PET-adapted treatment for newly diagnosed advanced Hodgkin lymphoma (AHL2011): a randomised, multicentre, non-inferiority, phase 3 study

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Summary

Background Increased-dose bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone ($BEACOPP_{escalated}$) improves progression-free survival in patients with advanced Hodgkin lymphoma compared with doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD), but is associated with increased risks of haematological toxicity, secondary myelodysplasia or leukaemia, and infertility. We investigated whether PET monitoring during treatment could allow dose de-escalation by switching regimen ($BEACOPP_{escalated}$ to ABVD) in early responders without loss of disease control compared with standard treatment without PET monitoring.

Methods AHL2011 is a randomised, non-inferiority, phase 3 study done in 90 centres across Belgium and France. Eligible patients were aged 16–60 years and had newly diagnosed Hodgkin lymphoma, excluding nodular lymphocyte predominant subtype, an Eastern Cooperative Oncology Group performance status score less than 3, a life expectancy of at least 3 months, an Ann Arbor disease stage III, IV, or IIB with mediastinum-to-thorax ratio of 0·33 or greater than or extranodal localisation, and had received no previous treatment for Hodgkin lymphoma. Randomisation was unmasked and done centrally by the permuted block method. Patients were randomly assigned to standard treatment ($BEACOPP_{escalated}$ given every 21 days for six cycles) or PET-driven treatment. All patients received two cycles of upfront $BEACOPP_{escalated}$, after which PET assessment was done (PET2). In the standard treatment group, PET2 patients completed two additional cycles of $BEACOPP_{escalated}$ induction therapy irrespective of PET2 findings. In the PET-driven treatment group, patients with positive PET2 scans received the further two cycles of $BEACOPP_{escalated}$ and those with a negative PET2 scan switched to two cycles of ABVD for the remaining induction therapy. In both treatment groups, PET at the end of induction therapy was used to decide whether to continue with consolidation therapy in those with negative scans or start salvage therapy in patients with positive scans (either two cycles of ABVD in PET2-negative patients in the PET-driven arm or two cycles of $BEACOPP_{escalated}$). $BEACOPP_{escalated}$ consisted of bleomycin 10 mg/m² and vincristine 1·4 mg/m² intravenously on day 8, etoposide 200 mg/m² intravenously on days 1–3, doxorubicin 35 mg/m² and cyclophosphamide 1250 mg/m² intravenously on day 1, 100 mg/m² oral procarbazine on days 1–7, and 40 mg/m² oral prednisone on days 1–14. ABVD was given every 28 days (doxorubicin 25 mg/m², bleomycin 10 mg/m², vinblastine 6 mg/m², and dacarbazine 375 mg/m² intravenously on days 1 and 15). The primary endpoint was investigator-assessed progression-free survival. Non-inferiority analyses were done by intention to treat and per protocol. The study had a non-inferiority margin of 10%, to show non-inferiority of PET-guided treatment versus standard care with 80% power and an alpha of 2·5% (one-sided). This study is registered with ClinicalTrials.gov, number NCT01358747.

Findings From May 19, 2011, to April 29, 2014, 823 patients were enrolled—413 in the standard care group and 410 in the PET-driven group. 346 (84%) of 410 patients in the PET-driven treatment group were assigned to receive ABVD and 51 (12%) to continue receiving $BEACOPP_{escalated}$ after PET2. With a median follow-up of 50·4 months (IQR 42·9–59·3), 5-year progression-free survival by intention to treat was 86·2%, 95% CI 81·6–89·8 in the standard treatment group versus 85·7%, 81·4–89·1 in the PET-driven treatment group (hazard ratio [HR] 1·084, 95% CI 0·737–1·596; p=0·65) and per protocol the values were 86·7%, 95% CI 81·9–90·3 and 85·4%, 80·7–89·0, respectively (HR 1·144, 0·758–1·726; p=0·74). The most common grade 3–4 adverse events were leucopenia (381 [92%] in the standard treatment group and 387 [95%] in the PET-driven treatment group), neutropenia (359 [87%] and 366 [90%]), anaemia (286 [69%] *vs* 114 [28%]), thrombocytopenia (271 [66%] and 163 [40%]), febrile neutropenia (145 [35%] and 93 [23%]), infections (88 [22%] and 47 [11%]), and gastrointestinal disorders (49 [11%] and 48 [11%]). Serious adverse events related to treatment were reported in 192 (47%) patients in the standard treatment group and 114 (28%) in the PET-driven treatment group, including infections (84 [20%] of 412 *vs* 50 [12%] of 407) and febrile neutropenia (21 [5%] *vs* 23 [6%]). Six (1%) patients in the standard care group died from treatment-related causes (two from septic shock, two from pneumopathy, one from heart failure, and one from acute myeloblastic leukaemia), as did two (<1%) in the PET-driven treatment group (one from septic shock and one from acute myeloblastic leukaemia).

Interpretation PET after two cycles of induction BEACOPP$_{escalated}$ chemotherapy safely guided treatment in patients with advanced Hodgkin lymphoma and allowed the use of ABVD in early responders without impairing disease control and reduced toxicities. PET staging allowed accurate monitoring of treatment in this trial and could be considered as a strategy for the routine management of patients with advanced Hodgkin lymphoma.

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Introduction

Six to eight cycles of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) chemotherapy of which four cycles can be considered the induction part of the treatment (doxorubicin, bleomycin, vinblastine, and dacarbazine) is widely used as standard treatment for Hodgkin lymphoma. However, standard treatment of six cycles, of which four cycles can be considered as induction treatment of escalated BEACOPP (increased bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone; BEACOPP$_{escalated}$), which was developed by the German Hodgkin Study Group (GHSG),[1] delivers more drugs at higher dose intensities and seems to improve patients' outcomes. BEACOPP$_{escalated}$ ovides 10-year failure-free survival of 82% (95% CI 78–86) and overall survival of 86% (83–90).[2] Four studies have shown improved disease control with BEACOPP$_{escalated}$ and a 15% improvement in 3-year progression-free survival compared with ABVD in patients with advanced Hodgkin lymphoma.[3–6] A meta-analysis[7] has also shown overall survival benefit in favour of BEACOPP$_{escalated}$ compared with ABVD, although formal proof of this benefit in a randomised trial is not available. A drawback of treatment with BEACOPP$_{escalated}$ chemotherapy, however, is marked and frequent—albeit manageable—immediate haematological toxicity and a higher risk of secondary myelodysplasia and leukaemia than with ABVD.[2,8] Additionally, BEACOPP$_{escalated}$-associated gonadal toxicity is

Research in context

Evidence before this study

We searched Medline up to Aug 22, 2018, for papers reporting prospective trials of PET-guided treatment for advanced Hodgkin lymphoma, with the search terms "Hodgkin", "lymphoma", "advanced or Stage III IV", and "PET2 or interim PET", with no language restrictions. At the time of planning the AHL2011 trial, two randomised phase 3 studies in patients with advanced Hodgkin lymphoma that had compared upfront ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) and an escalated BEACOPP regimen (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone; BEACOPP$_{escalated}$) showed that the latter significantly reduced the risk of treatment failure but at the cost of increased toxicity. Since the AHL2011 study started, two studies and one meta-analysis have been published that confirmed the benefit of BEACOPP$_{escalated}$ over ABVD. To minimise exposure to BEACOPP$_{escalated}$ without compromising disease control, PET performed after two cycles of chemotherapy, a timepoint that has strong prognostic value, could allow guidance of dose intensity for further chemotherapy. One phase 3 study of PET-guided treatment, the HD18 study, tested giving four instead of six or eight cycles of BEACOPP$_{escalated}$ in two cycles of chemotherapy, negative patients with advanced Hodgkin lymphoma after upfront BEACOPP$_{escalated}$, and showed that two further cycles of BEACOPP$_{escalated}$ was non-inferior to four or six further cycles.

Added value of this study

To our knowledge, AHL2011 is the first multicentre study that compares head-to-head standard and PET-driven treatment strategies in patients with advanced Hodgkin lymphoma. We used Deauville criteria enhanced by maximum standardised uptake value thresholds to classify PET-positive and PET-negative patients. The proportion of patients in the PET-driven group eligible for de-escalated treatment with ABVD reached 84%, which is around double the 48% reported previously, and we saw no loss of disease control compared with standard BEACOPP$_{escalated}$ treatment. Delivering ABVD in PET-negative patients was also associated with less grade 3–4 haematological toxicity than previously reported in the HD18 study. Assessment with PET after four cycles of treatment provided prognostic information and identified a subset of patients with particularly poor outcomes. Indeed, the full interim PET assessment indicated three subgroups of patients with significantly different outcomes.

Implications of all the available evidence

Cumulative evidence from six trials show that PET-driven strategies after upfront BEACOPP$_{escalated}$ provide improved disease control compared with upfront ABVD and could be a useful treatment option for patients with advanced Hodgkin lymphoma . The de-escalation of treatment in patients with negative PET scans after two cycles of BEACOPP$_{escalated}$ by switching to ABVD seems to be a safe treatment option for routine practice. Using Deauville scores of less than 4 and maximum standardised tumour uptake values of less than 40% to indicate PET negativity allowed accurate identification of patients eligible for de-escalation treatment. Our interim PET staging approach after two and four cycles of chemotherapy could be considered for use in the routine management of patients with advanced Hodgkin lymphoma.

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a concern in young patients and the risk increases with the number of cycles delivered and the age of patients (higher risk in older patients).[9]

Due to the toxicity issues, we wanted to identify whether de-escalation of dose intensity after upfront BEACOPP$_{escalated}$ could be beneficial in terms of safety and efficacy, and whether any patients would benefit from longer treatment with BEACOPP$_{escalated}$ rather than switching to ABVD. Interest has been growing in the early use of fluorodoxyglucose (FDG) PET to improve prediction of response to treatment and to drive therapy decisions for patients with Hodgkin lymphoma. PET done after two courses of chemotherapy (PET2) can predict progression-free survival[10,11] with a negative predictive value of 98% in patients treated with BEACOPP$_{escalated}$.[12] Thus, PET2 might enable identification of early responders who are suitable for ABVD chemotherapy de-escalation after two cycles of upfront BEACOPP$_{escalated}$.[12,13] We designed the AHL2011 study to assess a PET-driven strategy after two cycles of BEACOPP$_{escalated}$ to decide the subsequent treatment in PET2-negative patients (switch ABVD) and PET2-positive patients (continue with BEACOPP$_{escalated}$) compared with standard care of six cycles of BEACOPP$_{escalated}$ without PET2 monitoring in patients with advanced Hodgkin lymphoma.

Methods

Study design and participants

This open-label, multicentre, randomised, phase 3 study was designed by the Lymphoma Study Association scientific committee and done in 90 centres across Belgium and France (appendix pp 6–8). Eligible patients were aged 16–60 years and had newly diagnosed Hodgkin lymphoma according to WHO 2008 criteria, excluding nodular lymphocyte predominant subtype; an Eastern Cooperative Oncology Group performance status score less than 3; minimum life expectancy of 3 months; and Ann Arbor disease stage III, IV, or IIB with a mediastinum-to-thorax ratio of 0·33 or greater or extranodal localisation. Additionally, eligible patients had to have received no previous treatment for Hodgkin lymphoma and had a baseline PET scan (PET0) done before treatment that showed at least one hypermetabolic lesion. Patients also had to have negative HIV, hepatitis C virus, and human T-lymphotropic serology and normal liver (bilirubin <2·5 times the upper limit of normal), renal (creatinine ≤150 µmol/L), and haematological functions (leucocyte count ≥2000 per µL [≥2·0×10^9 per L] and platelet count ≥100×10^3 per µL [≥100×10^9 per L]) unless abnormalities were related to Hodgkin lymphoma. We excluded patients with severe cardiopulmonary (left ejection ventricular fraction <50% or respiratory insufficiency prohibiting bleomycin use) or metabolic disease (uncontrolled diabetes mellitus) that would interfere with normal application of the study treatment protocols. The complete eligibility criteria are in the study protocol (appendix p 28).

See Online for appendix

All patients provided written, informed consent before enrolment. The study was approved by the French and Belgian Health authorities, the Dijon Hospitals Ethics Committee and by the institutional review boards of each participating site in Belgium, and was done in accordance with the Declaration of Helsinki and the International Conference on Harmonisation Guidelines for Good Clinical Practice.

Randomisation and masking

Patients were enrolled by centre with the LYSARC e-Rando system. The software used was version 6.0–6.2 Capture System (CS) Randomization from Clinsight. Each patient was created in CS online, and all the information required for inclusion were entered. The patient was directly randomly assigned if all inclusion criteria were met. Patients were randomly assigned (1:1) to receive standard treatment or PET-driven treatment. Randomisation was done centrally with the permuted block method and stratified according to Ann Arbor stage (IIB *vs* III–IV) and international prognosis score (IPS; 0–2 *vs* ≥3). The randomisation list was generated by LYSARC. Patients and investigators were not masked to treatment allocation.

All PET images were sent through a web platform[14] and masked for independent central review by three expert reviewers (AB-R, VE, MM).

Procedures

During induction treatment, all patients received two cycles of upfront BEACOPP$_{escalated}$, after which PET was done. In the standard treatment group patients completed four cycles of BEACOPP$_{escalated}$ irrespective of the findings on PET2. In the PET-driven treatment group, patients with positive PET2 scans continued with two further cycles of induction BEACOPP$_{escalated}$ and those with negative PET2 scans switched to ABVD for the remaining two cycles of chemotherapy (appendix p 1). Consolidation treatment for all patients was decided based on the results of PET at the end of the four cycles of induction chemotherapy (PET4). If the PET4 scan was negative, patients in the standard treatment group received two further cycles of BEACOPP$_{escalated}$ and those in the PET-driven treatment group received two further cycles of BEACOPP$_{escalated}$ or ABVD. PET4-positive patients in both treatment groups were classified as non-responders and salvage therapy was considered at the discretion of the investigator.

BEACOPP$_{escalated}$ was repeated every 21 days and included 10 mg/m² bleomycin and 1·4 mg/m² vincristine given intravenously on day 8, 200 mg/m² etoposide given intravenously on days 1–3, 35 mg/m² doxorubicin and 1250 mg/m² cyclophosphamide given intravenously on day 1, 100 mg/m² procarbazine given orally on days 1–7, and 40 mg/m² prednisone given orally from day 1 to 14. ABVD was repeated every 28 days and included 25 mg/m² doxorubicin, 10 mg/m² bleomycin, 6 mg/m² vinblastine,

and 375 mg/m² dacarbazine given intravenously on days 1 and 15. Commercial granulocyte-colony-stimulating factor administration was mandatory during treatment with $BEACOPP_{escalated}$ and was given on day 9 of each cycle until neutrophil count reached more than 1000 per µL ($>1{\cdot}0\times10^9$ per L), and was optional after ABVD cycles. Chemotherapy dose reductions were permitted according to the rules detailed in the study protocol (appendix pp 31–33). 800 mg sulfamethoxazole and 160 mg trimethoprim given 3 days per week and valacyclovir 1000 mg/day were given to all patients during all cycles of chemotherapy as prophylaxis against opportunistic infections.

All eligible patients had a baseline PET scan. PET2 was scheduled 3 weeks after the second induction cycle of $BEACOPP_{escalated}$ and PET4 was scheduled 2 or 3 weeks after the completion cycle of induction chemotherapy (four cycles). Patients were scanned on the same camera for all PET scans. Whole-body acquisition from groin to head was started within 60 min (within 10 min more or less) of injection of 5 MBq/kg ^{18}F-FDG.

All PET images were centrally reviewed by three expert reviewers. The interpretations of PET2 and PET4 were binary based on the Deauville criteria for ^{18}F-FDG uptake[15,16] (Deauville scores 1–3 negative and Deauville scores 4 or 5 positive), and the final decision was based on at least two concordant responses. To improve the inter-observer reproducibility of PET2 and PET4 interpretations, we supplemented Deauville scores 4 and 5 (visual judgement of moderate and marked uptake) with tumour maximum standardised uptake value thresholds of 40% and 100% greater than in the liver, respectively.[20] The centrally reviewed PET results were sent back to the investigators, together with the per-protocol recommended treatment allocation for patients in the PET-driven treatment group.

The following assessments were mandatory: chest x-ray at baseline to estimate the mediastinum-to-thorax ratio; CT after four cycles of chemotherapy, at the end of treatment, and every 6 months thereafter until the end of follow-up; bonemarrow aspiration at baseline and after four cycles of chemotherapy (end of induction) to confirm complete remission in patients with positive baseline results; and haematological laboratory assessments before each cycle of chemotherapy and at least twice per week during the treatment period. Response to treatment was assessed with Cheson 2007 criteria.[21] PET2 or PET4 positivity without these criteria being met was not taken to indicate progression-free survival. Study treatment was stopped if patients showed lymphoma progression, had toxic effects from study treatment, concomitant illness or protocol violations that precluded continuation of study treatment, started a new treatment for Hodgkin lymphoma, withdrew consent, or refused to continue treatment.

Treatment-emergent adverse events were assessed after each cycle of chemotherapy and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3, and treatment-related toxicities were reported by study group.

We also assessed fertility parameters of patients younger than 45 years before and after study treatment (appendix pp 35, 36, 37, 78, and 79), the results of which will be reported elsewere. We report here on the number of pregnancies after treatment completion in both treatment groups.

Whether the maximum standardised uptake value reduced between PET0 and PET2 or PET4 and whether reductions affected responses (event-free, disease-free, progression-free, and overall survival) in both treatment groups was assessed and will be reported elsewhere.

The relative dose intensity of the $BEACOPP_{escalated}$ regimen drugs was assessed according to the following formula for each drug:

$$\frac{\text{administered dose / expected dose}}{\text{observed administration duration / expected administration duration}}\times 100$$

We did some prespecified subgroup analyses of progression-free survival comparing responders and non-responders at PET2 and PET4 and comparing also patients according to the results of the full PET strategy combining the results of both PET2 and PET4.

Outcomes

The primary endpoint was progression-free survival based on investigator assessment and defined as the time from randomisation to first progression, relapse, or death from any cause or last follow-up. The key secondary endpoints were safety, overall response, event-free survival, disease-free survival, and overall survival. Event-free survival was defined as the time from randomisation to the first documented disease progression, relapse, start of a new antilymphoma therapy, death from any cause, or last follow-up. Disease-free survival was defined as the time that complete response was recorded to the date of first documented disease progression, relapse or death related to lymphoma, toxicity from the study treatment (including treatment-related secondary cancer), unknown cause, or last follow-up. Overall survival was defined as the time from randomisation to death from any cause or last follow-up.

Additional secondary endpoints were assessment of the reduction in the maximum standardised PET uptake value over treatment and its correlation with response and survival outcomes, and the study of fertility parameters in patients younger than 45 years. Biological and genetic parameters influencing early response to treatment and progression-free survival assessed by PET will be reported elsewhere.

Statistical analysis

We assessed the efficacy of PET-driven treatment compared with standard treatment in terms of progression-free survival. We hypothesised non-inferiority based on a clinical acceptable margin of 10%

on progression-free survival at 5 years, corresponding to 5-year progression-free survival greater than 75% in the PET-driven group (ie, non-inferior to standard treatment but better than the 70% 5-year progression-free survival reported with ABVD[3,4]), and non-inferiority was established if the upper limit of the hazard ratio (HR) was lower than 1·77 with an alpha of 2·5% (one-sided test) and a power of 80%. The sample size calculation used an exponential model and was based on an estimate of 85% 5-year progression-free survival in the standard treatment group. Non-inferiority was tested in a post-hoc analysis using the Com-Nougue test.[22] We calculated that 97 progression-free survival events were required to achieve 80% power with a one-sided significance level set at 0·025 in the final analysis. We planned to enrol 810 patients; the power calculation did not account for dropouts. An interim analysis of the primary endpoint to test for futility was planned according to the Lan-DeMets sequential design[23] after 50% of the scheduled events needed for the final analysis had been recorded. This was done in 2015 (data cutoff date July 1, 2014) and showed no significant difference in progression-free survival between the two study groups, leading the data and safety monitoring committee to recommend continuing the study.

	Standard treatment group (n=413)	PET-driven treatment group (n=410)
Median (IQR) age (years)	31 (23–41)	29 (24–40)
Men	263 (64%)	253 (62%)
Women	150 (36%)	157 (38%)
ECOG score		
0	203 (49%)	193 (47%)
1	181 (44%)	184 (45%)
2	27 (7%)	31 (8%)
Missing	2 (<1%)	2 (<1%)
B symptoms	282 (68%)	278 (68%)
Ann Arbor stage		
I	0	2 (<1%)
II	44 (11%)	52 (13%)
III	114 (28%)	115 (28%)
IV	255 (62%)	241 (59%)
Stage IIA	2 (<1%)	7 (2%)
Stage IIB	42 (10%)	45 (11%)
Mediastium to thorax ratio ≥0·33	41 (98%)	45 (100%)
Extra nodal localisation	6 (14%)	4 (9%)
Bulky mass		
≥10 cm	143 (35%)	134 (33%)
<10 cm	233 (56%)	229 (56%)
Missing	37 (9%)	47 (11%)
Bone marrow involved	33 (8%)	32 (8%)
International prognosis score		
0–2	160 (39%)	183 (45%)
≥3	250 (61%)	225 (55%)
Missing	3 (<1%)	2 (<1%)
Pathology review		
Hodgkin lymphoma		
Nodular sclerosis	273 (74%)	264 (74%)
Mixed cellularity	20 (5%)	22 (6%)
Lymphocyte-depleted	2 (<1%)	3 (<1%)
Lymphocytes rich	2 (<1%)	1 (<1%)
Interfollicular	1 (<1%)	0
Unclassified	51 (14%)	61 (17%)
Grey zone lymphoma	20 (5%)	3 (<1%)
Anaplastic large cell lymphoma ALK negative	0	2 (<1%)
EBV-associated B-cell lymphoproliferative disorder	1 (<1%)	0
Insufficient material	1 (<1%)	1 (<1%)
Missing	42 (10%)	53 (13%)

Data are number (%) unless stated otherwise. ECOG=Eastern Cooperative Oncology Group. ALK=anaplastic lymphoma kinase. EBV=Epstein-Barr virus.

Table 1: **Baseline characteristics**

The data cutoff for the analyses presented here was Oct 31, 2017. The analysis of progression-free and overall survival was done by intention to treat (ITT), including all patients randomly assigned to a treatment group. Prespecified sensitivity analyses included an unstratified analysis and a per-protocol analysis that excluded patients with major protocol deviations, which was considered to be more conservative and to support the non-inferiority objective. Major protocol violations were unconfirmed diagnosis of Hodgkin lymphoma, at least one inclusion or exclusion criterion not respected, first cycle of chemotherapy not received or not received at full dose, PET2 or PET4 not done at the right time, central review of PET2 or PET4 not done, and further treatment not assigned according to PET results. Safety was assessed in patients who received at least one dose of study treatment.

Survival estimates with 95% CIs were calculated with the Kaplan-Meier method. The survival distributions were compared with the log-rank test, and Cox proportional hazard regression models were used to estimate HRs and associated 95% CIs.

To compare the relative effect of the full PET-driven strategy on progression-free and overall survival by baseline characteristics found to influence outcomes in a univariate analysis, a Cox proportional hazard regression model was fitted, including PET profile (PET2 and PET4) and IPS as explanatory variables. Response and PET2 and PET4 results were expressed with 95% exact Clopper Pearson CI limits and compared with the χ^2 test.

Differences between groups were significant if p values were less than 0·025 for progression-free survival and overall survival in respect to the one-sided hypothesis and less than 0·05 for all other analyses.

All outputs were produced with SAS (version 9.3). This study is registered with ClinicalTrials.gov, number NCT01358747.

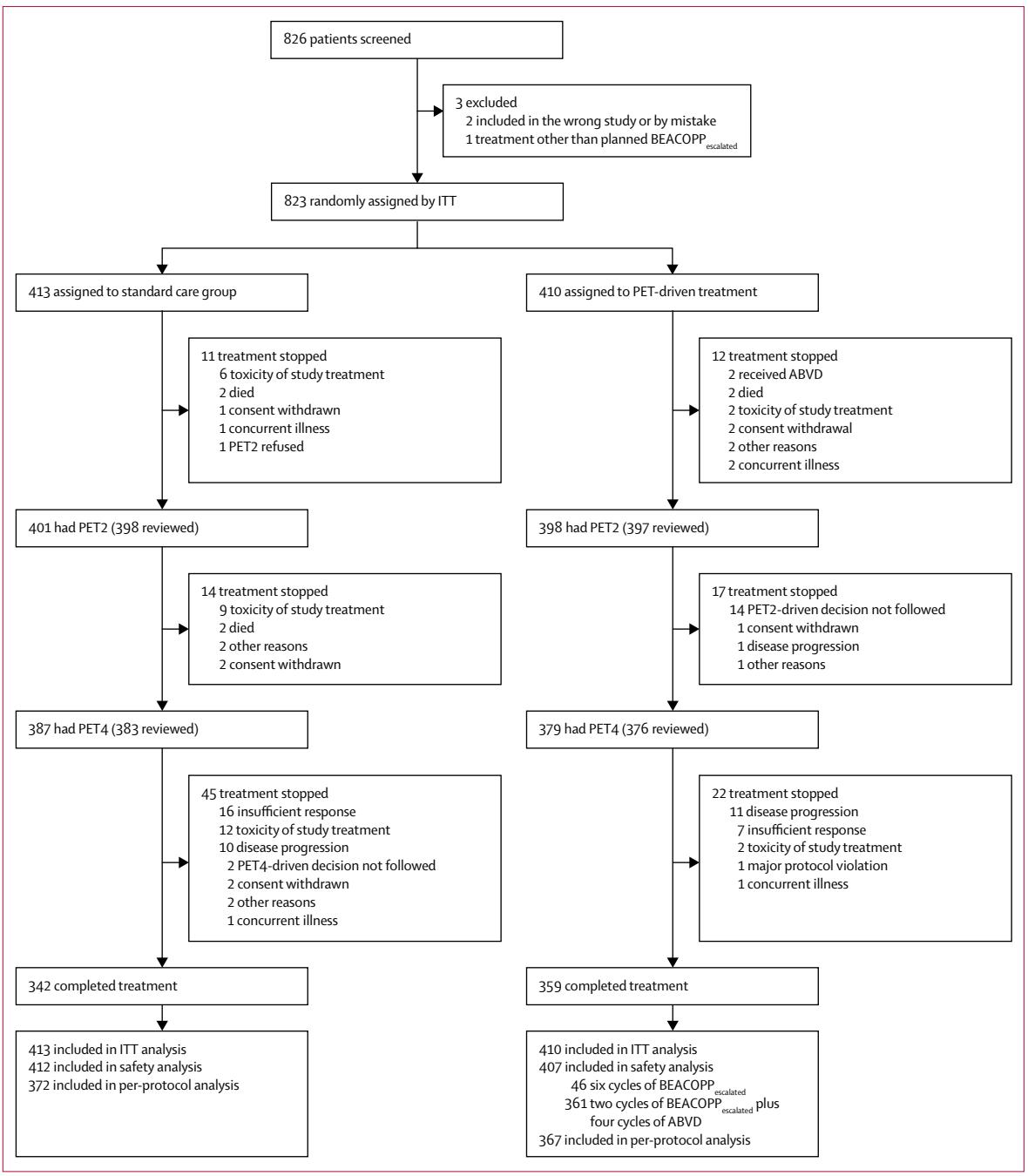

Figure 1: **Trial profile**
In the standard care group, one patient stopped treatment after 4 cycles and did not do PET2, and one patient who stopped treatment after five cycles and did not do PET4 . In the PET-driven treatment group, two patients who did not do PET4 completed the treatment. ABVD=doxorubicin, bleomycin, vinblastine, dacarbazine. $BEACOPP_{escalated}$=increased-dose bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone. ITT=intention to treat. PET2=PET after two induction cycles. PET4=PET after four induction cycles. *One patient is included in the toxicity of study treatment and withdrew categories.

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. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results
From May 19, 2011, to April 29, 2014, 826 patients were assessed for eligibility and 823 were enrolled and randomly assigned to receive either standard treatment (n=413) or PET-driven treatment (n=410). The characteristics of the patients were well balanced across the

	Standard treatment group (n=413)		PET-driven treatment group (n=410)	
	Number of patients (%)	5-year progression-free survival (95% CI)	Number of patients (%)	5-year progression-free survival (95% CI)
PET after two induction cycles				
Reviewed	398 (96%)		397 (97%)	
Negative	349 (88%)	88·4% (83·3–92)	346 (87%)	89·4% (84·9–92·6)
Positive	49 (12%)	73·5% (58·7–83·6)	51 (13%)	68·2% (53·4–79·2)
PET after four induction cycles				
Reviewed	383 (93%)		376 (92%)	
Negative	356 (93%)	90·1% (85·3–93·3)	360 (96%)	89·2% (84·8–92·3)
Positive	27 (7%)	51·9% (31·9–58·5)	16 (4%)	37·5% (25·4–59·8)

Data are number (%) unless stated otherwise.

Table 2: **Metabolic response according to PET central review after two and four cycles of chemotherapy**

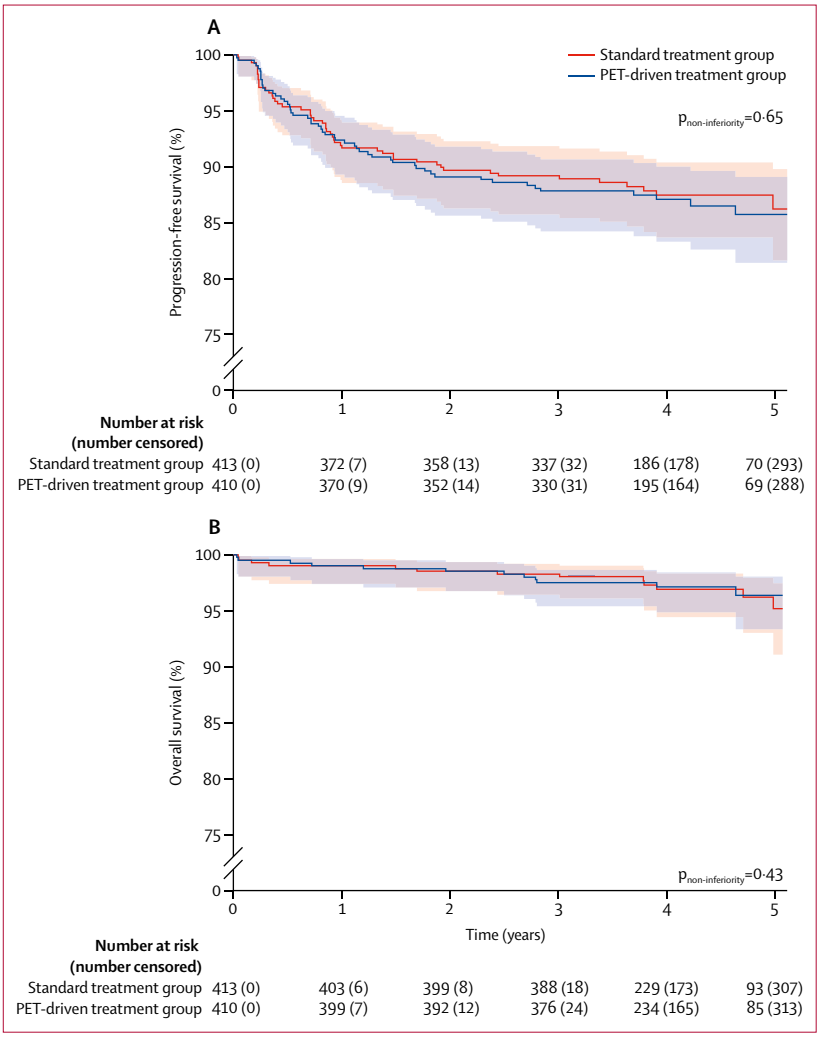

Figure 2: **Kaplan-Meier curves of survival outcomes by treatment group in the intention-to-treat population**
(A) Progression-free survival. (B) Overall survival. Data are survival estimates with 95% CIs.

two treatment groups at baseline (table 1). The median age at baseline was 30 years (IQR 24–41), 516 (63%) of 823 patients were men, 560 (68%) had B symptoms, 725 (89%) had stage III or IV disease and 87 (11%) a stage IIB with risk factors, and 475 (58%) had an IPS of 3 or greater. 728 (88%) of 823 patients had biopsy pathology assessed centrally, among whom 700 (96%) had a confirmed diagnosis of Hodgkin lymphoma. Most cases of misdiagnosis were grey zone lymphoma with features intermediate between diffuse large B-cell lymphoma and Hodgkin lymphoma. 342 (83%) patients in the standard treatment group and 359 (88%) in the PET-driven treatment group completed the planned treatment (figure 1). Ten patients in the standard care group and 12 patients in the PET-driven treatment group discontinued treatment because of disease progression, and 27 and four, respectively, discontinued because of treatment-related toxicity (figure 1).

799 (97%) of 823 patients had evaluable PET2 scans and 795 (99%) of these were reviewed centrally. PET2 scans were negative in 695 (87%) patients (table 2). In the ITT population, 346 (84%) of the 410 patients in the PET-driven group were assigned to receive ABVD and 51 (12%) to four additional cycles of $BEACOPP_{escalated}$ (table 2). 14 (4%) patients did not receive the allocated treatment because of clinician decision: nine patients were given $BEACOPP_{escalated}$ instead of ABVD and five received ABVD instead of $BEACOPP_{escalated}$.

At the time of the analysis, median follow-up was 50·4 months (IQR 42·9–59·3). Progression-free survival events occurred in 103 (13%) of 823 patients: 41 (10%) of 413 in the standard treatment group and 47 (12%) of 410 in the PET-driven treatment group progressed or relapsed and two (<1%) and four (1%), respectively, died from lymphoma. Eight (1%) of 823 patients died from toxicity of the study treatment (six in the standard treatment group *vs* two in the PET-driven treatment group), four because of toxicity of additional treatment (three *vs* one), two because of concurrent illness (one in each group) and five for other or unknown reasons (two *vs* three). In the ITT analysis, the estimated 5-year progression-free survival was similar in both treatment groups (86·2%, 95% CI 81·6–89·8 in the standard treatment group and 85·7%, 81·4–89·1 in the PET-driven treatment group; stratified HR 1·084, 95% CI 0·737–1·596, $p_{non\text{-}inferiority}$=0·65; unstratified HR 1·066, 0·725–1·569, $p_{non\text{-}inferiority}$=0·63; figure 2). Median progression-free survival was not reached in either treatment group by the end of the follow-up.

The prespecified per-protocol analysis involved 739 (90%) patients with no major protocol deviations of 823 enrolled (figure 1). 41 (10%) of 413 in the standard treatment group and 43 (10%) of 410 patients in the PET-driven treatment group were excluded from the per-protocol analysis because of unconfirmed Hodgkin lymphoma diagnosis (n=21 and n=5, respectively), one or more unmet inclusion or exclusion criteria (n=4 and n=3), the first cycle of chemotherapy not being received or not being given at full dose (n=7 and n=8), PET2 or PET4 not being done at the right time (n=5 and n=7), PET2 or PET4 not being centrally reviewed (n=3 and

	Number of patients (%)	5-year progression-free survival (95%CI)	Univariate analysis		Multivariate analysis	
			HR (95% CI)	p value	HR (95% CI)	p value
PET assessments						
PET2 and PET4 negative	654 (79%)	92·5 (90·1–94·3)	..	..	..	..
PET2 positive, PET4 negative	62 (8%)	75·4 (62·5–84·4)	3·59 (2·01–6·40)	<0·0001	2·57 (1·33–4·92)	0·0046
PET4 positive	43 (5%)	46·5 (31·2–60·4)	13·14 (7·98–21·62)	<0·0001	10·37 (6·03–17·79)	<0·0001
Sex						
Female	516 (63%)	88·2 (81·9–92·5)	..	..	..	..
Male	307 (37%)	84·6 (81·1–87·5)	1·73 (1·11–2·68)	0·013	1·41 (0·84–2·35)	0·19
Eastern Cooperative Oncology Group score						
0	396 (48%)	87·8 (84–90·8)	..	..	..	..
1	365 (44%)	84·3 (78·7–88·5)	1·14 (0·75–1·72)	0·53	0·85 (0·52–1·38)	0·44
2	58 (7%)	86·1 (74·1–92·8)	1·29 (0·61–2·74)	0·50	1·27 (0·57–2·84)	0·34
B symptoms						
No	263 (32%)	88·6 (83·5–92·2)	..	..	..	..
Yes	560 (68%)	84·7 (80·8–87·9)	1·41 (0·90–2·18)	0·12	1·06 (0·60–1·83)	0·037
Ann Arbor stage						
IIB	87 (11%)	86·3 (76·3–92·3)	..	..	..	..
III–IV	725 (89%)	85·8 (82·5–88·5)	1·00 (0·53–1·86)	0·43	1·25 (0·57–2·74)	0·32
Bulk						
<10 cm	462 (63%)	87·8 (83·4–91·1)	..	..	..	..
≥10 cm	277 (37%)	83·6 (78·4–87·7)	1·60 (1·05–2·42)	0·027	1·246 (0·76–2·01)	0·79
International prognosis score						
0–2	343 (42%)	91·9 (88·4–94·4)	..	..	..	..
≥3	475 (58%)	83·7 (79·9–86·9)	1·92 (1·24–2·94)	0·0025	1·60 (0·72–2·03)	0·044

HR=hazard ratio. PET2=PET after two cycles of chemotherapy. PET4=PET after four cycles of chemotherapy.

Table 3: **Analysis of progression-free survival**

n=4), or treatment not being assigned according to PET2 or PET4 results (n=1 and n=16). In the per-protocol analysis, 5-year progression-free survival was 86·7% (95% CI 81·9–90·3) in the standard treatment group *vs* 85·4% (80·7–89·0) in the PET-driven treatment group (HR 1·144 [95% CI 0·758–1·726], p=0·74).The post-hoc Com-Nougue non-inferiority test gave a similar conclusion by rejecting the null hypothesis (p=0·0047).

Overall survival was similar in the two treatment groups. Overall survival events occurred in ITT and per protocol populations in 13 (3%) of 413 and 10 (3%) of 372 in the standard treatment group, respectively and 12 (3%) of 410 and 12 (3%) of 367 in the PET-driven treatment group, respectively. In the ITT population, 5-year overall survival was 95·2% (95% CI 91·1–97·4) in the standard treatment group and 96·4% (93·3–98·1) in the PET-driven treatment group (HR 0·936, 95% CI 0·427–2·051, p=0·43; figure 2). In the per-protocol population, the 5-year overall survival values were 95·6% (95% CI 91·2–97·8) and 95·9% (92·5–97·8), respectively (HR 1·248, 95% CI 0·53–2·88, p=0·69). For event-free and disease-free survival, estimates were also similar in the two treatment groups in the ITT population (appendix pp 1–2). 5-year event-free survival was 76·8% (95% CI 71·7–81·0) in the standard treatment group compared with 78·6% (73·9–82·6) in the PET-driven treatment group (HR 0·925, 95% CI 0·686–1·248, p=0·31) and 5-year disease-free survival was 89·9% (85·1–93·2) compared with 90·0% (86·0–92·9; 1·099, 0·667–1·711, p=0·66).

Response rates assessed according to Cheson 2007 criteria after end of induction and end of treatment were similar in the standard and PET-driven groups (appendix, p 2).

766 (93%) of 823 patients had evaluable PET4 scans, of which 759 (99%) were assessed centrally. 716 (94%) of 759 were deemed to have negative scans (table 2). In 654 (86%) of 716 patients with negative PET4 scans, results had also been negative on PET2 scans, whereas in the remaining 62 (9%) the result had converted from positive on PET2 to negative on PET4. 43 patients (6%) with positive PET4 were removed from the study, among whom 13 (2%) had had a previous negative PET2 result, including six patients in the PET-driven treatment group, and 30 (4%) a previous positive PET2.

A positive result on PET2 or PET4 was associated with an increased risk of relapse or progression, regardless of treatment group: 5-year progression-free survival was 70·7% (95% CI, 60·7–78·6) in patients with a positive PET2 scan versus 88·9% (85·7–91·4) in patients with a negative PET2 scan (HR 3·59, 95% CI 2·32–5·56,

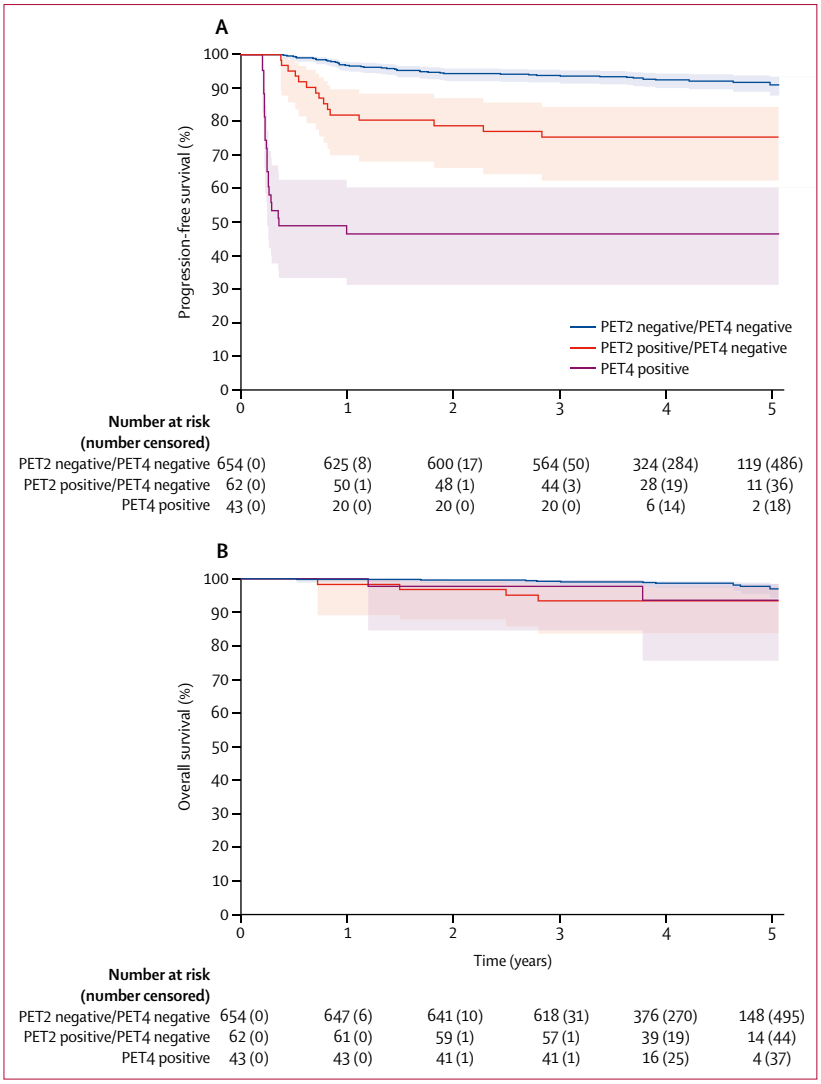

Figure 3: **Kaplan-Meier curves of survival outcomes by PET response**
(A) Progression-free survival. (B) Overall survival. Data are survival estimates with 95% CIs. PET2=PET after two induction cycles. PET4=PET after four induction cycles.

p<0·0001). 5-year progression-free survival was lower in PET4-positive patients compared with those who had negative PET4 scans (46·5%, 95% CI 31·2–60·4 *vs* 89·6%, 86·5–92·0; HR 10·9, 95% CI 6·75–17·61, p<0·0001). The 5-year progression-free survival estimates among PET4-positive patients were similar in the two treatment groups (table 2). 20 (47%) of the 43 patients had progressive disease at the time of the positive PET4 examination and received salvage chemotherapy. Of the remaining 23 patients, 21 continued $BEACOPP_{escalated}$, one received radiotherapy on a residual mediastinal mass, and one proceeded to salvage therapy. Analysis of the full PET-driven strategy by response assessment after two cycles of chemotherapy (PET2) and at end of induction (PET4) identified three prognostic subgroups (f). PET4-positive patients had a lower 5-year progression-free survival than those with negative PET4 scans, irrespective of PET2 results: 75·4% (95% CI 62·5–84·4) in PET2-positive and PET4-negative patients, and 90·9% (95% CI 87·7–93·3) in PET2-negative and PET4-negative patients versus 46·5% (95% CI 31·2–60·4) in PET4-positive patients; both p<0·0001).

Progression-free survival was also significantly different among PET4-negative patients according to PET2 results (HR 3·588, 95% 2·01–6·40, p<0·0001; table 3).

Other factors associated with decreased 5-year progression-free survival were baseline IPS of 3 or more (82·8%, 95% CI 78·5–86·3 in the standard treatment group *vs* 90·3%, 85·8–93·4 in the PET-driven treatment group; HR 1·91, 95% CI 1·25–2·94, p=0·0025), male sex (84·6%, 81·1–87·5 *vs* 88·2%, 81·9–92·5; HR 0·577, 0·37–0·89, p=0·013), and tumour bulk of 10 cm or greater (83·6%, 78·4–87·7 *vs* 87·8, 83·4–91·1; HR 1·60, 1·05–2·24, p=0·027). Eastern Cooperative Oncology Group performance status score, age, Ann Arbor stage, B symptoms, and mediastinum-to-thorax ratio 0·33 or greater had no effect on progression-free survival. Multivariable analysis showed that full PET assessment had prognostic value independently of IPS (table 3).

Patients with a positive PET2 result wre associated with reduced 5-year overall survival compared with those with negative results (92·4% *vs* 96·7%; HR 3·73, 95% CI 1·50–9·24, p=0·0029), whereas patients with a positive PET4 scan did not have an increased risk of death compared with those with a negative PET4 scan (93·6% *vs* 96·8%; 2·569, 0·58–11·28, p=0·19). With the current follow-up, the full PET-driven strategy (PET2 and PET4 combined) had only a marginal effect on overall survival, with 5-year estimate among patients with negative PET2 and PET4 scans being 97·1% (95% CI 94·2–98·5) compared with 93·5% (83·6–98·0) among those with positive PET2 and negative PET4 scans and 93·6% (75·6–98·4, p value for whole comparison=0·039) among those with positive PET4 scans (figure 3). No standard clinical or biological factors, including IPS, were found to significantly affect the risk of death.

The safety population included 819 patients (figure 1). The median relative dose intensity of each drug composing the $BEACOPP_{escalated}$ regimen was similar in the two treatment groups and reached 95% or more of the planned dose in each cycle (appendix p 4). The planned full dose of each drug was achieved in at least 85% of patients (appendix p 5). Overall, 467 (57%) of the 819 patients in the safety population required at least one dose reduction (264 [64%] of 412 patients in the standard care group and 203 [50%] of 407 patients in the PET-driven treatment group). Chemotherapy discontinuation was mainly related to haematological toxicity and infections. 31 patients discontinued treatment because of toxicity of the study treatment, mainly in the standard treatment group (27 [7%] of 413 compared with four [<1%] of 410 in the PET-driven treatment group).

	Standard treatment group (n=412)				PET-driven treatment group (n=407)			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
Blood and lymphatic system disorders								
Anaemia	402 (98%)	249 (60%)	37 (9%)	0	394 (97%)	107 (26%)	7 (2%)	0
Leucopenia	189 (46%)	138 (33%)	243 (59%)	0	273 (67%)	102 (25%)	285 (70%)	0
Neutropenia	157 (38%)	65 (16%)	294 (71%)	0	221 (54%)	60 (15%)	306 (75%)	0
Febrile neutropenia	0	129 (31%)	16 (4%)	0	0	85 (21%)	8 (2%)	0
Thrombocytopenia	342 (83%)	148 (36%)	123 (30%)	0	306 (75%)	99 (24%)	64 (16%)	0
Gastrointestinal disorders								
Mucositis	101 (25%)	13 (3%)	3 (<1%)	0	91 (22%)	18 (4%)	1 (<1%)	0
Vomiting	161 (39%)	9 (2%)	1 (<1%)	0	141 (35%)	10 (2%)	0	0
Diarrhoea	93 (23%)	6 (1%)	1 (<1%)	0	88 (22%)	7 (2%)	0	0
Other	280 (68%)	16 (3%)	1 (<1%)	0	291 (72%)	11 (3%)	1 (<1%)	0
General disorders								
Fatigue	262 (64%)	16 (4%)	1 (<1%)	0	228 (56%)	11 (3%)	0	0
Fever	132 (32%)	5 (1%)	3 (1%)	0	125 (31%)	1 (<1%)	1 (<1%)	0
Other	87 (21%)	5 (1%)	3 (1%)	0	96 (24%)	5 (1%)	0	0
Infections and infestations								
Sepsis	3 (<1%)	0	27 (7%)	2 (<1%)	2 (<1%)	0	14 (3%)	0
Lung infection	17 (4%)	12 (3%)	0	0	16 (4%)	4 (1%)	0	0
Other	118 (29%)	45 (11%)	4 (1%)	0	120 (30%)	23 (6%)	5 (1%)	1 (<1%)
Investigation								
AST and/or ALT increased	136 (33%)	12 (3%)	3 (<1%)	0	132 (32%)	9 (2%)	2 (<1%)	0
Creatinine increased	14 (3%)	1 (<1%)	1 (<1%)	0	25 (6%)	0	0	0
Other	92 (22%)	16 (4%)	1 (<1%)	0	80 (20%)	13 (3%)	0	0
Nervous system disorders								
Peripheral neuropathy	85 (21%)	8 (2%)	0	0	87 (21%)	2 (<1%)	0	0
Other	66 (16%)	6 (2%)	0	0	66 (16%)	5 (1%)	0	0
Respiratory, thoracic, and mediastinal disorder								
Pneumonitis	4 (1%)	3 (<1%)	0	0	5 (1%)	3 (<1%)	1 (<1%)	0
Other	121 (29%)	11 (3%)	1 (<1%)	2 (<1%)	108 (26%)	11 (3%)	2 (<1%)	0
Vascular disorders								
Thromboembolic event	20 (5%)	7 (2%)	1 (<1%)	0	29 (7%)	7 (2%)	1 (<1%)	0
Hypotension	18 (4%)	4 (1%)	2 (<1%)	0	12 (3%)	0	2 (<1%)	0
Other	23 (6%)	3 (<1%)	2 (<1%)	0	24 (6%)	2 (<1%)	1 (<1%)	0
Skin and subcutaneous disorders	122 (30%)	4 (1%)	0	0	125 (31%)	8 (2%)	0	0
Metabolism and nutrition disorder	58 (14%)	5 (1%)	0	0	40 (10%)	5 (1%)	0	0
Cardiac disorders								
Dysrhythmia	17 (4%)	1 (<1%)	0	0	14 (3%)	0	0	0
Other	24 (6%)	1 (<1%)	1 (<1%)	1 (<1%)	12 (3%)	4 (1%)	0	0
Renal and urinary disorders								
Haematuria	6 (2%)	0	0	0	1 (<1%)	0	0	0
Other	20 (5%)	7 (2%)	0	0	15 (4%)	0	1 (<1%)	0
Immune system disorder	6 (2%)	1 (<1%)	0	0	9 (2%)	2 (<1%)	0	0
Hepatobiliary disorders	5 (1%)	2 (<1%)	1 (<1%)	0	4 (1%)	0	1 (<1%)	0
Secondary malignancy possibly related to Hodgkin lymphoma treatment	0	2 (<1%)	7 (2%)	1 (<1%)	0	0	4 (1%)	1 (<1%)

Data are n (%). Adverse events that occurred in at least 10% of patients in either group and all grade 3–5 adverse events are shown. AST=aspartate aminotransferase. ALT=alanine aminotransferase.

Table 4: **Adverse events per treatment group in the safety population**

The most common treatment-emergent adverse events of any cause or grade were haematological toxicity, gastrointestinal disorders, and general disorders such as fatigue, fever, and infections (table 4). The most common grade 3–4 adverse events were leucopenia (381 [92%] of 412 in the standard treatment group and 387 [95%] of

407 in the PET-driven treatment group), neutropenia (359 [87%] and 366 [90%]), anaemia (286 [69%] and 114 [28%]), thrombocytopenia (271 [66%] and 163 [40%]), febrile neutropenia (145 [35%] and 93 [23%]), infections (88 [22%] and 47 [11%]), and gastrointestinal disorders (49 [11%] and 48 [11%]). Serious adverse events related to treatment were reported in 192 (47%) patients in the standard treatment group and 114 (28%) in the PET-driven treatment group, and were mainly infections (84 [20%] and 50 [12%], respectively) and febrile neutropenia (21 [5%] and 23 [6%]). Six (1%) patients in the standard treatment group died from serious adverse events deemed related to study treatment (two from septic shock, two from pneumopathy leading to acute distress syndrome, one from heart failure, and one from acute myeloblastic leukaemia), as did two (<1%) in the PET-driven treatment group (one from septic shock after the first cycle of BEACOPP$_{escalated}$, and one from acute myeloblastic leukaemia).

In a preplanned analysis, 15 secondary primary malignancies have been reported, including ten (2%) among patients in the standard treatment group (four acute myeloid leukaemia, one non-Hodgkin lymphoma, two breast cancer, two cutaneous basal-cell carcinoma, and one lung cancer) and five (1%) among patients in the PET-driven treatment group (one acute myeloid leukaemia, two non-Hodgkin lymphoma, one renal cancer, and one thyroid cancer). 73 pregnancies have been reported since the start of treatment including 28 (7%, 95% CI 5–10) in the standard treatment group and 45 (11%, 8–15) in the PET-driven treatment group (p=0·036). Assisted reproduction was required in six (21%) and three (7%) pregnancies, respectively.

Discussion

To our knowledge, AHL2011 is the first large phase 3 randomised study that has compared standard treatment with PET-driven treatment head to head in patients with advanced Hodgkin lymphoma. Interim PET monitoring of chemotherapy response led to similar outcomes as standard treatment. Reducing treatment intensity in patients who achieved early metabolic response was safe and does not compromise disease control in these patients. Indeed, the primary endpoint of the study was met, with patients in the standard treatment group having a 5-year progression-free survival of 86·2% (95% CI 81·6–89·8) and those in the PET-driven treatment group 85·7% (81·4–89·1). PET2 was negative in 84% of patients in the ITT population (88% in patients assessable for PET2) and, therefore, our findings suggest that high-dose-intensity chemotherapy beyond the first two cycles of BEACOPP$_{escalated}$ is not needed in most patients. Indeed, 97% of PET2-negative patients were assigned ABVD and received ABVD in this study. Furthermore, the frequency of early treatment-related toxicity and the risk of treatment discontinuation due to toxicity were lower among patients who received ABVD than among those who continued taking BEACOPP$_{escalated}$ Long-term toxicity might also be reduced although follow-up so far is too short to draw firm conclusions. In this analysis, we observed lower incidence of secondary primary malignancies in patients who received ABVD than in those who continued BEACOPP$_{escalated}$, as has been found in previous studies.[2,8] Additionally, there were significantly more pregnancies reported in the PET-driven treatment group than in the standard treatment group. Further fertility parameters are to be analysed.

The secondary endpoints results of the biological and genetic parameters related to the Hodgkin lymphoma cells and the tumour microenvironment that affected PET2 and PET4 responses and progression-free survival will be reported elsewhere.

As well as Deauville scores 4 and 5, we applied maximum standardised uptake value thresholds for ^{18}F-FDG in tumours compared with the liver, as has been recommended,[18,19] which improved accuracy when deciding which patients were eligible for ABVD de-escalation treatment and who should continue to receive BEACOPP$_{escalated}$. Use of maximum standardised uptake values might help nuclear medicine physicians and clinicians to make treatment decisions because values for the liver and residual tumour mass can be easily obtained. We recommend this modification to the definition of PET2 positivity and to make decisions about PET-driven BEACOPP$_{escalated}$ dose de-escalation in routine practice.

Choosing the Deauville score cutoff for positive PET results is important to minimise the risk of false-positive results. The HD18 study[24] included Deauville score 3 in the definition of PET2 positivity, which more than doubled the proportion of patients with positive results, leading to non-inferiority of treatments, compared with all other previous studies of PET-guided chemotherapy for advanced Hodgkin lymphoma, which used Deauville scores of 4 and 5 to indicate PET positivity and in which outcomes were inferior for PET2-positive patients.[25–28] The inappropriate Deauville score cutoff used in the HD18 study had three main consequences: the prognostic value of PET2 was decreased, only 48% of patients were eligible to reduce BEACOPP$_{escalated}$ treatment to four cycles instead of six or eight, and the apparent good outcomes among patients with positive PET2 scans is probably overestimated, as this group is likely to include an increased number of patients with false-positive PET2 results. Thus, the PET-guided strategy proposed by the GHSG[1] should not be adapted to include patients with Deauville score 3 after two cycles of BEACOPP$_{escalated}$. The GHSG has shown that outcomes are similar in patients with Deauville scores of 3 and 1–2 and have further stated that patients with Deauville score 3, who represented about 25% of the whole HD18 cohort, could benefit from a de-escalated strategy.[29] Unfortunately, whether de-escalation would have been possible to four cycles of BEACOPP$_{escalated}$ in patients with a Deauville score of 3 in

the HD18 study without impaired outcome cannot be established from the findings.

In our study, 30 (30%) of 100 patients with positive PET2 scans did not achieve a complete metabolic response after two additional cycles of BEACOPP$_{escalated}$ and 13 PET2-negative patients had changed to positive by the time of PET4. The use of PET4 brought additional prognostic value to PET2 results and identified a subset of 5% of patients with very poor outcomes regardless of PET2 result. Conversely, negative results on PET2 and PET4, which was seen in 79% of patients in the ITT population (86% of patients assessed for both PET2 and PET4) was associated with particularly favourable outcomes. Therefore, the full PET-driven strategy including PET2 and PET4 has a strong independent prognostic value for progression-free survival and improved risk stratification for death and disease progression of patients with advanced Hodgkin lymphoma independently of IPS. Our full PET-driven treatment strategy could be further developed to identify patients for whom different treatment options could be proposed compared with those who have the maximum probability of long-term disease control with a safer treatment, such as two cycles of BEACOPP$_{escalated}$ plus four cycles of ABVD. Our results also suggest that PET4 at end of induction therapy (after 4 cycles of chemotherapy) is probably more suitable for management of patients than PET at the end of treatment. First, negative results on PET2 and PET4 are associated with improved outcomes. Second, the 62 patients with positive PET2 scans who had negative PET4 scans maintained a high probability of a favourable progression-free survival without treatment modification. Third, PET4 permitted early identification of patients with progressive disease who needed salvage therapy.

The progression-free survival of patients receiving standard treatment (six cycles of BEACOPP$_{escalated}$) in this trial is similar to that reported with the same regimen in the GHSG HD15 at 5 years (90·3%, 95% CI 87·6–93·8) and HD18 at 3 years (91·4%, 87·0–95·7) studies.[24,30] Of note, similar disease control was achieved in this trial without radiotherapy, unlike the HD15 and HD18 studies in which 11% and 13% of the randomised patients, respectively, received radiotherapy. Further supporting these findings, the relative dose intensity of chemotherapy in our standard treatment group was satisfactory and the proportion of patients with stage IV disease or IPS greater than 3 was greater in AHL2011 than in all other studies of PET-driven treatment except the Southwest Oncology Group S0816 study.[25]

Although cross-trial comparisons may be done with caution, with the improved accuracy of the criteria for PET positivity, the de-escalated PET-driven strategy used in our study was applicable in a higher proportion of patients than in the HD18 study (84% *vs* 48%). In addition, the toxicity observed in PET2-negative patients who received two cycles of BEACOPP$_{escalated}$ plus four cycles of ABVD seems lower than that in patients who received four cycles of BEACOPP$_{escalated}$ in the HD18 study with fewer cases of grade 3 or worse anaemia (24% *vs* 39%) and thrombocytopenia (36% *vs* 57%). The frequency of leucopenia, febrile neutropenia, or sepsis were similar in PET2-negative patients in both studies. Lastly, no excess of pulmonary toxicity related to bleomycin was seen with two cycles of BEACOPP$_{escalated}$ plus four cycles of ABVD in our study. Our results also compare favourably with those of the ECHELON-1 study,[31] which compared treatment of advanced Hodgkin lymphoma with ABVD or doxorubicin, vinblastine, and dacarbazine plus brentuximab vedotin, even with differences in the populations of patients enrolled in the two studies: patients in our study were younger (median age 30 years *vs* 36 years), presented more frequently with stage IIB disease with tumour bulk 10 cm or greater or extranodal localisation (12% *vs* 0), slightly less frequent stage IV disease (60% *vs* 64%), more frequent B symptoms (68% *vs* 59%), and IPS greater than 3 (31% *vs* 26%). Although doxorubicin, vinblastine, and dacarbazine plus brentuximab vedotin showed significant improvement in modified progression-free survival compared with the ABVD group (82·1% *vs* 77·2%), the survival achieved was disappointing. Additionally, doxorubicin, vinblastine, and dacarbazine plus brentuximab vedotin was associated with more toxicity-related serious adverse events (43%), infections worse than grade 3 (18%), and treatment discontinuations related to toxicity (4%) than were seen in the PET-driven treatment group of our study (28%, 10%, and 1%, respectively).

PET-driven strategies were also developed for use after upfront ABVD (appendix p 3).[25–28] PET2 negativity after ABVD ranges from 80% to 84%, compared with 88% after two cycles of BEACOPP$_{escalated}$ in the present study. In addition, the 89·4% 5-year progression-free survival reached in PET2-negative patients after upfront BEACOPP$_{escalated}$ compares favourably to that in patients with negative PET2 scans after ABVD (3-year progression-free survival ranges from 79% to 87%),[25–28] resulting in more patients with better outcomes when using upfront BEACOPP$_{escalated}$. PET2 positivity after upfront ABVD in three studies that enrolled patients with similar features to those enrolled in the AHL2011 study was associated with consistent 64% or lower 3-year progression-free survival, despite a switch to BEACOPP$_{escalated}$, and, therefore, is inferior to the 70·7% 5-year progression-free survival we report after upfront BEACOPP$_{escalated}$. The RATHL study[28] provided better results in PET2-positive patients (3-year progression-free survival 67·5%), but patients in that study had a more favourable baseline profile, with stage II disease in 42% of patients and IPS 3 or greater in only 37%. Altogether, PET-driven strategies after ABVD showed inferior results to those after upfront BEACOPP$_{escalated}$ with less ability to control disease among a higher number of PET2-positive patients despite intensification of treatment. The aggregated data suggest

that the dose intensity of upfront treatment matters for improved outcome in patients with less favourable features.

This study has several limitations. We used a progression-free survival non-inferiority design with a predefined wide margin of 10% between the two treatment groups. At the time the study was launched, this margin seemed relevant because in the worst case non-inferiority of the PET-driven treatment group would be declared with a 5-year progression-free survival greater than 75% compared with standard treatment (ie, higher than the 70% 5-year progression-free survival reported with standard ABVD) and with a balance of effectiveness to toxicity that was probably better than is seen with six cycles of $BEACOPP_{escalated}$. However, we found that the difference in 5-year progression-free survival was much lower (–0·5%, 95% CI –6·1 to 5·0) than the predefined margin and consequently no meaningful difference was detected between the two treatment groups. The ITT analysis was chosen rather than a per-protocol primary analysis of the main endpoint, although the latter is a more conservative approach for demonstrating estimate equivalence for progression-free survival in a non-inferiority study. Primary ITT analysis was preferred because it was difficult to anticipate how many patients would be excluded due to treatment assignment depending on centrally reviewed interim PET scans and the adherence of investigators to this strategy was unknown before the study. The PET-driven strategy was generally well applied, with only 14 (4%) of the 397 patients who had PET2 central review in the PET-driven treatment group not following the treatment assigned per protocol. We did, however, prespecify a per-protocol analysis as a sensitivity analysis and the findings supported the ITT analysis results and suggested that the conclusions were reliable.

In summary, PET used after two cycles of $BEACOPP_{escalated}$ can safely guide subsequent treatment and supports the use of a response-adapted strategy to deliver four cycles of ABVD in patients who achieve early response to treatment without impairing the disease control (treatment was non-inferior compared with six cycles of $BEACOPP_{escalated}$). The full PET-driven strategy allowed de-escalation of BEACOPP-based chemotherapy, consequently improving its tolerability in most patients with advanced stage Hodgkin lymphona. PET4 provided additional prognostic information to PET2 and could identify patients with particularly poor prognosis. Full interim PET staging with the modified Deauville score allowed accurate monitoring of treatment and thus could be considered as a strategy for the routine management of patients with advanced Hodgkin lymphoma.

Contributors

R-OC, RB, PB, JL, HG, AS, JD, A-CG, TG, BJ, KB, EN-V, PF, FM, RD, HF, PQ, AT, HM, L-MF, TL, AD, and MA clinically managed patients at participating study centres. PD, LM, and AT-G did the pathology central review. AB-R, VE, and MM did the PET central review. NM supervised the statistical plan and the statistical analysis. R-OC is the principal investigator, led the design of the study, and drafted the report. All authors contributed to data interpretation, reviewed the drafts, and approved the final version.

Declaration of interests

R-OC has received grants, personal fees and non-financial support from Gilead, Roche, and Takeda, personal fees and non-financial support from Bristol-Myers Squibb, Celegne, and Merck Sharpe & Dohme, and personal fees from Abbvie. PB has received personal fees from Bristol-Myers Squibb, Merck Sharpe & Dohme, and Takeda, grants from Takeda Millenium, and non-financial support from Roche. AS has received personal fees from Takeda. EN-V has received personal fees from Keocyt and Sanofi. FM has received personal fees from Celegne, Gilead, Janssen, and Roche/Genentech. RD has received personal fees from Bristol-Myers Squibb, Celegne, Gilead, Janssen, Karyopharm, Roche, Sanofi, and Takeda. MM has received personal fees from Roche China. The other authors declare no competing interests.

Data sharing

No additional data are available for this Article.

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