had no confounding impact on the primary objective and thus does not interfere with the interpretation of the trial results. Second, although HD16 is a large, randomized trial, the proportion of PET-2–positive patients differed by chance between treatment groups, with more patients in the experimental group having a positive PET-2. However, our study design, which limits the comparative analysis to the PET-negative subgroups from each randomization group, addresses this aspect and makes an influence on our study results unlikely. Finally, we could not evaluate all potential late effects that might provide quantifiable information on the advantages of omitting radiotherapy, because these adverse effects occur 20 years or more after treatment.

Strengths of our study include the solid study design and the large number of patients and centers from several countries contributing, all of which support firm conclusions of the observed effects. Because most participating centers were private practices or primary care hospitals, results reflect a real-world setting in high-income countries.

In conclusion, the GHSG HD16 trial demonstrates that PET after two cycles of ABVD allows for identifying patients who are at high risk for treatment failure. However, we failed to meet the primary objective of the trial, as PET-guided omission of radiotherapy results in poorer tumor control compared with CMT. We therefore recommend proceeding with consolidation radiotherapy as a standard of care for patients achieving a metabolic response after two cycles of ABVD.

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AFFILIATIONS

[1]German Hodgkin Study Group (GHSG), Department I of Internal Medicine, Center for Integrated Oncology Aachen Bonn Cologne Duesseldorf, University of Cologne, Cologne, Germany
[2]Department of Nuclear Medicine, University of Cologne, Cologne, Germany
[3]Cantonal Hospital Baselland, Liestal, Switzerland
[4]Swiss Group for Clinical Cancer Research (SAKK), Bern, Switzerland
[5]IIIrd Medical Department, Paracelcus Medical University and Salzburg Cancer Research Institute, Salzburg, Austria
[6]Salzburg Cancer Research Institute and AGMT (Arbeitsgemeinschaft Medikamentöse Tumortherapie), Salzburg, Austria
[7]Medizinische Klinik und Poliklinik II, Universitätsklinikum Würzburg, Würzburg, Germany
[8]Dres. med. Just/Düwel/Riesenberg/Steinke/Schäfer, Studiengesellschaft, Bielefeld, Germany
[9]Department of Internal Medicine I, Klinikum Bremen Mitte, Bremen, Germany
[10]University of Tübingen, Tübingen, Germany
[11]Medizinische Klinik III, Universitätsklinik Regensburg, Regensburg, Germany
[12]Amsterdam University Medical Center, Vrije Universiteit, Department of Hematology, Amsterdam, Netherlands
[13]Department of Internal Medicine III, Klinikum "Rechts der Isar", Munich, Germany
[14]Department of Internal Medicine 5, Haematology/Oncology, University of Erlangen, Erlangen, Germany
[15]Department of Medical Oncology, Klinikum Nürnberg, Paracelsus Medical University, Nürnberg, Germany
[16]Department of Hematology, Oncology and Palliative Care, Klinikum Ernst von Bergmann, Potsdam, Germany
[17]Clinic for Hematology, Oncology and Immunology, Philipps University, Marburg, Germany
[18]Department of Haematology, University Hospital Essen, University of Duisburg-Essen, Essen, Germany
[19]University of Heidelberg, Heidelberg, Germany
[20]Department of Internal Medicine III, University Hospital Ulm, Ulm, Germany
[21]Department of Radiotherapy, University Hospital of Muenster, Muenster, Germany
[22]Department of Radiotherapy, University of Cologne, Cologne, Germany
[23]Institute of Pathology, Julius Maximilian University of Würzburg and Comprehensive Cancer Center Mainfranken, Würzburg, Germany

CORRESPONDING AUTHOR

Andreas Engert, MD, German Hodgkin Study Group, Department I of Internal Medicine, University Hospital of Cologne, Kerpener Str. 62, D-50924 Cologne, Germany; e-mail: a.engert@uni-koeln.de.

EQUAL CONTRIBUTION

M.F. and H.G. contributed equally to this work.

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AUTHOR CONTRIBUTIONS

Conception and design: Michael Fuchs, Helen Goergen, Hans Eich, Volker Diehl, Markus Dietlein, Peter Borchmann, Andreas Engert

Administrative support: Erhardt Schäfer, Markus Dietlein

Provision of study materials or patients: Richard Greil, Stephanie Sasse, Martin Soekler, Martin Vogelhuber, Ulrich Bernd Keller, Stefan W. Krause, Martin Wilhelm, Julia Thiemer, Ulrich Dührsen, Julia Meissner, Andreas Viardot, Bastian von Tresckow, Markus Dietlein, Andreas Engert

Collection and assembly of data: Michael Fuchs, Helen Goergen, Carsten Kobe, Georg Kuhnert, Andreas Lohri, Richard Greil, Stephanie Sasse, Max S. Topp, Erhardt Schäfer, Bernd Hertenstein, Martin Soekler, Martin Vogelhuber, Josée M. Zijlstra, Ulrich Bernd Keller, Stefan W. Krause, Martin Wilhelm, Georg Maschmeyer, Julia Thiemer, Ulrich Dührsen, Julia Meissner, Andreas Viardot, Hans Eich, Christian Baues, Andreas Rosenwald, Bastian von Tresckow, Markus Dietlein, Peter Borchmann, Andreas Engert

Data analysis and interpretation: Michael Fuchs, Helen Goergen, Carsten Kobe, Richard Greil, Martin Soekler, Georg Maschmeyer, Volker Diehl, Andreas Rosenwald, Bastian von Tresckow, Markus Dietlein, Peter Borchmann, Andreas Engert

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

Positron Emission Tomography–Guided Treatment in Early-Stage Favorable Hodgkin Lymphoma: Final Results of the International, Randomized Phase III HD16 Trial by the German Hodgkin Study Group

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Michael Fuchs
Honoraria: Amgen, Affimed, Celgene, Takeda

Richard Greil
Honoraria: Celgene, Roche, Merck, Takeda, AstraZeneca, Novartis, Amgen, Bristol-Myers Squibb, MSD Oncology, Sandoz, AbbVie, Gilead Sciences, Daiichi Sankyo
Consulting or Advisory Role: Celgene, Novartis, Roche, Bristol-Myers Squibb, Takeda, AbbVie, AstraZeneca, Janssen Pharmaceuticals, MSD Oncology, Merck, Gilead Sciences, Daiichi Sankyo
Research Funding: Celgene (Inst), Merck (Inst), Takeda (Inst), AstraZeneca (Inst), Novartis (Inst), Amgen (Inst), Bristol-Myers Squibb (Inst), MSD Oncology (Inst), Sandoz (Inst), Gilead Sciences (Inst), Roche (Inst)
Travel, Accommodations, Expenses: Roche, Amgen, Janssen-Cilag, AstraZeneca, Novartis, MSD Oncology, Celgene, Gilead Sciences, Bristol-Myers Squibb

Max S. Topp
Consulting or Advisory Role: Amgen, Regeneron, Roche, Novartis, Kite Pharmaceuticals, Gilead Sciences
Research Funding: Regeneron (Inst), Kite Pharmaceuticals (Inst), Roche (Inst), Boehringer Ingelheim (Inst)
Travel, Accommodations, Expenses: Amgen, Celgene, Boehringer Ingelheim, Regeneron

Erhardt Schäfer
Stock and Other Ownership Interests: Celgene, Roche

Ulrich Bernd Keller
Honoraria: Gilead Sciences, Amgen, Bristol-Myers Squibb, Roche, Takeda, Merck Serono, Janssen-Cilag, Hexal
Consulting or Advisory Role: Roche, Bristol-Myers Squibb, Hexal, Janssen-Cilag, Takeda, Gilead Sciences, Merck Serono, AstraZeneca
Research Funding: Roche (Inst), Janssen-Cilag (Inst), Bristol-Myers Squibb (Inst), Takeda (Inst)
Travel, Accommodations, Expenses: Roche, Bristol-Myers Squibb, Takeda, Celgene

Stefan W. Krause
Honoraria: MSD Oncology, Takeda
Research Funding: Siemens Healthcare Diagnostics (Inst)
Travel, Accommodations, Expenses: Gilead Sciences
Other Relationship: Gilead Sciences, Celgene

Georg Maschmeyer
Honoraria: Gilead Sciences, Bristol-Myers Squibb, Janssen-Cilag, AstraZeneca, Merck Serono
Travel, Accommodations, Expenses: Janssen-Cilag, Bristol-Myers Squibb

Ulrich Dührsen
Honoraria: Roche
Research Funding: Amgen (Inst), Roche (Inst)

Julia Meissner
Travel, Accommodations, Expenses: MSD Oncology, Bristol-Myers Squibb, Takeda, Hexal, Celgene

Andreas Viardot
Honoraria: Roche, Pfizer
Consulting or Advisory Role: Amgen, Kite Pharmaceuticals, Gilead Sciences, Roche
Travel, Accommodations, Expenses: Janssen, Roche, Kite Pharmaceuticals, AbbVie, Bristol-Myers Squibb

Bastian von Tresckow
Honoraria: Roche, Takeda, MSD Oncology
Consulting or Advisory Role: Amgen, Pfizer, Takeda, MSD Oncology
Research Funding: Novartis (Inst), MSD Oncology (Inst), Takeda (Inst)
Travel, Accommodations, Expenses: MSD, Takeda, Novartis

Andreas Engert
Honoraria: Hexal, Chugai Pharma, MSD Oncology
Consulting or Advisory Role: Takeda, Bristol-Myers Squibb
Research Funding: Takeda (Inst), Bristol-Myers Squibb (Inst), Affimed Therapeutics (Inst)

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