PET-guided treatment in patients with advanced-stage Hodgkin's lymphoma (HD18): final results of an open-label, international, randomised phase 3 trial by the German Hodgkin Study Group

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Summary

Background The intensive polychemotherapy regimen eBEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone in escalated doses) is very active in patients with advanced-stage Hodgkin's lymphoma, albeit at the expense of severe toxicities. Individual patients might be cured with less burdensome therapy. We investigated whether metabolic response determined by PET after two cycles of standard regimen eBEACOPP (PET-2) would allow adaption of treatment intensity, increasing it for PET-2-positive patients and reducing it for PET-2-negative patients.

Methods In this open-label, randomised, parallel-group phase 3 trial, we recruited patients aged 18–60 years with newly diagnosed, advanced-stage Hodgkin's lymphoma in 301 hospitals and private practices in Germany, Switzerland, Austria, the Netherlands, and the Czech Republic. After central review of PET-2, patients were assigned (1:1) to one of two parallel treatment groups on the basis of their PET-2 result. Patients with positive PET-2 were randomised to receive six additional cycles of either standard eBEACOPP (8×eBEACOPP in total) or eBEACOPP with rituximab (8×R-eBEACOPP). Those with negative PET-2 were randomised between standard treatment with six additional cycles of eBEACOPP (8×eBEACOPP) or experimental treatment with two additional cycles (4×eBEACOPP). A protocol amendment in June, 2011, introduced a reduction of standard therapy to 6×eBEACOPP; after this point, patients with positive PET-2 were no longer randomised and were all assigned to receive 6×eBEACOPP and patients with negative PET-2 were randomly assigned to 6×eBEACOPP (standard) or 4×eBEACOPP (experimental). Randomisation was done centrally using the minimisation method including a random component, stratified according to centre, age (<45 *vs* ≥45 years), stage (IIB, IIIA *vs* IIIB, IV), international prognostic score (0–2 *vs* 3–7), and sex. eBEACOPP was given as previously described; rituximab was given intravenously at a dose of 375 mg/m² (maximum total dose 700 mg). The primary objectives were to show superiority of the experimental treatment in the PET-2-positive cohort, and to show non-inferiority of the experimental treatment in the PET-2-negative cohort in terms of the primary endpoint, progression-free survival. We defined non-inferiority as an absolute difference of 6% in the 5-year progression-free survival estimates. Primary analyses in the PET-2-negative cohort were per protocol; all other analyses were by intention to treat. This trial was registered with ClinicalTrials.gov, number NCT00515554.

Findings Between May 14, 2008, and July 18, 2014, we recruited 2101 patients, of whom 137 were found ineligible before randomisation and a further 19 were found ineligible after randomisation. Among 434 randomised patients (217 per arm) with positive PET-2, 5-year progression-free survival was 89·7% (95% CI 85·4–94·0) with eBEACOPP and 88·1% (83·5–92·7) with R-eBEACOPP (log-rank p=0·46). Patients with negative PET-2 randomly assigned to either 8×eBEACOPP or 6×eBEACOPP (n=504) or 4×eBEACOPP (n=501) had 5-year progression-free survival of 90·8% (95% CI 87·9–93·7) and 92·2% (89·4–95·0), respectively (difference 1·4%, 95% CI –2·7 to 5·4). 4×eBEACOPP was associated with fewer severe infections (40 [8%] of 498 *vs* 75 [15%] of 502) and organ toxicities (38 [8%] of 498 *vs* 91 [18%] of 502) than were 8×eBEACOPP or 6×eBEACOPP in PET-2-negative patients. Ten treatment-related deaths occurred: four in the PET-2-positive cohort (one [<1%] in the 8×eBEACOPP group, three [1%] in the 8×R-eBEACOPP group) and six in the PET-2-negative group (six [1%] in the 8×eBEACOPP or 6×eBEACOPP group).

Interpretation The favourable outcome of patients treated with eBEACOPP could not be improved by adding rituximab after positive PET-2. PET-2 negativity allows reduction to only four cycles of eBEACOPP without loss of tumour control. PET-2-guided eBEACOPP provides outstanding efficacy for all patients and increases overall survival by reducing treatment-related risks for patients with negative PET-2. We recommend this PET-2-guided treatment strategy for patients with advanced-stage Hodgkin's lymphoma.

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Introduction

Patients with advanced-stage Hodgkin's lymphoma can be cured with modern chemotherapy regimens.[1,2] The intensive eBEACOPP regimen (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone in escalated doses) developed by the German Hodgkin Study Group (GHSG) has produced excellent tumour control in the entire group of patients with advanced-stage Hodgkin's lymphoma.[3–5] Favourable outcomes are, however, accompanied by a high incidence of severe acute and long-term toxicities, which can have a major effect on patients' lives even many years after treatment.[6–8] Within the heterogeneous group of patients diagnosed with advanced-stage Hodgkin's lymphoma, a low individual risk of treatment failure might allow the use of a less intensive treatment to avoid toxicities. However, none of the established staging systems based on the Ann Arbor classification in combination with various clinical risk factors can reliably predict the individual risk of treatment failure.

The introduction of functional imaging using ^{18}F-fluoro-2-deoxy-D-glucose (^{18}F-FDG) PET for metabolic response assessment has opened up the possibility of a more individualised treatment approach.[9] ^{18}F-FDG-PET response after two cycles of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) chemotherapy appears to overcome the prognostic effect of even the International Prognostic Score.[10–13] We thus hypothesised that interim PET imaging after two cycles of the GHSG standard regimen eBEACOPP (PET-2) might discriminate between low-risk and high-risk patients. Based on this hypothesis, the GHSG HD18 study aimed to answer two questions.

First, we wanted to assess whether treatment intensification with the addition of the anti-CD20 antibody rituximab to standard eBEACOPP would improve progression-free survival in presumably high-risk patients with positive PET-2. However, a pre-planned interim analysis showed no difference in progression-free survival at 3 years, futility was concluded, and results were published early.[14]

Second, assuming a favourable outcome in presumably low-risk patients with negative PET-2, we asked whether a substantial treatment reduction from eight to only four cycles of eBEACOPP would be possible without compromising progression-free survival in this patient group. With this treatment reduction, we intended to reduce the burden of therapy for our patients.

Here we report the final analysis of the GHSG HD18 study.

Methods

Study design and patients

This open-label, multicentre, international, randomised phase 3 trial was done in 301 hospitals and private practices in Germany, Switzerland, Austria, the Netherlands, and the Czech Republic. The trial was designed by the GHSG

Research in context

Evidence before this study

Early interim ^{18}F-fluoro-2-deoxy-D-glucose (^{18}F-FDG PET) after two cycles of chemotherapy (PET-2) has shown a high positive and negative predictive value in patients with advanced-stage Hodgkin's lymphoma receiving ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine). Treatment modification based on PET-2 results might improve the outcome. We searched MEDLINE between Jan 1, 2000, and Jan 1, 2017, with the search terms "interim PET" or "PET-2" and "Hodgkin*" to identify studies that assessed the predictive effect of early interim functional imaging with PET-2. The results from both uncontrolled and controlled studies suggest that PET-2 has a high positive predictive value in advanced-stage Hodgkin's lymphoma after upfront ABVD, and that treatment intensification might be of moderate benefit in these patients. The negative predictive value in patients receiving upfront ABVD seems to be less robust. We found no evidence from controlled trials on the prognostic or predictive value of PET-2 for patients receiving BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone) besides the HD18 study.

Added value of this study

A positive PET after two cycles of BEACOPP in escalated doses (eBEACOPP) did not identify a high-risk patient cohort in our phase 3 trial, neither in patients treated with a total of eight or six cycles. The negative predictive value of PET-2, however, allowed reduction from eight to four cycles of eBEACOPP without loss of tumour control. As a result from the reduced treatment intensity, the incidence of severe adverse events was significantly reduced and overall survival was significantly improved.

Implications of all the available evidence

PET-2 positivity does not identify a high-risk patient cohort when the current GHSG standard treatment is used. However, PET-2 negativity allows the reduction to a highly effective, short, and very safe treatment of only four cycles of eBEACOPP. To our knowledge, the survival outcomes of patients in the HD18 study exceed any data from controlled trials reported so far. Because a large number of contributing centres from different countries and all levels of care generated the presented data, the results of HD18 should be widely applicable in countries with access to ^{18}FDG-PET for response assessment.

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See Online for appendix

steering committee and approved by the ethics committees of all participating centres.

We recruited patients aged 18–60 years with newly diagnosed, histology-proven, classical or nodular lymphocyte-predominant Hodgkin's lymphoma in advanced stages (that is, clinical stage III–IV or stage II with B symptoms and one or both risk factors of large mediastinal mass [≥ a third of the maximal thoracic diameter] or extranodal lesions). Histology samples taken by the primary care pathologist at diagnosis were reassessed by at least one of a panel of six lymphoma expert pathologists. Other inclusion criteria were an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2, HIV negativity, and freedom from concurrent disease that would preclude treatment according to protocol (appendix p 1). All patients provided written informed consent before study entry according to the Good Clinical Practice guidelines of the International Conference on Harmonisation and national regulations.

Randomisation and masking

Patients were registered at the GHSG central office by telephone and baseline documentation was required to be sent in by fax before start of treatment. A restaging including contrast-enhanced CT and PET scan was done after two cycles of eBEACOPP. After central review of PET-2, patients were assigned (1:1) to one of two parallel treatment groups on the basis of their PET-2 result: patients with positive PET-2 were randomly assigned to receive six additional cycles of either eBEACOPP (8×eBEACOPP in total) or eBEACOPP combined with rituximab (8×R-eBEACOPP). Patients with negative PET-2 were randomly assigned to receive either six additional cycles of eBEACOPP (8×eBEACOPP in total) or two additional cycles (4×eBEACOPP). Patients with progressive disease were taken off protocol. In all four groups, radiotherapy was recommended for lesions of at least 2·5 cm in the largest diameter with residual ^{18}F-FDG uptake after chemotherapy. Based on the results of our HD15 trial,[1] a protocol amendment in June, 2011, introduced a reduction of standard therapy from eight to six cycles of eBEACOPP in total. Because the required sample size for the treatment group comparison in the PET-2-positive cohort had already been reached, randomisation between eBEACOPP and R-eBEACOPP after positive PET-2 was stopped at this point, and all patients with positive PET-2 were subsequently assigned to receive the new standard treatment of 6×eBEACOPP. The standard treatment for patients with negative PET-2 was also adjusted, and randomisation of those patients between standard (6×eBEACOPP) and experimental (4×eBEACOPP) treatment continued.

Randomisation was done centrally using the minimisation method including a random component, stratified according to centre, age (<45 *vs* ≥45 years), stage (IIB–IIIA *vs* IIIB–IV), international prognostic score (0–2 *vs* 3–7), and sex. Patients and investigators were not masked to treatment allocation.

Procedures

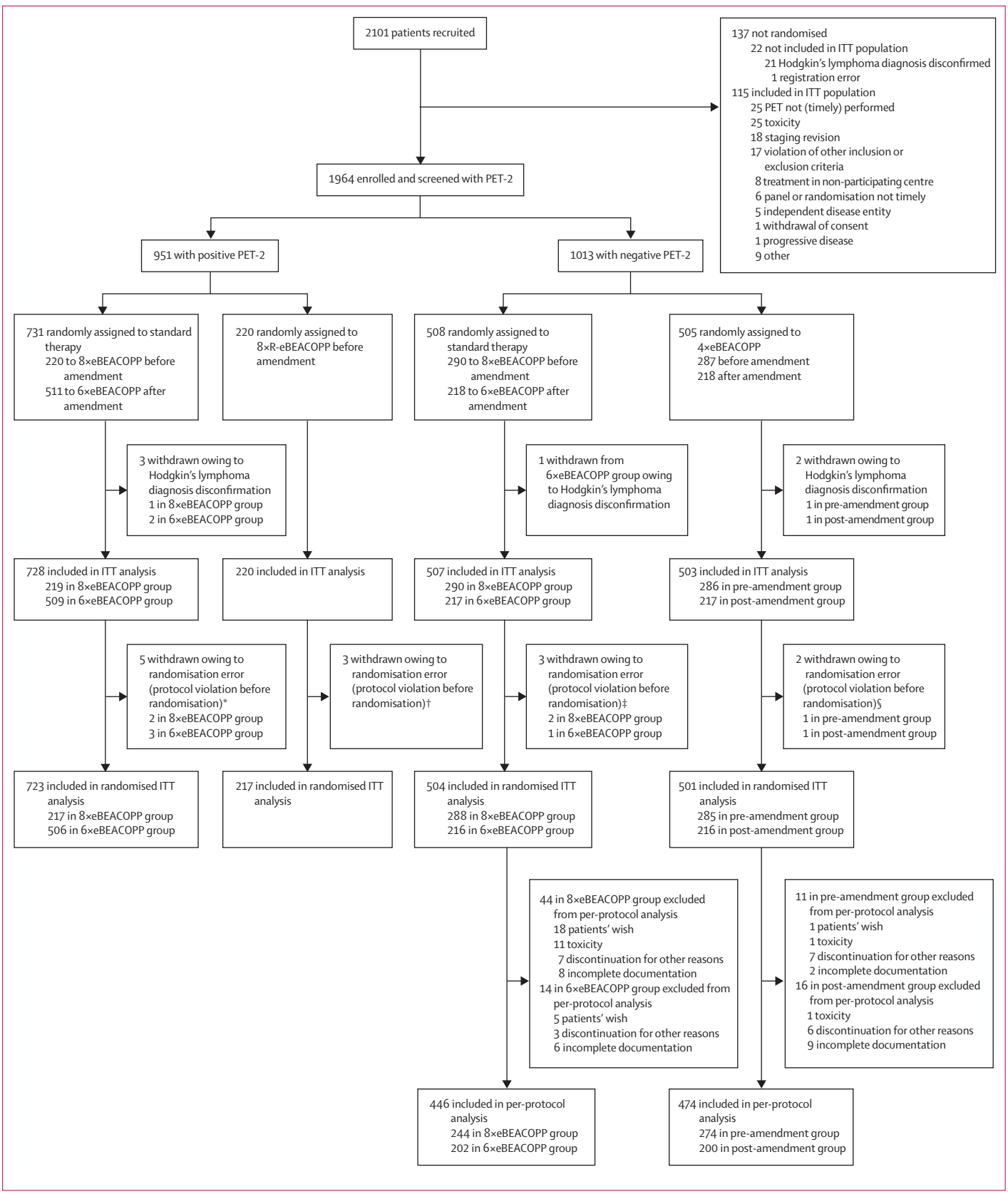
Procedures are described in detail in the appendix (pp 1,2). eBEACOPP including mandatory granulocyte colony-stimulating factor was given as previously described.[1] In the R-eBEACOPP group, rituximab was given intravenously at a dose of 375 mg/m² (maximum total dose 700 mg).[14] Blood counts were monitored at least twice weekly, and additional liver and kidney function tests were required once per cycle in all groups.

CT-based response assessments were done after the second and last cycle of chemotherapy, and after radiotherapy if applicable. PET-2, scheduled between day 17 and day 21 of the second cycle of eBEACOPP, was assessed with ^{18}F-FDG uptake higher than the mediastinal blood pool—ie, Deauville score 3—as cutoff for PET positivity. A multidisciplinary panel of experts, which included some of the authors (CK, HE, CB, MF, GK, and MD), from medical oncology, nuclear medicine, radiation oncology, and radiology, who were masked to local findings, centrally reviewed PET-2 and CT scans as well as x-rays and clinical information. After the end of chemotherapy (ie, after the assigned cycles of eBEACOPP), ^{18}F-FDG-PET including central expert review was repeated in case of CT-based partial response including residual nodal lesions of at least 2·5 cm. In case of positivity at this point, consolidating radiotherapy with a total dose of 30 Gy was recommended.

Outcomes

The primary efficacy endpoint was progression-free survival, defined as the time from completion of staging until progression, relapse, or death from any cause. If none of these events had occurred, progression-free survival was censored at the date of last information on the disease status. Secondary endpoints were overall survival (defined as time from completion of staging until death from any cause, or censored at the date of last information

Figure 1: **Trial profile**
ITT is defined as the set of all patients except for those with disconfirmed diagnosis of Hodgkin's lymphoma, registration errors, or withdrawal of trial consent including anonymisation of all study documents. Randomised ITT contains all ITT patients randomised according to protocol. Per protocol contains all randomised ITT patients without severe protocol deviation, having complete therapy documentation or progressive disease or death during therapy. PET-2=PET after two cycles of chemotherapy. ITT=intention-to-treat. eBEACOPP=bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, prednisone, and procarbazine in escalated dose. R-eBEACOPP=eBEACOPP with rituximab. *One had toxicity and one received treatment in non-participating centre in the 8×eBEACOPP group. One had staging revision, one received treatment in non-participating centre, and one had protocol violation categorised as other in the 6×eBEACOPP group. †One had toxicity and two had protocol violation categorised as other. ‡One received treatment in non-participating centre and one had protocol violation categorised as other in the 8×eBEACOPP group. One received treatment in non-participating centre in the 6×eBEACOPP group. §One had staging revision in the pre-amendment group and one received treatment in non-participating centre in the post-amendment group.


2101 patients recruited
137 not randomised
22 not included in ITT population
21 Hodgkin's lymphoma diagnosis disconfirmed
1 registration error
115 included in ITT population
25 PET not (timely) performed
25 toxicity
18 staging revision
17 violation of other inclusion or exclusion criteria
8 treatment in non-participating centre
6 panel or randomisation not timely
5 independent disease entity
1 withdrawal of consent
1 progressive disease
9 other
1964 enrolled and screened with PET-2
951 with positive PET-2
1013 with negative PET-2
731 randomly assigned to standard therapy
220 to 8×eBEACOPP before amendment
511 to 6×eBEACOPP after amendment
220 randomly assigned to 8×R-eBEACOPP before amendment
508 randomly assigned to standard therapy
290 to 8×eBEACOPP before amendment
218 to 6×eBEACOPP after amendment
505 randomly assigned to 4×eBEACOPP
287 before amendment
218 after amendment
3 withdrawn owing to Hodgkin's lymphoma diagnosis disconfirmation
1 in 8×eBEACOPP group
2 in 6×eBEACOPP group
1 withdrawn from 6×eBEACOPP group owing to Hodgkin's lymphoma diagnosis disconfirmation
2 withdrawn owing to Hodgkin's lymphoma diagnosis disconfirmation
1 in pre-amendment group
1 in post-amendment group
728 included in ITT analysis
219 in 8×eBEACOPP group
509 in 6×eBEACOPP group
220 included in ITT analysis
507 included in ITT analysis
290 in 8×eBEACOPP group
217 in 6×eBEACOPP group
503 included in ITT analysis
286 in pre-amendment group
217 in post-amendment group
5 withdrawn owing to randomisation error (protocol violation before randomisation)*
2 in 8×eBEACOPP group
3 in 6×eBEACOPP group
3 withdrawn owing to randomisation error (protocol violation before randomisation)†
3 withdrawn owing to randomisation error (protocol violation before randomisation)‡
2 in 8×eBEACOPP group
1 in 6×eBEACOPP group
2 withdrawn owing to randomisation error (protocol violation before randomisation)§
1 in pre-amendment group
1 in post-amendment group
723 included in randomised ITT analysis
217 in 8×eBEACOPP group
506 in 6×eBEACOPP group
217 included in randomised ITT analysis
504 included in randomised ITT analysis
288 in 8×eBEACOPP group
216 in 6×eBEACOPP group
501 included in randomised ITT analysis
285 in pre-amendment group
216 in post-amendment group
44 in 8×eBEACOPP group excluded from per-protocol analysis
18 patients' wish
11 toxicity
7 discontinuation for other reasons
8 incomplete documentation
14 in 6×eBEACOPP group excluded from per-protocol analysis
5 patients' wish
3 discontinuation for other reasons
6 incomplete documentation
11 in pre-amendment group excluded from per-protocol analysis
1 patients' wish
1 toxicity
7 discontinuation for other reasons
2 incomplete documentation
16 in post-amendment group excluded from per-protocol analysis
1 toxicity
6 discontinuation for other reasons
9 incomplete documentation
446 included in per-protocol analysis
244 in 8×eBEACOPP group
202 in 6×eBEACOPP group
474 included in per-protocol analysis
274 in pre-amendment group
200 in post-amendment group

on the patient being alive), occurrence of second malignancies, proportion of patients achieving complete response, occurrence of Hodgkin's lymphoma-specific death, and treatment-related toxicities of Common Terminology Criteria for Adverse Events (CTCAE) grades 3 and 4. Further secondary endpoints were late toxicity and quality of life, the results of which will be published separately when longer follow-up is available. To provide a summary measure for severe toxicities, we defined treatment-related morbidity as any organ toxicity of CTCAE grade 3 or 4 or anaemia, thrombocytopenia, or infection of grade 4.

Statistical analysis

The primary objective of the study in patients with positive PET-2 was to show superiority of the combined immuno-chemotherapy R-eBEACOPP compared with standard eBEACOPP. The trial was designed to detect an improvement of at least 15% in 5-year progression-free survival with a power of 80% and a two-sided significance level of 5%. We only included patients with positive PET-2 randomised before the implementation of the protocol amendment in 2011 in the comparison. First results of this study question have been published.[14] This paper provides updated results including longer follow-up and a descriptive analysis of those patients receiving the new standard treatment after the amendment had come into effect.

The primary objective of the study in patients with negative PET-2 was to show non-inferiority of treatment with a reduced number of cycles compared with standard treatment in terms of progression-free survival. We defined clinically relevant inferiority as an absolute difference of 6% or more in the 5-year progression-free survival estimates. Non-inferiority of the less intensive treatment would be established if the lower limit of the two-sided 95% CI for the difference in the 5-year progression-free survival estimates was above –6%. Assuming progression-free survival of 88% after 5 years with standard therapy, the test on non-inferiority could be done with 80% power after 5 years of follow-up, if 870 patients with negative PET-2 would be evaluable in the per-protocol analysis. To this end, a total of 2100 patients were to be included in the trial. Statistical monitoring revealed that the desired power could already be reached, and on Oct 26, 2016, the independent data and safety monitoring committee recommended performing and publishing the final analysis of the study.

The analysis of patients with negative PET-2 was affected by the 2011 amendment, by which standard treatment was reduced from 8×eBEACOPP to 6×eBEACOPP. Primarily, the groups receiving 8×eBEACOPP and 6×eBEACOPP were pooled and compared with the total group of patients assigned to 4×eBEACOPP. To assess whether the conclusions of this study would also hold true with the updated standard treatment of six cycles, the main analyses were repeated descriptively within the subgroup of patients randomly assigned after the amendment had come into effect. For analyses not dependent on follow-up (eg, therapy adherence and acute treatment-related toxicity), we compared the outcomes following 8×eBEACOPP (standard therapy up to amendment), 6×eBEACOPP (standard therapy after amendment), and 4×eBEACOPP (experimental treatment) directly.

We compared time-to-event endpoints using the Kaplan-Meier method, including hazard ratios (HRs) and 95% CIs obtained from Cox regression models. Cumulative incidences of second malignancies were estimated according to Kaplan-Meier accounting for death as a competing risk, and compared between treatment groups using subdistribution hazard ratios (sHRs) and 95% CIs obtained from Cox regression models. Other secondary endpoints were analysed by means of descriptive statistics, with p values resulting from Fisher's exact test where applicable. In patients with negative PET-2, progression-free survival and overall

	PET-2-positive cohort			PET-2-negative cohort	
	8×eBEACOPP (n=217)	6×eBEACOPP (n=506)	8×R-eBEACOPP (n=217)	6×eBEACOPP or 8×eBEACOPP (n=504)	4×eBEACOPP (n=501)
Time of recruitment (range)	May, 2008, to May, 2011	May, 2011, to July, 2014	Dec, 2008, to May, 2011	May, 2008, to July, 2014	May, 2008, to July, 2014
Age (years)*					
Median (IQR)	30 (23–40)	31 (24–42)	29 (23–41)	32 (24–44)	33 (25–44)
18–19	18 (8%)	30 (6%)	21 (10%)	34 (7%)	44 (9%)
20–29	84 (39%)	195 (39%)	91 (42%)	186 (37%)	166 (33%)
30–39	59 (27%)	142 (28%)	45 (21%)	104 (21%)	122 (24%)
40–49	41 (19%)	84 (17%)	42 (19%)	91 (18%)	89 (18%)
50–60	15 (7%)	55 (11%)	18 (8%)	89 (18%)	80 (16%)
Sex					
Female	88 (41%)	211 (42%)	86 (40%)	188 (37%)	188 (38%)
Male	129 (59%)	295 (58%)	131 (60%)	316 (63%)	313 (62%)

(Table 1 continues on next page)

	PET-2-positive cohort			PET-2-negative cohort	
	8×eBEACOPP (n=217)	6×eBEACOPP (n=506)	8×R-eBEACOPP (n=217)	6×eBEACOPP or 8×eBEACOPP (n=504)	4×eBEACOPP (n=501)
(Continued from previous page)					
Ann Arbor stage					
IIA	0	0	1 (<1%)	0	0
IIB	49 (23%)	96 (19%)	54 (25%)	40 (8%)	42 (8%)
IIIA	41 (19%)	93 (18%)	29 (13%)	156 (31%)	156 (31%)
IIIB	58 (27%)	118 (23%)	51 (24%)	131 (26%)	122 (24%)
IVA	20 (9%)	63 (12%)	26 (12%)	59 (12%)	60 (12%)
IVB	49 (23%)	136 (27%)	56 (26%)	118 (23%)	121 (24%)
GHSG risk factors					
Large mediastinal mass†	95 (44%)	199/505 (39%)	100 (46%)	79 (16%)	88 (18%)
Extranodal involvement	66 (30%)	124 (25%)	49 (23%)	80 (16%)	60 (12%)
Involvement of three or more nodal areas	182 (84%)	429 (85%)	170 (78%)	457 (91%)	442 (88%)
Elevated erythrocyte sedimentation rate	152 (70%)	345/505 (68%)	159 (73%)	297/502 (59%)	286 (57%)
ECOG performance status					
0	110 (51%)	302 (60%)	106 (49%)	319 (63%)	314 (63%)
1	101 (47%)	185 (37%)	104 (48%)	174 (35%)	181 (36%)
2	6 (3%)	19 (4%)	7 (3%)	11 (2%)	6 (1%)
International prognostic score factors‡					
Albumin <4 g/dL	136/216 (63%)	314 (62%)	137/215 (64%)	252/502 (50%)	248/499 (50%)
Haemoglobin <10·5 g/dL	48/216 (22%)	107 (21%)	46/215 (21%)	73/502 (15%)	70/499 (14%)
Leucocytes ≥15 000/mm³	54/216 (25%)	134 (26%)	54/215 (25%)	92/502 (18%)	76/499 (15%)
Male sex	128/216 (59%)	295 (58%)	129/215 (60%)	314/502 (63%)	312/499 (63%)
Age ≥45 years	31/216 (14%)	102 (20%)	30/215 (14%)	122/502 (24%)	123/499 (25%)
Clinical stage IV	69/216 (32%)	199 (39%)	81/215 (38%)	177/502 (35%)	180/499 (36%)
Lymphocytes <600/mm³ or <8% of white blood cells	20/216 (9%)	52 (10%)	22/215 (10%)	20/502 (4%)	30/499 (6%)
International prognostic score					
0–1	58/216 (27%)	129 (25%)	62/215 (29%)	176/502 (35%)	174/499 (35%)
2–3	131/216 (61%)	284 (56%)	108/215 (50%)	255/502 (51%)	257/499 (52%)
4–7	27/216 (13%)	93 (18%)	45/215 (21%)	71/502 (14%)	68/499 (14%)
Histologic subtype					
Classical Hodgkin's lymphoma	182/186 (98%)	201/209 (96%)	172/184 (93%)	309/332 (93%)	315/333 (95%)
Nodular sclerosis	119/186 (64%)	123/209 (59%)	105/184 (57%)	189/332 (57%)	175/333 (53%)
Mixed cellularity	23/186 (12%)	34/209 (16%)	29/184 (16%)	65/332 (20%)	74/333 (22%)
Lymphocyte-rich	1/186 (1%)	6/209 (3%)	4/184 (2%)	14/332 (4%)	14/333 (4%)
Lymphocyte-depleted	1/186 (1%)	0/209	3/184 (2%)	1/332 (<1%)	1/333 (<1%)
Not further specified	38/186 (20%)	38/209 (18%)	31/184 (17%)	40/332 (12%)	51/333 (15%)
Nodular lymphocyte predominant Hodgkin's lymphoma	4/186 (2%)	8/209 (4%)	12/184 (7%)	23/332 (7%)	18/333 (5%)

Data are n (%), unless otherwise indicated. PET-2=PET after two cycles of chemotherapy. eBEACOPP=bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone in escalated dose. R-eBEACOPP=eBEACOPP with rituximab. GHSG=German Hodgkin Study Group. ECOG=Eastern Cooperative Oncology Group. *Age range was 18–60 years for all groups. †The mediastinal mass is considered as large if it measures at least a third of the transverse diameter of the thorax. ‡Only for patients with complete data for score determination.

Table 1: **Baseline characteristics of the randomised intention-to-treat set**

survival were primarily analysed in the per-protocol set, excluding all patients with severe protocol deviations, because this was considered the more conservative analysis for non-inferiority objectives in the trial protocol. Sensitivity analyses were done according to the intention-to-treat (ITT) principle, excluding only patients whose diagnosis of Hodgkin's lymphoma was disconfirmed by the pathology panel, those with registration errors, and those who withdrew their consent to participate in the trial. All other analyses were done according to ITT. We did post-hoc subgroup analyses in patients with clinical stages III and IV only and in patients with positive PET-2

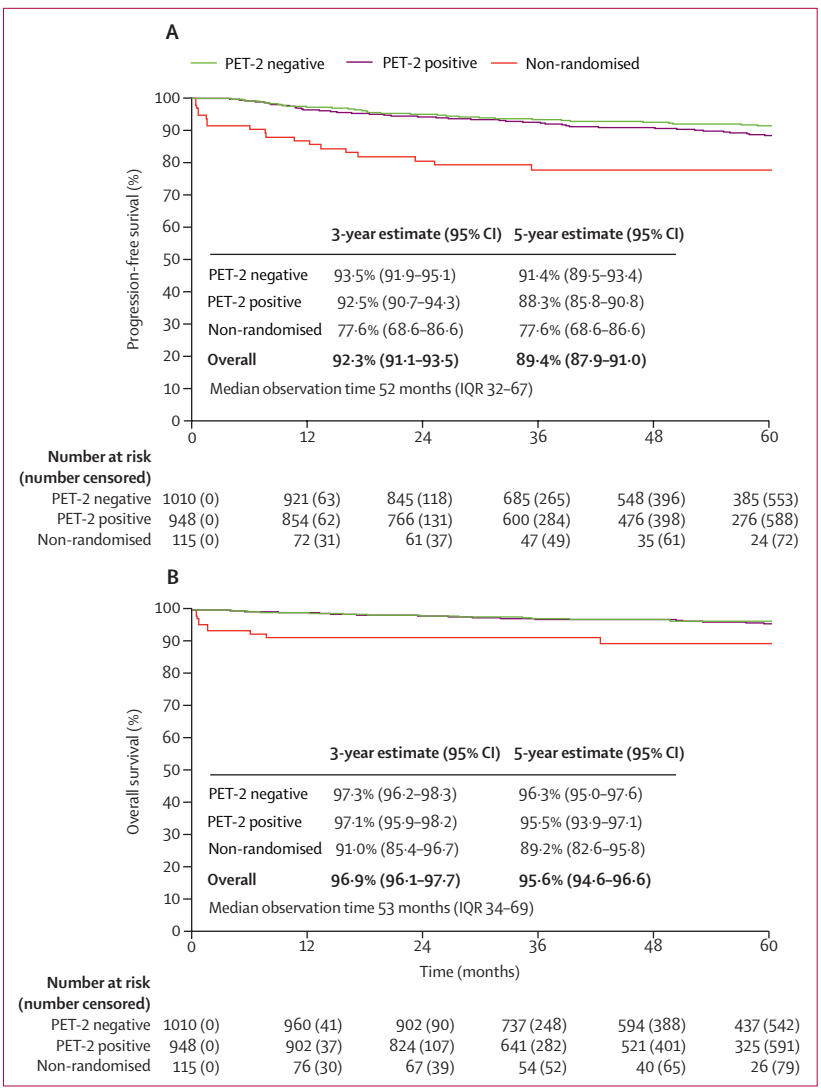


Figure 2: **Progression-free survival and overall survival for ITT set**
Kaplan-Meier estimates of (A) progression-free survival and (B) overall survival in the ITT set. ITT is defined as the set of all patients except for those with disconfirmed diagnosis of Hodgkin's lymphoma, registration errors, or withdrawal of trial consent including anonymisation of all study documents, and so includes non-randomised patients. ITT=intention-to-treat. PET-2=PET after two cycles of chemotherapy.

receiving 6×eBEACOPP analysed according to Deauville score. We used SAS version 9.4 for all analyses. This trial was registered with ClinicalTrials.gov, number NCT00515554.

Role of the funding source

The Deutsche Krebshilfe reviewed the trial protocol for adherence to good clinical practice. Roche Pharma AG provided the study drug rituximab and financial support. The funders had no role in study design, data collection, data analysis, data interpretation, or writing of the report. All authors had full access to all the data and the corresponding author had final responsibility for the decision to submit for publication.

Results

Between May 14, 2008, and July 18, 2014, we enrolled 2101 patients, of whom 137 were not randomised (figure 1). Another 19 patients were excluded from the randomised comparisons owing to ineligibility for randomisation that had not been detected earlier (figure 1). 1945 patients were randomised according to protocol and comprise the randomised ITT set. Of these, 434 patients with positive PET-2 were randomly assigned to either 8×eBEACOPP (n=217) or 8×R-eBEACOPP (n=217), and another 506 were assigned to standard treatment with 6×eBEACOPP after June, 2011. 1005 patients with negative PET-2 were randomly assigned to either standard treatment with 8×eBEACOPP (n=288) or 4×eBEACOPP (n=285) before June, 2011, and standard treatment with 6×eBEACOPP (n=216) or 4×eBEACOPP (n=216) after June, 2011. In the subgroup with negative PET-2, the per-protocol set comprises 920 (92%) patients (figure 1).

Patient characteristics for the randomised ITT set were similar between randomised treatment groups (table 1). The median age was 32 years (range 18–60, IQR 24–43); 1184 patients (61%) were male and 761 (39%) were female. Most patients had stage III or IV disease (n=1663, 86%).

Following central expert review, PET-2 was rated positive in 940 (48%) patients from the randomised ITT set, comprising the 434 patients randomised before June, 2011, and the 506 patients treated with 6×eBEACOPP afterwards. The rating of our central expert panel corresponded with the local assessment in 1541 (80%) of 1936 patients with the respective information available. Concordance was higher among those patients with PET-2 finally declared as negative (897 [90%] of 1000 patients [information missing in five] *vs* 644 [69%] of 936 patients with positive PET-2 [information missing in four]). Patients with positive and negative PET-2 differed in many baseline characteristics including age, performance status, and clinical risk factors (appendix p 4).

In the ITT set, the total 5-year estimate of progression free survival was 89·4% (95% CI 87·9–91·0) and the total 5-year estimate of overall survival was 95·6% (94·6–96·6). There were no significant differences between patients with positive and negative PET-2 regarding progression-free survival (p=0·30) and overall survival (p=0·49; figure 2).

For the PET-2-positive cohort, detailed results on therapy administration and side-effects have already been reported.[14] After completion of chemotherapy, 155 patients (36%) had PET-positive residual disease and received radiotherapy (table 2). With a median follow-up of 66 months (IQR 53–76), estimated 5-year progression-free survival in the randomised comparison was 89·7% (95% CI 85·4–94·0) with 8×eBEACOPP and 88·1% (83·5–92·7) with 8×R-eBEACOPP (log-rank p=0·46; figure 3). Nine patients (4%) in the 8×eBEACOPP group and 14 (6%) in the 8×R-eBEACOPP group had died during the follow-up period (table 2); estimated 5-year overall

	PET-2-positive cohort		PET-2-negative cohort	
	8×eBEACOPP (n=217)	8×R-eBEACOPP (n=217)	8×eBEACOPP or 6×eBEACOPP (n=504)	4×eBEACOPP (n=501)
Observation time (months)				
For disease status	68 (54–77)	65 (52–73)	53 (35–69)	54 (33–69)
For survival status	69 (57–77)	66 (54–77)	56 (36–71)	57 (36–72)
Status after chemotherapy				
Central PET review after chemotherapy	167 (77%)	163 (75%)	162 (32%)	154 (31%)
Radiotherapy recommended	76 (35%)	91 (42%)	17 (3%)	14 (3%)
Radiotherapy documented	72 (33%)	83 (38%)	16 (3%)	17 (3%)
Tumour events				
Progression	1 (<1%)	4 (2%)	1 (<1%)	3 (1%)
Early relapse (within 1 year after end of treatment)	6 (3%)	5 (2%)	7 (1%)	12 (2%)
Late relapse	7 (3%)	8 (4%)	17 (3%)	20 (4%)
Any tumour event	14 (6%)	17 (8%)	25 (5%)	35 (7%)
Causes of death				
Hodgkin's lymphoma	1 (<1%)	1 (<1%)	3 (1%)	4 (1%)
Toxicity of study treatment	1 (<1%)	3 (1%)	6 (1%)	0
Toxicity of salvage therapy	3 (1%)	4 (2%)	2 (<1%)	2 (<1%)
Second malignancy	2 (1%)	2 (1%)	11 (2%)	1 (<1%)
Other disease*	2 (1%)	2 (1%)	1 (<1%)	1 (<1%)
Accident or suicide	0	2 (1%)	0	1 (<1%)
Unclear	0	0	2 (<1%)	0
Any event	9 (4%)	14 (6%)	25 (5%)	9 (2%)
Second malignancies				
Acute myeloid leukaemia or myelodysplastic syndrome	5 (2%)	4 (2%)	8 (2%)	2 (<1%)
Non-Hodgkin's lymphoma	3 (1%)	2 (1%)	5 (1%)	8 (2%)
Solid tumour	2 (1%)	8 (4%)	5 (1%)	3 (1%)
Any event	10 (5%)	8 (4%)	18 (4%)	13 (3%)
5-year cumulative incidence estimate†	4·0% (1·3–6·7)	3·5% (0·7–6·3)	3·8% (1·9–5·7)	3·3% (1·4–5·3)

Data are median (IQR), n (%), or % (95% CI). PET-2=PET after two cycles of chemotherapy. eBEACOPP=bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone in escalated dose. R-eBEACOPP=eBEACOPP with rituximab.*Including non-therapy-related infection (n=3), pulmonary disease (n=1), and gastrointestinal disease (n=1). †Accounting for death as competing risk.

Table 2: **Outcomes of the randomised intention-to-treat set (patients with positive PET-2 recruited before June, 2011, and all patients with negative PET-2)**

survival was 96·4% (93·8–99·0) with 8×eBEACOPP and 93·9% (90·6–97·3) with 8×R-eBEACOPP (log-rank p=0·25; figure 3). No difference was found between groups in 5-year cumulative incidences of second malignancies (p=0·73; table 2). Patients receiving standard treatment with 6×eBEACOPP after June, 2011, had 3-year progression-free survival of 92·0% (89·3–94·6; median follow-up 36 months [IQR 28–51]) and 3-year overall survival of 98·0% (96·7–99·3; median follow-up 37 months [29–52]; appendix p 6).

Among patients with negative PET-2, severe protocol deviations were more frequent in the 8×eBEACOPP group compared with the 6×eBEACOPP and 4×eBEACOPP groups (table 3). The mean total relative chemotherapy dose was 86% (SD 15) in the 8×eBEACOPP, 93% (10) in the 6×eBEACOPP, and 97% (SD 6) in the 4×eBEACOPP group. In accordance with this finding, dose reductions were more frequent in later cycles of therapy and they were mostly reductions of vincristine, etoposide, and cyclophosphamide (appendix p 9).

Most patients in each treatment group had at least one adverse event (table 3). A decrease of treatment cycles led to a decrease of severe infections (p=0·0005), organ toxicities (p<0·0001), and treatment-related morbidity (p<0·0001; table 3).

After completion of chemotherapy in the PET-2-negative cohort, a change to a positive PET scan led to a recommendation of consolidating radiotherapy in 31 patients (3%) with no difference between treatment groups (table 2).

In the PET-2-negative cohort, 5-year cumulative incidences of second malignancies did not differ between the 8×eBEACOPP or 6×eBEACOPP group and the 4×eBEACOPP group (p=0·37; table 2). At a median follow-up of 56 months (IQR 36–72), 25 patients (5%) in the 8×eBEACOPP or 6×eBEACOPP group and nine (2%) in the 4×eBEACOPP had died (table 2). Five of the six fatal treatment-related toxic events in the 8×eBEACOPP or 6×eBEACOPP group were infections, occurring after five (n=2), six (n=2), and eight (n=1) cycles. The most

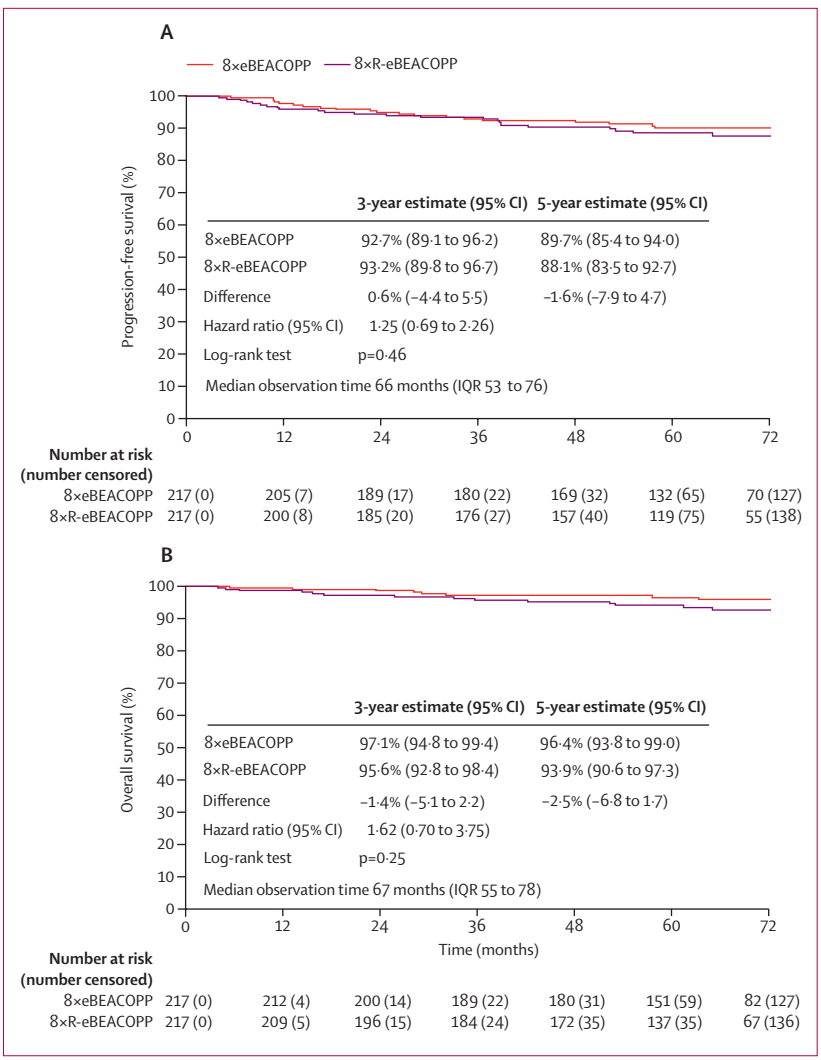


Figure 3: **Progression-free survival and overall survival for patients with positive PET-2**
Kaplan-Meier estimates of (A) progression-free survival and (B) overall survival for patients with positive PET-2, in the randomised intention-to-treat set. PET-2=PET after two cycles of chemotherapy. eBEACOPP=bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, prednisone, and procarbazine in escalated dose. R-eBEACOPP=eBEACOPP with rituximab.

frequent cause of death was second malignancy, including deaths from acute myeloid leukaemia (n=5), non-Hodgkin's lymphoma (n=3), and solid tumours (n=3) in the 8×eBEACOPP or 6×eBEACOPP group, and only one death occurring from acute myeloid leukaemia in the 4×eBEACOPP group.

Progression-free survival at 5 years was 90·8% (95% CI 87·9–93·7) in the 8×eBEACOPP or 6×eBEACOPP group and 92·2% (89·4–95·0) in the 4×eBEACOPP group (figure 4; per-protocol analysis). The 95% CI for the 5-year difference ranged from −2·7% to 5·4% and excluded the predefined non-inferiority margin of −6% (figure 4). Overall survival at 5 years was 95·4% (93·4–97·4) in the 8× eBEACOPP or 6×eBEACOPP group and 97·7% (96·2–99·3) in the 4×eBEACOPP group, and indicated a significant advantage of the shorter treatment regimen (figure 4). Results for the randomised ITT set were similar (appendix p 10).

In the subgroup of patients randomised after standard treatment had been changed from eight to six cycles in 2011, progression-free survival at 3 years was 91·8% (95% CI 87·8 to 95·8) in the 6×eBEACOPP group and 94·6% (91·3 to 97·9) in the 4×eBEACOPP group (difference 2·8%, 95% CI −2·4 to 7·9). Overall survival at 3 years was 97·5% (95·2 to 99·7) in the 6×eBEACOPP group and 98·8% (97·2 to 100·0) in the 4×eBEACOPP group (p=0·53; appendix p 8).

Results of post-hoc analyses in 1777 patients with clinical stage III or IV correspond well with the overall results (appendix pp 11–14). The 5-year estimates for the entire subgroup were 89·0% (95% CI 87·3–90·7) for progression-free survival and 95·4% (94·3–96·6) for overall survival.

In a further post-hoc analysis of PET-2-positive patients receiving standard treatment with 6×eBEACOPP after June, 2011, those with Deauville score 3 after two cycles of eBEACOPP had particularly good outcomes, whereas for those with Deauville score 4, progression-free survival and overall survival were inferior, but still on a high level (3-year progression-free survival 95·9% [95% CI 93·2–98·6] *vs* 87·6% [83·0–92·3], log-rank p=0·0007; 3-year overall survival 99·0% [97·6–100·0] *vs* 96·8% [94·5–99·1], log-rank p=0·011; appendix p 7).

Discussion

Two major findings have emerged from the GHSG HD18 trial for patients with newly diagnosed advanced-stage Hodgkin's lymphoma. First, a negative PET scan after initial therapy with two cycles of eBEACOPP allows a reduction of treatment cycles from eight to four without a negative effect on progression-free survival. The reduction is associated with markedly improved tolerability and thereby a significantly improved overall survival. Second, a positive PET scan after two cycles of eBEACOPP does not imply the need for intensification of chemotherapy, as reflected by the excellent progression-free survival of patients with positive PET-2 regardless of treatment group. This finding questions the described prognostic effect of PET-2 positivity in the present context.[12,15–17]

Our results must be put into perspective with the recently published RATHL study evaluating a PET-2-guided strategy with upfront ABVD.[15] Our trial and RATHL used different inclusion criteria (age 18–60 years *vs* >18 years), different definitions of advanced-stage disease—ie, RATHL included more patients with less advanced disease than did our study—(282 [14%] patients with Ann Arbor stage II of 1945 patients *vs* 500 [42%] of 1203), and different interpretation of Deauville score 3 (positive *vs* negative). However, distribution of the International Prognostic Score in both trials was comparable, implying a certain similarity in the patient cohorts. In patients with negative PET-2, four cycles of

eBEACOPP used in HD18 resulted in progression-free survival of 95·3% at 3 years, whereas it was only 84·4% with two cycles of ABVD followed by 4 cycles of ABVD or AVD (ABVD omitting bleomycin) in the RATHL trial. Thus, the negative predictive value of PET seems to be higher after initial treatment with two cycles of eBEACOPP than after two cycles of ABVD. This observation is in accordance with the insufficient negative predictive value of PET-2 in an Italian trial[18] of ABVD-treated patients.

Compared with our previous and current standards of eight and six cycles of eBEACOPP, respectively, the excellent outcome for patients with negative PET-2 could now be achieved with a significantly decreased incidence of severe adverse events. Particularly, severe infections were observed less frequently with four cycles of eBEACOPP—occurring in the same range as that reported with PET-2-guided ABVD or AVD.[15] In our trial, only two (<1%) of 501 patients developed second acute myeloid leukaemia, and we did not observe a single case of treatment-related mortality in patients randomly assigned to treatment with four cycles. Regarding potentially life-threatening adverse events, we found no disadvantage of four cycles of eBEACOPP over PET-2-guided ABVD in this indirect comparison. Of note, the superior progression-free survival in HD18 could be achieved within a much shorter treatment duration of only 12 weeks compared with 24 weeks with six cycles of ABVD or AVD in the RATHL trial. However, eBEACOPP remains an intensive treatment, inducing neutropenic fever in about 20% and the need for platelet transfusions in about 25% of all patients. Thus, although the reduced-intensity treatment is safe, it still needs specialised care and relevant resources from the medical infrastructure.

The outcome differences between ABVD or eBEACOPP applied upfront are even more pronounced in the PET-2-positive cohort. In the RATHL trial, treatment was escalated from ABVD to BEACOPP after a positive PET-2 and 3-year progression-free survival reached 67·5%.[15] This result is clearly inferior to the 3-year progression-free survival of 88% observed with six cycles of eBEACOPP among patients with Deauville score 4 in our trial. Because patients in both studies received eBEACOPP from the third cycle onwards, the observed difference could most likely be explained by the initial treatment with two cycles of either ABVD or eBEACOPP. Therefore, patients with insufficient response to ABVD seem to be unable to reach adequate outcomes with subsequent eBEACOPP therapy. In accordance with this observation, even escalation to high-dose chemotherapy with autologous stem cell support was not able to improve the outcome over standard ABVD for patients with positive PET-2 after initial treatment with ABVD.[2,16] Thus, initiation of therapy with two cycles of eBEACOPP appears to be mandatory to achieve optimal progression-free survival in advanced-stage Hodgkin's lymphoma.

After we completed enrolment of patients with positive PET-2 into the randomised part of the HD18 study, the

	8 × eBEACOPP (n=288)	6 × eBEACOPP (n=216)	4 × eBEACOPP (n=501)
Severe protocol deviations			
Discontinuation due to toxicity	11 (4%)	0	2 (<1%)
Patient withdraws from chemotherapy	18 (6%)	4 (2%)	1 (<1%)
Administration of more than target number of chemotherapy cycles	0	0	6 (1%)
Other or unknown*	7 (2%)	4 (2%)	7 (1%)
Any severe protocol deviation	36 (13%)	8 (4%)	16 (3%)
Toxicity and supportive measures†			
Haematological toxicities of CTCAE grade III or IV			
Anaemia	164 (57%)	110 (51%)	195 (39%)
Thrombopenia	212 (74%)	150 (70%)	286 (57%)
Leukopenia	268 (93%)	199 (93%)	438 (88%)
Anaemia, thrombopenia or leukopenia	274 (95%)	202 (94%)	447 (90%)
Infection	50 (17%)	25 (12%)	40 (8%)
Organ toxicities of CTCAE grade III or IV			
Nausea or vomiting	31 (11%)	18 (8%)	32 (6%)
Mucositis	26 (9%)	13 (6%)	28 (6%)
Gastrointestinal tract disorders	15 (5%)	14 (7%)	11 (2%)
Respiratory tract disorders	16 (6%)	4 (2%)	10 (2%)
Nervous system disorders	37 (13%)	15 (7%)	17 (3%)
Any organ toxicity‡	62 (22%)	29 (13%)	38 (8%)
Toxicities of CTCAE grade III or IV			
Any toxicity‡	280 (98%)	205 (95%)	455 (91%)
Treatment-related morbidity			
Any organ toxicity of CTCAE grade III or IV‡	62 (22%)	29 (13%)	38 (8%)
Anaemia, thrombopenia or infection of CTCAE grade IV	169 (59%)	115 (53%)	187 (38%)
Treatment-related morbidity	189 (66%)	132 (61%)	204 (41%)
Onset of treatment-related morbidity			
Cycles 1–4	135 (47%)	100 (47%)	204 (41%)
Cycles 5– 6	30 (10%)	32 (15%)	NA
Cycles 7–8	24 (8%)	NA	NA
Febrile neutropenia			
Occurrence of febrile neutropenia	96 (33%)	49 (23%)	109 (22%)
Hospitalisation due to febrile neutropenia	71 (25%)	39 (18%)	90 (18%)
Onset of febrile neutropenia			
Cycles 1–4	69 (24%)	39 (18%)	109 (22%)
Cycles 5–6	16 (6%)	10 (5%)	NA
Cycles 7–8	11 (4%)	NA	NA
Supportive measures			
Use of G-CSF	286 (100%)	212 (99%)	495 (99%)
Platelet infusions	132 (46%)	72 (33%)	122 (24%)
Red blood cell transfusions	203 (71%)	129 (60%)	233 (47%)

Data are n (%). PET-2=positron emission tomography after two cycles of chemotherapy. eBEACOPP=bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone in escalated dose. CTCAE=Common Terminology Criteria for Adverse Events. G-CSF=granulocyte-colony stimulating factor. NA=not applicable. *Including patient refusal to continue with radiotherapy (n=1), no radiotherapy in spite of panel recommendation (n=1), radiotherapy without panel recommendation (n=4), violation of inclusion or exclusion criteria (n=3), lack of compliance (n=3), withdrawal of consent (n=2), treatment in non-participating centre (n=1), restaging not timely performed (n=1), unknown (n=2). †Documentation of chemotherapy missing in five (<1%) of 1005 patients; toxicity and supportive measures assessed in 287 patients in the 8 × eBEACOPP group, 215 patients in the 6 × eBEACOPP group, and 498 patients in the 4 × eBEACOPP group. ‡Also including urogenital tract, cardiac and skin disorders, drug fever, and allergy.

Table 3: **Therapy adherence, acute toxicities and supportive measures during chemotherapy of patients with negative PET-2, randomised intention-to-treat set**

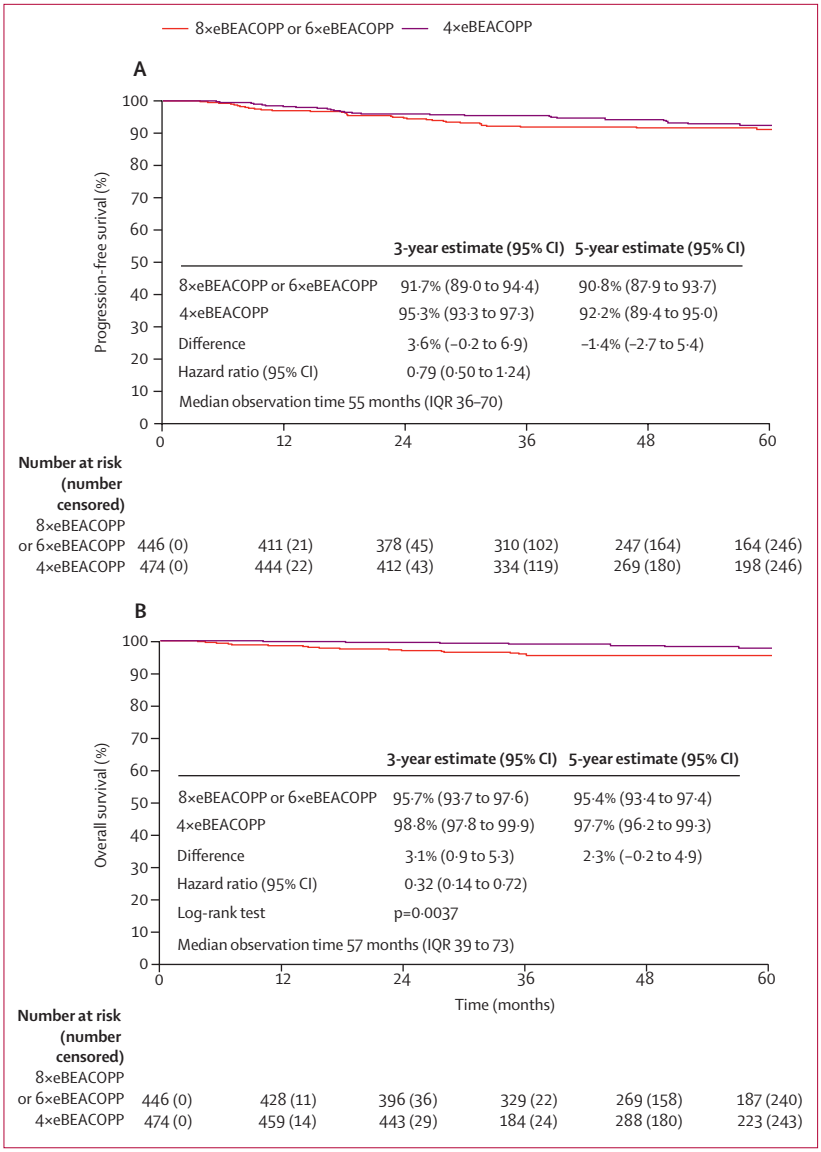


Figure 4: **Progression-free survival and overall survival for patients with negative PET-2**
Kaplan-Meier estimates of (A) progression-free survival and (B) overall survival for patients with negative PET-2, in the per-protocol set. PET-2=PET after two cycles of chemotherapy. eBEACOPP=bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, prednisone, and procarbazine in escalated dose.

standard of care was changed from eight to six cycles based on the results of our HD15 trial.[1] Subsequently, enrolled patients with positive PET-2 were treated with six cycles of eBEACOPP, resulting in similarly high tumour control but a more favourable safety profile compared with those treated with eight cycles. We can thus safely recommend using only six cycles of eBEACOPP for patients with positive PET-2.

Because factors that determine early response to therapy as measured by PET-2 are still unknown at baseline, the outcome of the overall treatment strategy should be discussed when informing patients about the different treatments. With PET-2-guided ABVD, 3-year progression-free survival is 83·7% among patients aged less than 60 years, and 79% for those with Ann Arbor stage III or IV disease.[15] In HD18, the corresponding numbers are 92·3% and 92·2%. This obvious advantage in progression-free survival when using eBEACOPP upfront is particularly relevant, not only because avoiding relapse and the subsequent necessity of further toxic treatments is the most important endpoint from the patients' perspective, but also because progression-free survival differences translate into overall survival differences over time in advanced-stage Hodgkin's lymphoma.[19-21]

Even with the reduced intensity for patients with negative PET-2, the burden of treatment remains relevant. New drugs with promising single-agent activity in relapsed or refractory Hodgkin's lymphoma might further improve the risk–benefit ratio in the treatment of advanced-stage Hodgkin's lymphoma.[22,23] We have modified the eBEACOPP regimen with the anti-CD30 antibody-drug conjugate brentuximab vedotin, resulting in a new regimen which was well tolerated in phase 2 and is being tested against standard eBEACOPP in a phase 3 trial (NCT02661503).[24] Another approach aims to improve the moderate efficacy of the ABVD regimen by adding brentuximab vedotin (NCT01712490).[25] A further step forwards would be if the survival outcomes reported in our trial can be reached by any of these new regimens with even less toxicity for patients with advanced-stage Hodgkin's lymphoma.

The following weaknesses of our analysis should be acknowledged. First, the definition of PET negativity was conservative and the PET-2-negative cohort was therefore relatively small, including only 1005 (52%) of all randomised patients. 10 years ago, when the HD18 study was planned, the GHSG deemed it unethical to put patients at risk for treatment failure with a less conservative approach. Today, a Deauville score of 3 is generally accepted as negative in advanced-stage Hodgkin's lymphoma, and, considering the excellent outcome of this subgroup when treated with six cycles, one could speculate that more patients could have received only four cycles of eBEACOPP without compromising the overall outcome.

Regarding the study in PET-2-negative patients, conclusions are affected by the change of standard treatment from eight to six cycles in the middle of the recruitment period, lessening the anticipated effect of the treatment de-escalation in the experimental arm. Although not yet finally conclusive owing to short follow-up, the experimental treatment compared favourably also with the updated standard, as reflected by similar progression-free survival and overall survival as well as markedly reduced toxicity. Thus, the study results remain important also when 6×eBEACOPP is regarded as the standard to be challenged.

Third, we could not yet evaluate all potential late effects. Among these events, infertility is of high relevance for patients with a wish for parenthood.[6,26] Additional studies

are underway to describe gonadal dysfunction in detail, and we recommend cooperation with centres for reproduction medicine and cryopreservation of sperm or oocytes before start of treatment. With respect to patient-reported outcomes, especially severe and persisting cancer-related fatigue is a relevant problem for about 25% of Hodgkin's lymphoma survivors and has a substantial effect on their social reintegration.[27] However, as treatment intensity is not correlated to the persistence of severe cancer-related fatigue in Hodgkin's lymphoma, we do not expect to see major differences between treatment groups in the present trial.[7]

Because we cannot estimate the representativeness of our study cohort from available data, we must acknowledge that patients at increased risk for severe side-effects might be underrepresented in our trial.[28] However, the median age in our trial cohort is very similar to registry data, indicating no major recruitment bias. Our results thus apply to most patients with newly diagnosed Hodgkin's lymphoma.

Finally, the results of our HD18 study are only applicable if the local infrastructure provides sufficient resources to safely administer intensive chemotherapy. These resources include costly prophylactic medications, blood products, and emergency in-patient care, as well as a dedicated and experienced medical and nursing staff.

Strengths of our study include the robust study design and the large patient number, both of which allow firm conclusions on the observed effects. Because most participating centres were private practices or primary care hospitals, the results reflect a real-world setting in high-income countries.

We conclude that PET-2-guided therapy with eBEACOPP combines outstanding efficacy with an acceptable safety profile for both PET-2-negative and PET-2-positive patients. PET-2-guided de-escalation has substantially reduced the treatment-related risks and at the same time improved the overall survival for early-responding patients. Survival outcomes in HD18 are clearly superior compared with any other controlled trial reported so far. We therefore strongly recommend this PET-2-guided treatment strategy for patients with advanced-stage Hodgkin's lymphoma.

Contributors

PB, AL, RG, DAE, JMZ, JMa, JMe, MF-B, AH, JD, MS, H-JB, WW, W-DL, TP, MST, FH, MB, UBK, DK, HO, NS, BH, WA, GM, and TV directed clinical activities at participating study centres. HS led the reference pathology. CK, HE, CB, MF, GK, and MD did the central PET review. HG led the statistical analyses of the data. MF directed activities at the GHSG central office. AE, VD, and PB led the design of the study protocol. AE is the principal investigator of the study. All authors contributed to data interpretation, reviewed the draft, and approved the final version of this report.

Declaration of interests

We declare no competing interests.

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