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Angaben zur Veröffentlichung / Publication details:

Borchmann, Peter, Justin Ferdinandus, Gundolf Schneider, Alden Moccia, Richard Greil, Mark Hertzberg, Valdete Schaub, et al. 2024. "Assessing the efficacy and tolerability of PET-guided BrECADD versus eBEACOPP in advanced-stage, classical Hodgkin lymphoma (HD21): a randomised, multicentre, parallel, open-label, phase 3 trial." The Lancet 404 (10450): 341–52. https://doi.org/10.1016/s0140-6736(24)01315-1.

Assessing the efficacy and tolerability of PET-guided BrECADD versus eBEACOPP in advanced-stage, classical Hodgkin lymphoma (HD21): a randomised, multicentre, parallel, open-label, phase 3 trial

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Summary

Background Intensified systemic chemotherapy has the highest primary cure rate for advanced-stage, classical Hodgkin lymphoma but this comes with a cost of severe and potentially life long, persisting toxicities. With the new regimen of brentuximab vedotin, etoposide, cyclophosphamide, doxorubicin, dacarbazine, and dexamethasone (BrECADD), we aimed to improve the risk-to-benefit ratio of treatment of advanced-stage, classical Hodgkin lymphoma guided by PET after two cycles.

Methods This randomised, multicentre, parallel, open-label, phase 3 trial was done in 233 trial sites across nine countries. Eligible patients were adults (aged ≤60 years) with newly diagnosed, advanced-stage, classical Hodgkin lymphoma (ie, Ann Arbor stage III/IV, stage II with B symptoms, and either one or both risk factors of large mediastinal mass and extranodal lesions). Patients were randomly assigned (1:1) to four or six cycles (21-day intervals) of escalated doses of etoposide (200 mg/m² intravenously on days 1–3), doxorubicin (35 mg/m² intravenously on day 1), and cyclophosphamide (1250 mg/m² intravenously on day 1), and standard doses of bleomycin (10 mg/m² intravenously on day 8), vincristine (1·4 mg/m² intravenously on day 8), procarbazine (100 mg/m² orally on days 1–7), and prednisone (40 mg/m² orally on days 1–14; eBEACOPP) or BrECADD, guided by PET after two cycles. Patients and investigators were not masked to treatment assignment. Hierarchical coprimary objectives were to show (1) improved tolerability defined by treatment-related morbidity and (2) non-inferior efficacy defined by progression-free survival with an absolute non-inferiority margin of 6 percentage points of BrECADD compared with eBEACOPP. An additional test of superiority of progression-free survival was to be done if non-inferiority had been established. Analyses were done by intention to treat; the treatment-related morbidity assessment required documentation of at least one chemotherapy cycle. This trial was registered at ClinicalTrials.gov (NCT02661503).

Findings Between July 22, 2016, and Aug 27, 2020, 1500 patients were enrolled, of whom 749 were randomly assigned to BrECADD and 751 to eBEACOPP. 1482 patients were included in the intention-to-treat analysis. The median age of patients was 31 years (IQR 24–42). 838 (56%) of 1482 patients were male and 644 (44%) were female. Most patients were White (1352 [91%] of 1482). Treatment-related morbidity was significantly lower with BrECADD (312 [42%] of 738 patients) than with eBEACOPP (430 [59%] of 732 patients; relative risk 0·72 [95% CI 0·65–0·80]; p<0·0001). At a median follow-up of 48 months, BrECADD improved progression-free survival with a hazard ratio of 0·66 (0·45–0·97; p=0·035); 4-year progression-free survival estimates were 94·3% (95% CI 92·6–96·1) for BrECADD and 90·9% (88·7–93·1) for eBEACOPP. 4-year overall survival rates were 98·6% (97·7–99·5) and 98·2% (97·2–99·3), respectively.

Interpretation BrECADD guided by PET after two cycles is better tolerated and more effective than eBEACOPP in first-line treatment of adult patients with advanced-stage, classical Hodgkin lymphoma.

Funding Takeda Oncology.

Lancet 2024; 404: 341–52

Published Online July 3, 2024 https://doi.org/10.1016/S0140-6736(24)01315-1

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Research in context

Evidence before this study

Brentuximab vedotin has shown a favourable risk–benefit ratio for relapsed or refractory classic Hodgkin lymphoma. Therefore, it has been studied as a first-line treatment for advanced-stage, classic Hodgkin lymphoma with doxorubicin, vinblastine, and dacarbazine. Brentuximab vedotin could be used to optimise the risk–benefit ratio of individualised treatment approaches in combinations with increased efficacy, such as escalated doses of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (eBEACOPP) guided by PET after two cycles (PET-2). We searched MEDLINE between Jan 1, 2000, and May 1, 2024, with the search terms "Brentuximab" and "Hodgkin*" for studies published in all languages that evaluated brentuximab vedotin in the first-line treatment of advanced-stage Hodgkin lymphoma. The results from a phase 2 study suggested that the combination of brentuximab vedotin with etoposide, cyclophosphamide, doxorubicin, dacarbazine, and dexamethasone (BrECADD) is feasible and resulted in high lymphoma control and a favourable toxicity profile. However, randomised data are scarce for this novel regimen and no data exist for its use in a PET-2-guided strategy.

Added value of this study

PET-2-guided BrECADD achieves high response rates, and most patients can be treated with four cycles. Most importantly, it is better tolerated and more effective in terms of progression-free survival than eBEACOPP. The rates of progression-free survival observed with BrECADD are the highest reported in a randomised controlled trial in patients with newly diagnosed, advanced-stage, classic Hodgkin lymphoma to date.

Implications of all the available evidence

Based on the results of this phase 3 trial, BrECADD sets a new benchmark in terms of primary cure rate and is set to be a standard treatment option for adult patients with newly diagnosed, advanced-stage, classic Hodgkin lymphoma.

Introduction

Advanced-stage, classical Hodgkin lymphoma mainly affects young adults with a median age at onset around 30 years. Before the development of polychemotherapeutic regimens, such as doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) in 1975,[1] survival outcomes were exceedingly poor.[2–4] Since then, the optimal risk–benefit ratio of chemotherapy regimens has been the subject of controversial scientific debate, because higher chemotherapy intensity increases efficacy, but might be offset by aggravated toxicities.[5] The German Hodgkin Study Group developed the intensive regimen of escalated doses of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (eBEACOPP) to eradicate malignant clones upfront with excellent progression-free survival rates.[6,7] However, the treatment burden for patients is high and persisting organ dysfunction can substantially affect a patient's long-term health-related quality of life.[8]

The CD30 cell surface protein is constitutively expressed at high levels in classical Hodgkin lymphoma and is therefore an attractive therapeutic target for pharmaceuticals, such as the antibody-drug conjugate brentuximab vedotin, which has shown a favourable risk–benefit ratio in relapsed or refractory classical Hodgkin lymphoma as a single agent.[9] We developed the regimen of brentuximab vedotin, etoposide, cyclophosphamide, doxorubicin, dacarbazine, and dexamethasone (BrECADD) incorporating brentuximab vedotin with intent to replicate the high efficacy of eBEACOPP while reducing acute and late or persisting treatment-related toxicities, including gonadal dysfunction and infertility, peripheral neuropathy, or secondary neoplasia.[10,11]

Based on phase 2 data, we hypothesised that BrECADD applied within an individualised treatment approach and guided by fluorodeoxyglucose PET after two cycles of therapy (PET-2) could improve the risk–benefit ratio compared with eBEACOPP for patients with newly diagnosed, advanced-stage, classical Hodgkin lymphoma.[10,11] This study had two coprimary objectives: to show reduced toxicity of BrECADD compared with eBEACOPP measured by treatment-related morbidity, and to show non-inferior efficacy of BrECADD compared with eBEACOPP in terms of progression-free survival.

Methods

Study design

This randomised, multicentre, parallel, open-label, phase 3 trial was done in 233 trial sites across nine countries: Germany, Austria, Switzerland, the Netherlands, Denmark, Sweden, Norway, Australia, and New Zealand. It was an intergroup study including the German Hodgkin Study Group, Swiss Group for Clinical Cancer Research, Arbeitsgemeinschaft Medikamentöse Tumortherapie, Nordic Lymphoma Group, and Australasian Leukaemia and Lymphoma Group. Ethics approval was granted by the Ethics Committee of the Medical Faculty at the University of Cologne (reference number 16-008). This trial is registered with ClinicalTrials.gov (NCT02661503).

Patients

Adult patients (aged ≤60 years) with advanced-stage, classical Hodgkin lymphoma were eligible for enrolment. Definition of advanced stages included Ann Arbor stage III/IV as well as stage II with B symptoms and one or both risk factors of large mediastinal mass (≥ a third of the maximum thoracic diameter) or extranodal lesions. Other inclusion criteria encompassed an Eastern

Cooperative Oncology Group performance status of 0–2, HIV negativity, and freedom from concurrent disease that would preclude treatment according to the protocol. Participants' sex and race were assessed by the investigator. Enrolment was done at the German Hodgkin Study Group central office. Following enrolment, histological diagnosis was to be reassessed by a lymphoma expert pathologist. All patients provided written informed consent before study entry according to the Good Clinical Practice guidelines of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use.

Randomisation and masking

Patients were randomly assigned (1:1) to eBEACOPP or BrECADD using the minimisation method including a random component and stratified according to area of recruitment (Europe *vs* Australia and New Zealand), age (<45 years *vs* ≥45 years), International Prognostic Score (0–2 *vs* 3–7), and sex (male *vs* female). Patients were enrolled locally by designated study team members including investigators and study nurses. Assignment of individual patients to one of the trial groups was done centrally in the German Hodgkin Study Group office as described in the protocol (appendix 2). Patients and investigators were not masked to treatment allocation.

Procedures

Detailed procedures are described in appendix 1 (p 1) and treatment with BEACOPP and BrECADD has been described previously.[12] In brief, cycles of BEACOPP (full dose level 4) were escalated doses of etoposide (200 mg/m² intravenously on days 1–3), doxorubicin (35 mg/m² intravenously on day 1), and cyclophosphamide (1250 mg/m² intravenously on day 1), and standard doses of bleomycin (10 mg/m² intravenously on day 8), vincristine (1·4 mg/m² intravenously on day 8), procarbazine (100 mg/m² orally on days 1–7), and prednisone (40 mg/m² orally on days 1–14). Cycles of BrECADD (full dose level 4) were brentuximab vedotin (1·8 mg/kg up to a maximum of 180 mg absolute dose intravenously on day 0), etoposide (150 mg/m² intravenously on days 1–3), cyclophosphamide (1250 mg/m² intravenously on day 1), doxorubicin (40 mg/m² intravenously on day 1), dacarbazine (250 mg/m² intravenously on days 2–3), and dexamethasone (40 mg/m² orally on days 1–4). BEACOPP and BrECADD cycles were administered in 21-day intervals, and blood counts were monitored at least twice per week. Treatment was initiated for all patients at the highest dose level 4. For both regimens, granulocyte-colony stimulating factor support (in pegylated or non-pegylated form as per investigator's discretion) was mandatory. Depending on observed toxicities, predefined de-escalation was mandatory for the subsequent cycles of eBEACOPP and BrECADD to dose level 3 (etoposide 175 mg/m² and cyclophosphamide 1100 mg/m² *vs* etoposide 125 mg/m² and cyclophosphamide 1100 mg/m²), level 2 (150 mg/m² and 950 mg/m² *vs* 100 mg/m² and 950 mg/m²), level 1 (125 mg/m² and 800 mg/m² *vs* 100 mg/m² and 800 mg/m²), or baseline (etoposide 100 mg/m², doxorubicin 25 mg/m², cyclophosphamide 650 mg/m² *vs* etoposide 100 mg/m², doxorubicin 35 mg/m², and cyclophosphamide 650 mg/m²).

PET-based or CT-based response assessments were done after the second cycle of chemotherapy and after the last cycle of chemotherapy. PET-2 was strongly recommended before and obligatory after the introduction of PET-2 treatment guidance, and PET-2 results will only be reported for the subgroup assessed after the respective amendment. A multidisciplinary expert panel centrally reviewed imaging results from PET-2 and PET after the last cycle as well as for all events of relapse or disease progression. PET positivity was defined as a Deauville score of 4 or higher.[13] Consolidative radiotherapy was recommended for PET-positive residual disease after end of chemotherapy. Following the availability of the German Hodgkin Study Group HD18 study results, the HD21 study was amended for PET-2-guidance to four cycles or six cycles of chemotherapy (5th protocol version, March 13, 2017).[12]

Outcomes

The coprimary endpoints were tolerability, defined by investigator-assessed treatment-related morbidity, and efficacy, assessed by progression-free survival including central review of all tumour events. Treatment-related morbidity was defined as the occurrence of any of the following events from the start of therapy to 30 days after the end of chemotherapy: acute non-haematological organ toxicity of Common Terminology Criteria for Adverse Events (CTCAE) grade 3 or 4 of system organ classes including disorders of the cardiac system, gastrointestinal system (excluding vomiting, nausea, and mucositis), hepatobiliary system, nervous system, renal and urinary system, respiratory system, thoracic system, and mediastinum; and acute haematological toxicity of grade 4 including anaemia, thrombocytopenia, and infections (as a clinically relevant outcome of neutropenia). Progression-free survival was defined as the time from randomisation until progression, relapse or death from any cause, or censored at the date of last information on the disease status.

Secondary outcomes were adverse events of any grade, frequency of complete response, overall survival (defined as time from randomisation until death from any cause or censored at the date of last information on the patient being alive), gonadal toxicity and function, second primary malignancies, event-free survival (defined as time from randomisation until premature discontinuation of randomised treatment for any reason, progression, relapse or death from any cause, or censored on the date the last information on the disease status was collected), and patient-reported outcomes, which will be published

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separately. Adverse events were documented by the investigators during study treatment and follow-up according to CTCAE, version 4.03.

Statistical analysis

We compared the rate of treatment-related morbidity using the Cochran–Mantel–Haenszel test stratified by area of recruitment, International Prognostic Score, age, and sex with a two-sided significance level of α=0·05. Efficacy evaluations could be performed only after superior treatment-related morbidity of BrECADD had been shown. Non-inferiority of progression-free survival was defined as an absolute difference of less than 6% at 5 years corresponding to a hazard ratio (HR) for BrECADD versus eBEACOPP of less than 1·69 (based on an a priori 5-year estimate of 90·5%). 154 progression-free survival events were estimated to yield a power of 90% at a two-sided significance level of 0·05. Thus, 1500 patients were to be enrolled. Regarding treatment-related morbidity, a reduction of at least 8·4 percentage points could be detected with a power of at least 90% with this sample size.

After reviewing the results of the treatment-related morbidity analysis conducted in 2022, the independent data monitoring committee recommended their early publication, including efficacy data, as they were considered highly relevant for patients and caregivers. Following scientific advice of the Paul-Ehrlich-Institute, we decided to amend an interim analysis of progression-free survival with an estimated follow-up of 36 months in the 9th version of the trial protocol of Dec 5, 2022. To maintain control of the type I error, efficacy stopping was based on O'Brien-Fleming boundaries with Lan-DeMets spending function, applying an information rate of 65% that resulted in a two-sided significance level of 0·0108 for the interim analysis of non-inferiority.

The final analysis of the primary efficacy endpoint included a test of superiority of BrECADD versus eBEACOPP, which was amended in the protocol after the successful interim analysis (10th protocol version, Dec 8, 2023). As both objectives were already met and the accumulation of 154 events was deemed unachievable within the trial duration, the final analysis was set at 48 months follow-up within this amendment. Determined by alpha spent in the interim analysis and an actual information rate of 71%, a two-sided significance level of 0·0392 remained for the final analysis.

All analyses were done in the intention-to-treat population, excluding only patients whose diagnosis of classical Hodgkin lymphoma was not confirmed by the pathology panel. The analysis of safety data, including adverse events and treatment-related morbidity, required the documentation of at least one chemotherapy cycle. Preplanned analyses of the coprimary endpoints were done in the per-protocol population, using the same methods as described above. The per-protocol population consisted of all patients from the intention-to-treat population without evidence of not meeting inclusion or exclusion criteria, who received the recommended number of chemotherapy cycles according to protocol (an additional or one less cycle was allowed), unless discontinuing because of acute toxicity or progressive disease, and have at least one PET-based or CT-based post-baseline response assessment.

Progression-free survival, as well as other time-to-event endpoints, were analysed by the Kaplan–Meier method, including HRs, corresponding CIs, and p values obtained from Cox regression models. The model for the primary test on superiority of progression-free survival was to be stratified by the area of recruitment, International Prognostic Score, age, and sex. The Schoenfeld residuals test was used to verify the proportional hazards assumption. Additional details on methods for secondary endpoints analyses are provided in appendix 1 (pp 1–2). We did post-hoc subgroup analyses by established baseline risk factors for both coprimary endpoints as well as by PET-2 status for progression-free survival. Post hoc, we estimated the effect of the binary treatment-related morbidity endpoint on patient-reported outcomes, including the global health status and the complete set of functioning scales of the European Organisation for Research and Treatment of Cancer Core Quality of Life questionnaire-C30 at the end of treatment. The multiple regression model for each scale consisted of age, sex, respective baseline score, and treatment-related morbidity

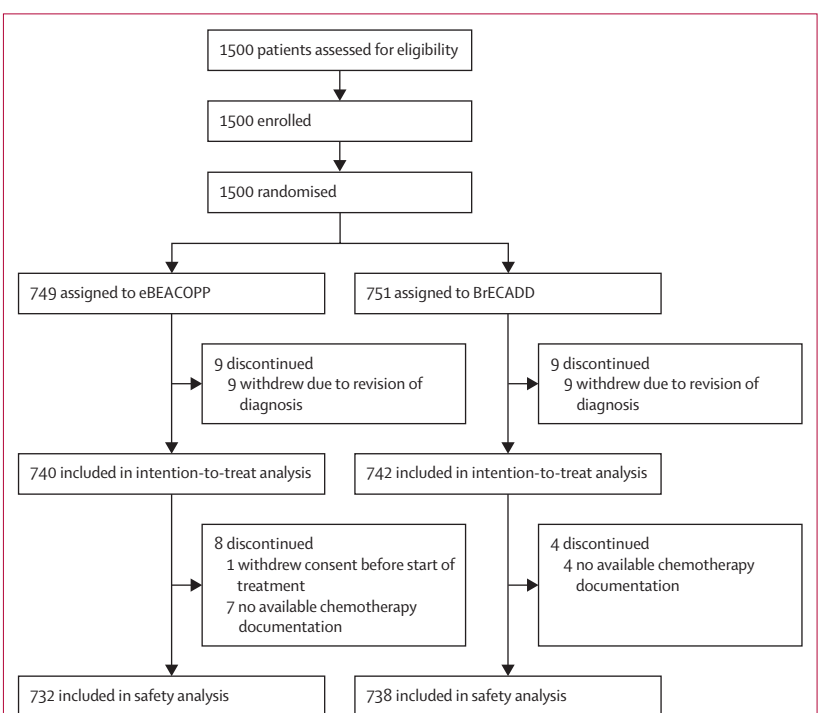

Figure 1: **Trial profile**
BrECADD=brentuximab vedotin, etoposide, cyclophosphamide, doxorubicin, dacarbazine, and dexamethasone. eBEACOPP=escalated doses of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone.

as predictors of the respective patient-reported outcomes. Detailed methods are provided in appendix 1 (p 2). SAS version 9.4 was used for all analyses.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between July 22, 2016, and Aug 27, 2020, 1500 patients were enrolled, of whom 749 were randomly assigned to eBEACOPP and 751 to BrECADD. The intention-to-treat population comprised 1482 patients, 740 in the eBEACOPP group and 742 in the BrECADD group, excluding nine patients per group whose classical Hodgkin lymphoma diagnosis was revised following pathology review (figure 1). Another 12 patients were excluded from the safety analysis because no chemotherapy cycle was documented (eight in the eBEACOPP group and four in the BrECADD group), leaving 732 patients in the eBEACOPP group and 738 in the BrECADD group in the safety analysis. Baseline characteristics were well balanced between treatment groups (table 1). The median age of patients was 31 years (IQR 24–42). 838 (56%) of 1482 patients were male and 644 (44%) were female. Most patients were White (1352 [91%] of 1482).

PET-2-guided treatment (introduced by amendment v4.0) was applied in 1346 (91%) of 1482 patients. Of those patients, 430 (64%) of 669 patients in the eBEACOPP group and 430 (64%) of 677 patients in the BrECADD group had a negative PET-2 and were assigned to four treatment cycles only (table 2). Overall, 1415 (95%) patients received the scheduled number of treatment cycles. Patients assigned to eBEACOPP and BrECADD had similar complete remission rates (567 [80%] of 713 and 584 [82%] of 716) at the end of chemotherapy. Consolidative radiotherapy was recommended by central review due to PET-positive residual disease for 127 patients (17%) in the eBEACOPP group and 125 patients (17%) in the BrECADD group. 112 (15%) patients and 104 (14%) patients, respectively, received radiotherapy.

Most patients in each treatment group had at least one adverse event (table 3). Overall, the occurrence of at least one treatment-related morbidity event was significantly lower with BrECADD (312 [42%] of 738 patients) than with eBEACOPP (430 [59%] of 732 patients; relative risk 0·72 [95% CI 0·65–0·80]; p<0·0001). The relative risk estimates were generally consistent among analysed subgroups (appendix 1 p 6). In the eBEACOPP group, 382 (52%) of 732 patients had haematological treatment-related morbidity events compared with 231 (31%) of 738 patients in the BrECADD group (p<0·0001), which was reflected by the reduction in red cell transfusions (384 [52%] of 732 *vs* 178 [24%] of 738) and platelet transfusions (248 [34%] *vs* 125 [17%]; table 3). The incidence of grade 3 or higher infections was similar (138 [19%] of 732 *vs* 150 [20%] of 737), whereas neutropenic fever grade 3 or higher was documented in 141 (21%) of 677 patients in the eBEACOPP group and 193 (28%) of 681 patients in the BrECADD group (table 3).

Most frequent reasons for dose reductions were leukopenia for eBEACOPP (241 [34%] of 715 patients with available data) and thrombocytopenia for BrECADD (147 [23%] of 635 patients). Dose reductions occurred more frequently with eBEACOPP than with BrECADD:

	eBEACOPP (n=740)	BrECADD (n=742)
Median age, years	31 (24–42)	31 (24–42)
Age group, years		
18–19	31 (4%)	27 (4%)
20–29	287 (39%)	292 (39%)
30–39	199 (27%)	212 (29%)
40–49	112 (15%)	92 (12%)
50–60	111 (15%)	119 (16%)
Sex		
Male	419 (56%)	419 (56%)
Female	321 (44%)	323 (44%)
Race		
White	672 (91%)	680 (92%)
Asian	13 (2%)	11 (1%)
Black	2 (<1%)	0
Other or unknown	53 (7%)	51 (7%)
Ann Arbor stage		
IIa	0	2 (<1%)
IIb	117/739 (16%)	115 (16%)
IIIa	132/739 (18%)	129 (17%)
IIIb	156/739 (21%)	164 (22%)
IVa	112/739 (15%)	104 (14%)
IVb	222/739 (30%)	228 (31%)
ECOG performance status		
0	517/735 (70%)	508/739 (69%)
1	200/735 (27%)	220/739 (30%)
2	18/735 (2%)	11/739 (1%)
Risk factors		
Large mediastinal mass	235/735 (32%)	253/739 (35%)
Extranodal involvement	175/735 (24%)	202/739 (27%)
Involvement of 3 or more nodal areas	655/735 (89%)	667/739 (90%)
High erythrocyte sedimentation rate	470/709 (66%)	481/708 (68%)
International Prognostic Score		
0–1	175 (24%)	195 (26%)
2–3	395 (53%)	390 (53%)
4–7	170 (23%)	157 (21%)

Data are n (%), median (IQR), or n/N (%). BrECADD=brentuximab vedotin, etoposide, cyclophosphamide, doxorubicin, dacarbazine, and dexamethasone. eBEACOPP=escalated doses of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone. ECOG=Eastern Cooperative Oncology Group.

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

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See **Online** for appendix 1

See **Online** for appendix 2

	eBEACOPP (n=740)	BrECADD (n=742)	Total (n=1482)
Response after two chemotherapy cycles			
Central PET review after two cycles (post-amendment)	669 (90%)	677 (91%)	1346 (91%)
Complete metabolic response (DS1–3) after two cycles	430/669 (64%)	430/677 (64%)	860/1346 (64%)
Therapy adherence			
Cycles received that were recommended	707 (95%)	708 (96%)	1415 (95%)
Status at end of chemotherapy			
Radiotherapy recommended	127 (17%)	125 (17%)	252 (17%)
Radiotherapy documented	112 (15%)	104 (14%)	216 (15%)
PFS events			
Patients with PFS events per IRC	65 (9%)	44 (6%)	109 (7%)
Tumour event	58 (8%)	37 (5%)	95 (6%)
Progression	15 (2%)	5 (1%)	20 (1%)
Early relapse, ≤1 year	23 (3%)	11 (1%)	34 (2%)
Late relapse, >1 year	20 (3%)	21 (3%)	41 (3%)
Death without previous tumour event	7 (1%)	7 (1%)	14 (1%)
Causes of death			
Hodgkin lymphoma	1 (<1%)	3 (<1%)	4 (<1%)
Toxicity of study treatment	3 (<1%)	0	3 (<1%)
Toxicity of salvage therapy	1 (<1%)	0	1 (<1%)
Second neoplasia	2 (<1%)	0	2 (<1%)
Cardiovascular	1 (<1%)	0	1 (<1%)
Respiratory	0	1 (<1%)	1 (<1%)
Infection	1 (<1%)	2 (<1%)	3 (<1%)
Suicide	0	1 (<1%)	1 (<1%)
Other disease	1 (<1%)	3 (<1%)*	4 (<1%)
Unclear	2 (<1%)	2 (<1%)*	4 (<1%)
Any event	12 (2%)	12 (2%)	24 (2%)
Second primary malignancies			
Acute myeloid leukaemia or myelodysplastic syndrome	6 (1%)	2 (<1%)	8 (1%)
Non-Hodgkin lymphoma	2 (<1%)	8 (1%)	10 (1%)
Solid tumour	5 (1%)	9 (1%)	14 (1%)
Any event	13 (2%)	19 (3%)	32 (2%)

Data are n (%) or n/N (%). BrECADD=brentuximab vedotin, etoposide, cyclophosphamide, doxorubicin, dacarbazine, and dexamethasone. DS=Deauville score. eBEACOPP=escalated doses of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone. IRC=independent review committee. PFS=progression-free survival. *Two cases with at least possible relationship to treatment according to sponsor review.

Table 2: **Outcomes**

	eBEACOPP (n=732)	BrECADD (n=738)
Common adverse events		
Anaemia		
Any grade	718 (98%)	705 (96%)
Grade ≥3	432 (59%)	220 (30%)
Red cell transfusions ≥1	384 (52%)	178 (24%)
Thrombocytopenia		
Any grade	682 (93%)	638 (86%)
Grade ≥3	530 (72%)	407 (55%)
Platelet transfusions ≥1	248 (34%)	125 (17%)
Leukopenia		
Any grade	717 (98%)	690 (93%)
Grade ≥3	691 (94%)	641 (87%)
Neutropenic fever		
Any grade	144/677 (21%)	194/681 (28%)
Grade ≥3	141/677 (21%)	193/681 (28%)
Infection		
Any grade	335 (46%)	358/737 (49%)
Grade ≥3	138 (19%)	150/737 (20%)
Cardiac disorders		
Any grade	135 (18%)	153 (21%)
Grade ≥3	9 (1%)	21 (3%)
Gastrointestinal disorders		
Any grade	328 (45%)	395/737 (54%)
Grade ≥3	32 (4%)	58/737 (8%)
Hepatobiliary disorders		
Any grade	148 (20%)	172/737 (23%)
Grade ≥3	22 (3%)	37/737 (5%)
Peripheral sensory neuropathy		
Any grade	360 (49%)	287/737 (39%)
Grade ≥3	17 (2%)	10/737 (1%)
Peripheral motor neuropathy		
Any grade	31 (4%)	28/737 (4%)
Grade ≥3	1 (<1%)	3/737 (<1%)
Nervous system disorder (other than neuropathy)		
Any grade	205 (28%)	192/737 (26%)
Grade ≥3	24 (3%)	12/737 (2%)
Renal and urinary disorders		
Any grade	90 (12%)	71/737 (10%)
Grade ≥3	10 (1%)	7/737 (1%)
Respiratory, thoracic, and mediastinal disorders		
Any grade	347 (47%)	282/737 (38%)
Grade ≥3	34 (5%)	24/737 (3%)
Skin and subcutaneous tissue disorders		
Any grade	312 (43%)	285/737 (39%)
Grade ≥3	13 (2%)	10/737 (1%)
Drug fever		
Any grade	57 (8%)	42/737 (6%)
Grade ≥3	10 (1%)	7/737 (1%)
Allergy		
Any grade	37 (5%)	31/737 (4%)
Grade ≥3	7 (1%)	3/737 (<1%)

(Table 3 continues on next page)

full-dose treatment at cycle four was administered in 422 (59%) of 720 patients in the BEACOPP group compared with 561 (78%) of 721 patients in the BrECADD group (appendix 1 p 3). In patients with positive PET-2, full-dose treatment at cycle six was given to 119 (43%) of 280 patients in the BEACOPP group versus 191 (67%) of 284 patients in the BrECADD group. Brentuximab vedotin was terminated prematurely in 18 (2%) of 738 patients in the BrECADD group. Vincristine, the

	eBEACOPP (n=732)	BrECADD (n=738)
(Continued from previous page)		
Avascular necrosis		
Any grade	4 (1%)	0/737
Grade ≥3	1 (<1%)	0/737
Treatment-related morbidity*		
Anaemia, thrombocytopenia, or infection of CTCAE grade 4	382 (52%)	231 (31%)
Organ toxicity of CTCAE grade 3–4	126 (17%)	139 (19%)
Treatment-related morbidity	430 (59%)	312 (42%)
Treatment-related morbidity: relative risk*	..	0·72 (0·65–0·80)

Data are n (%), n/N (%), or relative risk (95% CI). Only patients with documentation of at least one chemotherapy cycle were included. BrECADD=brentuximab vedotin, etoposide, cyclophosphamide, doxorubicin, dacarbazine, and dexamethasone. CTCAE=Common Terminology Criteria for Adverse Events. eBEACOPP=escalated doses of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone. *Common relative risk of at least one treatment-related morbidity (Cochran–Mantel–Haenszel test).

Table 3: **Adverse events and treatment-related morbidity**

corresponding tubulin inhibitor in the eBEACOPP regimen, was terminated early in 132 (18%) of 732 patients.

Organ toxicity relevant for treatment-related morbidity was documented in 126 (17%) of 732 patients in the eBEACOPP group and 139 (19%) of 738 patients in the BrECADD group (p=0·46) without notable differences for any predefined system organ classes (table 3). Sensory peripheral neuropathy of any grade was documented in 360 (49%) of 732 patients and 287 (39%) of 737 patients in the eBEACOPP and BrECADD groups, respectively, and was mainly grade 1 (244 [33%] and 231 [31%] with available data). Grade 2 sensory peripheral neuropathy occurred in 99 (14%) patients and 46 (6%) patients, and grade 3 in 17 (2%) patients and ten (1%) patients in the eBEACOPP group and BrECADD group, respectively. Grade 2 peripheral motor neuropathy was documented in nine (1%) patients and four (1%) patients, in the eBEACOPP group and BrECADD group respectively, and grade 3 or higher in only four patients overall.

1 year after treatment, toxicities had resolved fully or to grade 1 in 609 (93%) of 657 patients in the eBEACOPP group and 647 (96%) of 677 patients in the BrECADD group. Haematological treatment-related morbidity events resolved for almost all patients (one patient with persisting toxicities in the eBEACOPP group and no patients in the BrECADD group), which was also true for non-haematological treatment-related morbidity toxicities (six patients and two patients, respectively; appendix 1 pp 3–4). At 12-month follow-up, no sensory peripheral neuropathy was reported in 567 (86%) of 656 patients in the eBEACOPP group and 595 (88%) of 677 in the BrECADD group. Grade 1 peripheral sensory neuropathy was documented for 72 (11%) of 656 patients and 69 (10%) of 677 patients, respectively. Grade 2 peripheral sensory neuropathy was persistent at 1 year after treatment in 15 (2%) of 656 patients in the eBEACOPP group and 12 (2%) of 677 patients in the BrECADD group.

As the interim analysis successfully showed non-inferiority of BrECADD with a median follow-up of 40 months (appendix 1 p 7), we could test for superiority in the final analysis.[14] This test was positive, showing patients assigned to BrECADD had a 4-year progression-free survival rate of 94·3% (95% CI 92·6–96·1) whereas those assigned to eBEACOPP had a rate of 90·9% (88·7–93·1; HR 0·66 [95% CI 0·45–0·97]; p=0·035; figure 2A). An HR favouring BrECADD was observed across all large subgroups (appendix 1 pp 6, 8–9). Notably, HRs favouring BrECADD were generally lower in low-risk cohorts according to International Prognostic Score, Ann Arbor stage, or PET-2 response than with the respective high-risk subgroups. PET-2 negativity was associated with favourable progression-free survival in both groups (eBEACOPP, HR 0·65 [95% CI 0·39–1·09] and BrECADD, HR 0·41 [0·21–0·77]; figure 3). Corresponding progression-free survival for patients with negative PET-2 was 96·8% (95% CI 95·0–98·5) for BrECADD and 92·9% (90·4–95·4) for eBEACOPP, whereas patients with positive PET-2 showed a 4-year progression-free survival of 90·3% (86·6–94·3) and 87·8% (83·4–92·4), respectively. The 4-year event-free survival rate was 91·4% (89·3–93·5) for the BrECADD group and 88·2% (85·9–90·7) for the BEACOPP group. For the subgroup of patients with Ann Arbor stage III and IV, 4-year progression-free survival was 93·9% (91·9–95·9) in the BrECADD group, and 91·0% (88·7–93·4) in the eBEACOPP group, respectively.

The preplanned per-protocol analyses of the co-primary endpoints confirmed the intention-to-treat results. Details are provided in appendix 1 (p 5).

4-year overall survival rates were 98·6% (95% CI 97·7–99·5) for BrECADD and 98·2% (97·2–99·3) for eBEACOPP (figure 2B). Hodgkin lymphoma as the cause of death was documented in one patient in the eBEACOPP group and three patients in the BrECADD group (table 2). All three treatment-related deaths were documented in the eBEACOPP group.

After 4 years, gonadal function recovery as measured by follicle-stimulating hormone in 766 patients was more common after BrECADD than after eBEACOPP both in women (95·3% [95% CI 92·0–98·8] *vs* 72·5% [66·1–79·5]) and in men (86·0% [81·1–91·1] *vs* 39·2% [33·2–46·4]). There were 46 childbirths among 40 female patients or partners of male patients in the eBEACOPP group and 62 childbirths reported among 59 respective patients in the BrECADD group.

13 (2%) of 740 patients and 19 (3%) of 742 patients had second primary malignancies in the eBEACOPP group and BrECADD group, respectively (table 2).

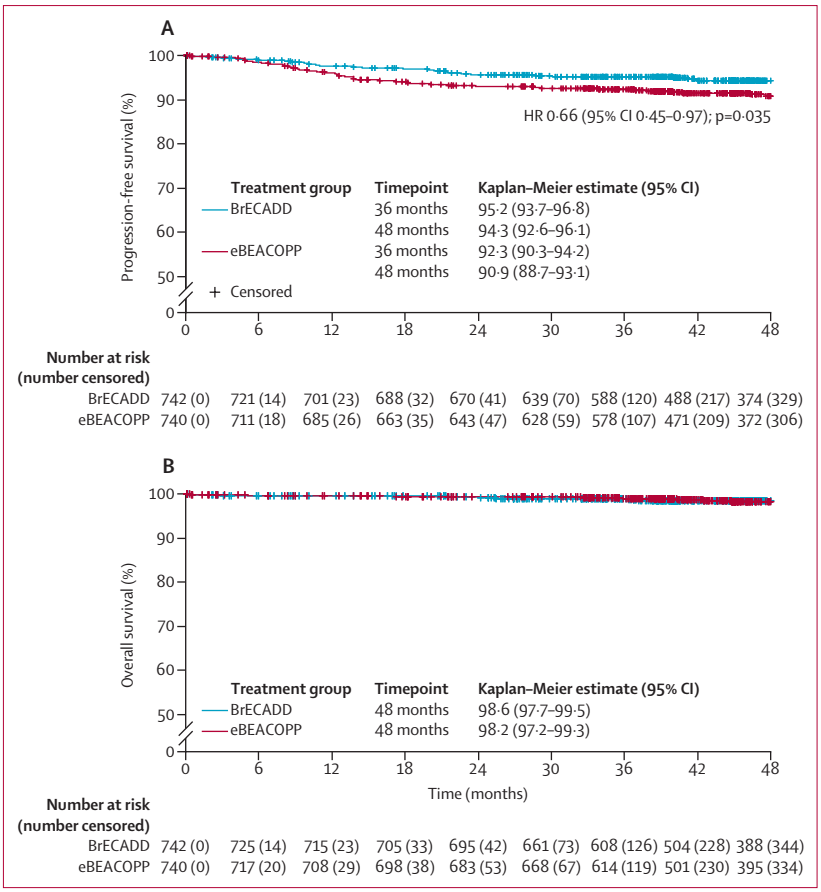

Figure 2: **Kaplan–Meier estimates of progression-free survival and overall survival**
Progression-free survival (A) and overall survival (B). HR and p value obtained by Cox regression stratified by area of recruitment, International Prognostic Score, age, and sex. BrECADD=brentuximab vedotin, etoposide, cyclophosphamide, doxorubicin, dacarbazine, and dexamethasone. eBEACOPP=escalated doses of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone. HR=hazard ratio.

According to the post-hoc analysis of patient-reported outcomes, the occurrence of a treatment-related morbidity event was significantly associated with a lower global health status as well as lower cognitive, physical, and social functioning at the end of treatment (appendix 1 p 4).

Discussion

This randomised, multicentre, open-label, phase 3 trial, for adult patients with newly diagnosed, classical Hodgkin lymphoma showed that BrECADD had superior efficacy regarding progression-free survival and superior tolerability in terms of treatment-related mortality compared with eBEACOPP. The trial was designed with the assumption that BrECADD would be as effective as eBEACOPP. However, after finding non-inferiority of BrECADD at an interim analysis,[14] the superiority test revealed a significant progression-free survival benefit of BrECADD versus eBEACOPP. With a 4-year progression-free survival of 94·3%, the primary cure rate of BrECADD is unprecedented in large, randomised trials for advanced-stage, classical Hodgkin lymphoma.

The increase in efficacy was driven by a reduction in refractory cases and early relapses, thereby reflecting the importance of early definitive disease control in classical Hodgkin lymphoma to achieve favourable, long-term outcomes. By using an individualised PET-2-guided strategy, most patients were treated with only 4 cycles (ie, 12 weeks) of BrECADD. Subgroup analyses indicate that patients with PET-2-negative disease derive the highest benefit from BrECADD compared with eBEACOPP with a 4-year progression-free survival rate of 96·8%. However, the proportion of patients with PET-2-negative disease was identical at 64% in both treatment groups. This observation has several implications. First, the excellent primary cure rate in these patients suggests that the definition of advanced-stage, classical Hodgkin lymphoma comprises patients with different individual risk profiles, which strongly supports individualised treatment approaches in the context of highly active therapies. The positive effect of a shortened treatment period on recovery from cancer-related fatigue and social reintegration supports this conclusion.[15,16] Second, dose adjustments might play a larger role when the number of chemotherapy cycles is reduced. Dose reductions were predefined for both groups in case of severe adverse events. Accordingly, the higher incidence of severe haematotoxicity with eBEACOPP led to more frequent dose reductions to prespecified lower dose levels during treatment than with BrECADD. Subsequently, BrECADD was administered more frequently at full dose, which specifically accounts for cyclophosphamide, doxorubicin, and etoposide possibly affecting the quality of responses and thus the long-term control of lymphoma. It also applies to the early discontinuation rate of the tubulin inhibitors, brentuximab vedotin, in the BrECADD regimen compared with vincristine in the eBEACOPP regimen, which was 2% for brentuximab vedotin but 18% for vincristine. The optimised feasibility of BrECADD supports its use as part of an individualised treatment strategy that enables a shortened treatment duration for adults with advanced-stage, classical Hodgkin lymphoma. Third, although PET-2-status still yields prognostic value in patients treated with BrECADD (figure 3), progression-free survival events occurred in less than one in ten patients with PET-2-positive disease treated with six cycles of BrECADD. By contrast with other recent prospective studies in classical Hodgkin lymphoma, the absolute number of progression-free survival events in this study is highest in the patients with PET-2-positive disease and not in those with PET-2-negative disease, confirming the appropriateness of an individualised PET-guided strategy with highly effective therapies.[17,18] However, this finding indicates that the cutoff for Deauville score of 4 or higher for PET-2 positivity still includes patients at low risk for treatment failure. The same assumption could apply to the previously established end-of-treatment PET-guided approach, which could overestimate the actual

number of patients benefiting from consolidating radiotherapy, which was not questioned in our study.[19] To optimise the selection of patients at lower risk, refinement of metabolic response criteria or the detection of minimal residual disease through circulating tumour DNA might be applicable for individualised treatment in the future.[20]

Our results need to be put into perspective with other established treatment approaches. Unfortunately, these indirect comparisons are hampered by different inclusion criteria and endpoint definitions. Although this limitation requires cautious interpretation, the reported progression-free survival rates can still provide some guidance. The RATHL-study (NCT00678327) investigated PET-2-guided de-escalation of ABVD to doxorubicin, vinblastine, and dacarbazine (AVD), which aimed to reduce pulmonary toxicity.[18] This strategy includes escalation to eBEACOPP for patients with PET-2-positive disease and all patients had a 3-year progression-free survival of 82·6%. Another approach aimed at increasing the efficacy of the ABVD regimen through the replacement of bleomycin with brentuximab vedotin (brentuximab vedotin-AVD). This regimen was investigated in the ECHELON-1 trial (NCT01712490) for superiority over ABVD. Treatment with six cycles was applied without interim-PET guidance for all patients. The ECHELON-1 trial showed that brentuximab vedotin-AVD was beneficial as assessed by modified progression-free survival, which reached 82·1% at 2 years, remained stable over time, and reached an investigator-assessed, 6-year progression-free survival of 82·3% (95% CI 79·1–85·0).[17] Notably, ECHELON-1 was open to enrol all patients older than 18 years, including those older than 60 years. By contrast, to be randomly assigned in this HD21 trial, patients had to be aged 18–60 years as eBEACOPP is not a standard of care in children or older patients. The corresponding 6-year progression-free survival rate for this age group in the ECHELON-1 trial was 84·4% (81·1–87·2).[17] In the ECHELON-1 trial, the progression-free survival benefit translated to an overall survival benefit over time, which is consistent with previously published analyses.[17,21] In summary, indirect comparisons with published ABVD-based approaches indicate a progression-free survival difference in favour of BrECADD of about 10% at 3 years of follow-up. Progression-free survival reflects the patient's chance of being cured and alive without requiring any further treatment. Overall, it is the most important endpoint from the patient's perspective.[22] Accordingly, information on the progression-free survival of different treatment strategies should be shared with patients with advanced-stage, classical Hodgkin lymphoma to enable informed decision making. Notably, a trial featuring a non-individualised treatment strategy challenges brentuximab vedotin-AVD by replacing brentuximab vedotin with the PD1 inhibitor nivolumab (nivolumab-AVD; NCT03907488). Superiority of nivolumab-AVD over brentuximab vedotin-AVD was met at interim analysis after 12 months of follow-up according to a conference report.[23] Although early data look promising, mature data to determine the primary cure rate and the risk–benefit ratio of this approach are still pending and cannot yet be discussed.[24] Finally, consolidative radiotherapy was applied in this study according to the German Hodgkin Study Group standard of care to PET-positive residual disease only, which provided small sample sizes and has not affected the incidence of second primary malignancies at a median follow-up of 10 years.[25] However, much longer follow-up from studies with or without consolidative radiotherapy for PET-positive residual disease is needed to assess risks and benefits of this approach.

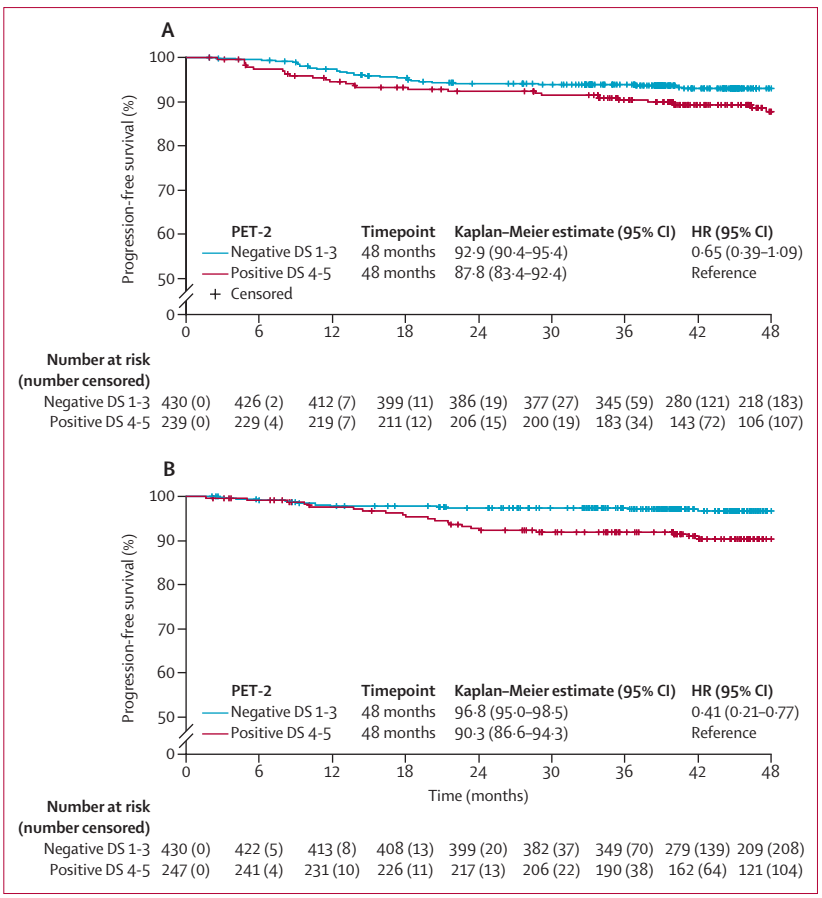

***Figure 3*: Kaplan–Meier estimates of progression-free survival by PET-2 status**
Progression-free survival for eBEACOPP (A) and BrECADD (B). HRs obtained by Cox regression. BrECADD=brentuximab vedotin, etoposide, cyclophosphamide, doxorubicin, dacarbazine, and dexamethasone. DS=Deauville score. eBEACOPP=escalated doses of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone. HR=hazard ratio. PET-2=PET after two cycles of therapy.

BrECADD was designed to overcome known issues of tolerability associated with eBEACOPP. We implemented treatment-related morbidity as an endpoint, which includes non-haematological and haematological acute adverse events of high severity. The substantial superiority of BrECADD compared with eBEACOPP was driven mainly by reduced haematotoxicity, which

approximately halved the need for red blood cell and platelet transfusions. However, a relevant proportion of patients (21% and 28%) had neutropenic fever in the eBEACOPP group and BrECADD group, with a pronounced first cycle effect. Approximately half of all events occurred during cycle 1 of eBEACOPP, which also occurred with BrECADD (appendix 1 p 5). This effect should be considered for patient management as neutropenic fever might require inpatient care. The similar incidence of non-haematological toxicities in both treatment groups might be explained at least partly by the fact that BrECADD was applied more frequently at full dose over the entire treatment period. Importantly, we did not observe any new toxicities due to the new drug combination in the BrECADD regimen.

As the treatment-related morbidity endpoint was preplanned but uniquely constructed for the purpose of this trial, its relevance to patients is unclear. We therefore analysed the effect of treatment-related morbidity on a validated set of patient-reported outcomes. The analysis supports the relevance of treatment-related morbidity to global health status and almost all areas of patient functioning after treatment and clearly supports its relevance to patients post hoc.

From the patient's perspective, the toxicities occurrence and resolution after treatment completion is important for the risk–benefit assessment of therapeutic measures.[26] Although BrECADD might increase rates of acute toxicities compared with ABVD-based regimens 12 months post-treatment, overall organ toxicities had resolved fully or to grade 1 in 96% of patients in the BrECADD group. However, persisting peripheral neuropathy can affect a patient's quality of life even at grade 2, which was not included in the treatment-related morbidity endpoint but limits activities of daily living by definition.[26] 1 year post BrECADD treatment, 10% of patients reported grade 1 peripheral neuropathy and only 2% of patients reported grade 2 symptoms of peripheral neuropathy. Overall, the probability of a complete recovery from relevant treatment-related adverse events after treatment with BrECADD is therefore considered to be high.

We observed high rates of gonadal function recovery in female and male patients, as well as high numbers of childbirth with BrECADD, which is most likely linked to the omission of procarbazine.[27] Normalisation of follicle-stimulating hormone levels in female patients occurs in more than 90% of female patients aged 18–40 years at diagnosis of advanced-stage, classical Hodgkin lymphoma treated with BrECADD. Accordingly, gonadal function recovery and fertility of women treated with BrECADD are similar to those reported among women treated with ABVD.[28] Overall, these observations are relevant for patients with an unfulfilled wish to conceive children at diagnosis.

Use of dacarbazine instead of procarbazine might also have contributed to the low incidence of secondary myelodysplasia or acute myeloid leukaemia in the BrECADD group (two of 742 patients). With the low-to-moderate effects on gonadal function, these observations indicate a limited general genotoxic potential of this new regimen, similar to that seen with ABVD or brentuximab vedotin-AVD.[17,29] However, the numbers are too small, and the observation period is too short to reach a definitive conclusion on second primary malignancies.

Anthracyclines are a cornerstone of chemotherapy for Hodgkin lymphoma but might cause dose-dependent cardiotoxicity and second neoplasms. A recent analysis of a large cohort of patients with former Hodgkin lymphoma revealed that cumulative doxorubicin exposure of more than 200 mg/m² is independently associated with a 1·5-fold increased risk of developing breast cancer.[30] Among contemporary strategies available for first-line treatment of advanced-stage, classical Hodgkin lymphoma, only response adapted treatment with eBEACOPP or BrECADD allows anthracycline exposure below this crucial threshold. Patients with PET-2-negative disease receive a cumulative dose of 160 mg/m² doxorubicin with the BrECADD regimen, and even the maximum anthracycline dose is 240 mg/m² with six cycles of BrECADD, which is still less than ABVD-based regimens (300 mg/m² for all patients). Moderate anthracycline exposure with PET-2-guided BrECADD might also reduce the risk of developing cardiomyopathy and congestive heart failure, which are known late cumulative dose-related effects of treatment with anthracyclines.[31]

The tolerability of intensive chemotherapy for advanced-stage, classical Hodgkin lymphoma is sex-dependent.[32] Female patients tend to suffer more treatment-related toxicities than male patients when treated with the same doses of polychemotherapy. This increase in toxicity is associated with a better progression-free survival. In this trial, female patients showed greater benefit than male patients in terms of treatment-related morbidity and progression-free survival, indicating a particularly favourable risk–benefit ratio of BrECADD for female patients.

Our analysis comes with limitations. First, adult patients older than 60 years were excluded because the standard treatment eBEACOPP is only recommended in patients aged 18–60 years. Accordingly, both safety and efficacy in this relevant cohort of adult patients with advanced-stage, classical Hodgkin lymphoma cannot be estimated from our trial. Based on the observed safety profile, the protocol was amended for patients aged 61–75 years for treatment with BrECADD in a separate phase 2 cohort. These results are not yet available and will be reported separately. Second, the results of this study are only applicable to clinical routine care, if the local health-care infrastructure provides sufficient resources to manage the relevant likelihood of fever and infection. The strengths of our trial include a robust study design and a large patient cohort, allowing us to draw firm conclusions. Additionally, central pathology

review and validation of the primary efficacy endpoint by central review increases the validity of the reported results. Moreover, the trial was conducted in several countries and at all different levels of patient care, including private practices and primary care hospitals. Therefore, our results reflect a real-world setting, at least in the participating countries.

In conclusion, PET-2-guided BrECADD showed unexpectedly high efficacy with improved tolerability, substantially surpassing that of eBEACOPP. With the individualised PET-2-guided, shortened treatment, the BrECADD regimen shows a favourable risk–benefit profile for most patients. Therefore, we recommend BrECADD as a standard treatment option for adult patients with newly diagnosed, advanced-stage, classical Hodgkin lymphoma.

Contributors

PB, JF, and GS wrote the first draft. GS did the statistical analysis. GS and HK directly accessed and verified the underlying data reported in the manuscript. PB, AM, RG, MHe, VS, AH, FK, JD, MHä, UN, JM, AZi, SMat, JMZ, AF, AV, BH, SMar, PG, SS, MST, WJ, VV, H-JB, AK, BU, ARa, RS, CMzB, MdW, KT-G, PK, and DM directed clinical activities at the participating study centres. AM, RG, MHe, JMZ, PK, and DM were national sponsor representatives for the study. ARo and WK did the central pathology review. JF, MF, HT-E, CB, MD, and CK did the central PET review. MF directed activities at the GHSG trial co-ordination centre. PB is the principal investigator of the study and led the design of the protocol. All authors contributed to data interpretation, had full access to all the data in the study, and had final responsibility for the decision to submit for publication.

Declaration of interests

PB reports consulting fees from Takeda, BMS, Roche, Amgen, Novartis, Celgene, Miltenyi Biotech, and Gilead; payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from Takeda, Novartis, BMS, Roche, MSD, Celgene, Miltenyi Biotech, Gilead, and AbbVie; and funding for scientific research from Takeda Oncology, MSD, and Novartis. JF reports funding and consulting fees from Takeda Oncology and payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from Takeda Oncology and Roche Pharma. 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Data sharing

Individual patient data from this trial will not be published in the public domain; however, the trial protocol is provided in appendix 2 and will be available online for an indefinite period.

Acknowledgments

This study was supported by a research grant from Takeda Oncology. We thank our patient representatives Lotte Kirch and Maximilian Büttner, whose experience and open-mindedness have substantially influenced our interpretation of the study results. We thank the members of the independent data monitoring committee, Walter Lehmacher, Martin Hutchings, Guido Schwarzer, Anton Hagenbeek, and Frank Morschhauser, for their valuable input and support.

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