A US Intergroup Trial of Response-Adapted Therapy of Stage III–IV Hodgkin Lymphoma using Early Interim FDG–PET imaging (SWOG S0816)

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Supplemental Materials for Intergroup Trial S0816

Eligibility (Details of Inclusion and Exclusion Criteria)

Patients between the ages of 18 and 60 were eligible for this trial if they had stage III-IV HL, as documented by central review of a diagnostic excisional or core needle biopsy. Fine needle aspirations and bone marrow biopsies were inadequate for entry onto this trial. Patients were required to have measurable disease with lymph nodes measuring at least 2 cm in longest diameter, no prior therapy for lymphoma, a performance status of 0-2 (Zubrod), no other serious medical ailments, and not be pregnant or nursing. Patients with a history of hypertension or cardiac symptoms were required to have an echocardiogram or multi-gated acquisition scan (MUGA scan) demonstrating no significant abnormalities, with a cardiac ejection fraction ≥ 45% within 42 days prior to registration. Patients could not be sero-positive for Hepatitis B or Hepatitis C. HIV testing was required prior to registration. HIV-positive patients could not have multi-drug resistant HIV infection, CD4 counts < 150/mcL or other concurrent AIDS-defining conditions. Women and men of reproductive potential were required to use an effective contraceptive method while being treated. A second registration to this trial was performed after patients completed the first two cycles of ABVD. To continue on the trial, patients must not have experienced disease progression during the first two cycles of ABVD, must have submitted baseline and interim PET/CT scans for centralized review to the CALGB Imaging Core Laboratory (CALGB ICL), and must have agreed to begin either continued ABVD or BEACOPP (escalated dose $BEACOPP^3$ for HIV-negative patients, standard dose $BEACOPP^9$ for HIV-positive patients) within 10 days after the interim PET/CT was performed.

ABVD Dose Modifications (applies to all cycles)

Hematologic Toxicity. Although it is common practice in the United States to attenuate doses, administer growth factors, or delay treatment due to cytopenias alone, recent studies have shown that this policy is unneccessary and inadvisable for patients receiving ABVD and results in suboptimal treatment outcomes.[8,9] Physicians were therefore advised that patients on this protocol should receive full doses of ABVD on schedule on Days 1 and 15 of each 28 day cycle without treatment delays, unless neutropenic fever or documented infections are present. In nearly all cases, counts have been shown to recover despite administration of the next course of full dose chemotherapy administered on time.[8,9] If febrile neutropenia occurred on this trial, prophylaxis with antibacterial therapy was recommended for the subsequent cycle (e.g., levofloxacin 500 mg PO daily, Days 4-13 and Days 18-27). Continued anti-bacterial antibiotic use thereafter was at the discretion of the treating physician. In addition, abbreviated G-CSF could be considered (e.g., G-CSF Days 5 to 10 and/or Days 18-23 of each cycle). If a second febrile neutropenia episode occurred, then the doses of vinblastine and doxorubicin were decreased to 75% of the last dose received for the next cycle (in addition to above antibiotic and G-CSF supportive care measures). Dose re-escalation was at the discretion of the treating physician.

Transfusions. Erythrocyte and platelet transfusions were administered as necessary at the discretion of the treating physician.

Severe infection. The occurrence of NCI CTC Version 3.0 Grade 3 or 4 infections due to chemotherapy-related neutropenia required a decrease in the doses of vinblastine and

doxorubicin to 75% of the last dose received. Re-escalation was at the discretion of the treating physician.

Impaired Hepatic Function. All patients with bilirubin ≤ 2 x the upper limit of normal (ULN) received a full initial dose of doxorubicin and vinblastine. If the bilirubin rose to > 2 x ULN (but ≤ 5 x ULN), the doxorubicin and vinblastine doses were reduced by 50% of the last dose received to avoid undue hepatic toxicity. Full doses were resumed once the bilirubin was ≤ 2 x ULN. If the bilirubin rose to > 5 x ULN, doxorubicin and vinblastine were omitted for that cycle. If hepatic function did not recover to ≤ 2 x ULN by the time the next cycle was due, then the patient was removed from protocol treatment. In cases of obstruction of the biliary duct by a tumor mass, a biliary drainage stent was recommended prior to chemotherapy.

Bilirubin	Doxorubicin Dose	Vinblastine Dose
≤ 2 x ULN	100%	100%
> 2 - 5 x ULN	50% (of last dose received)	50% (of last dose received)
> 5 x ULN	0%	0%

Neuropathy. Patients experiencing Grade 3 vinblastine-neuropathy (e.g., obstipation, weakness) had the dose of vinblastine reduced by 50% for all further cycles of ABVD. Patients experiencing Grade 4 vinblastine neuropathy had this drug omitted from all future cycles of ABVD.

Bleomycin-induced pneumonitis or pulmonary fibrosis is not predictable and is often difficult to diagnose clinically. Therefore a high resolution CT scan and pulmonary

function testing were recommended at the slightest suspicion of pulmonary toxicity. Since there are no pathognomonic histological or clinical findings for bleomycin-induced pneumonitis, the diagnosis was made on the basis of clinical, radiological and/or histological findings after excluding other differential diagnoses. If these studies suggested bleomycin toxicity, no further bleomycin was administered.

FDG-PET/CT Imaging

General PET/CT Considerations

This study required FDG-PET/CT imaging at diagnosis, after two cycles of ABVD chemotherapy, and at the conclusion of chemotherapy. FDG-PET imaging was used to assess the adequacy of ABVD chemotherapy for each individual patient and to determine whether treatment should be escalated due to a suboptimal response to two cycles of ABVD. Only full-ring dedicated PET/CT scanners were acceptable and older "stand-alone" FDG-PET scans were not adequate for entry to this study. The CT of the PET/CT was used for attenuation correction of PET data and anatomic localization. CT settings followed institutional guidelines (usually 120-140kV, at least 60mA). A documented daily quality control procedure had to be in place at each imaging facility.

Patient preparation for FDG PET/CT imaging

Non-diabetic patients were instructed to fast for at least 4 hours prior to the scan. Plain (unflavored water) was encouraged during the period of fasting and the uptake period to ensure good hydration. Diabetic patients were given morning appointments and instructed to take their usual anti-diabetic medication (oral hypoglycemic agent or

insulin) and to eat a light meal that morning. The time interval between the morning meal and PET/CT scan was approximately 3-4 hours in most cases. The blood glucose was measured on arrival and consideration given to re-scheduling the scan if the blood glucose level was higher than 200 mg/dl. Insulin was not administered to reduce the glucose level when the blood glucose was > 200 mg/dl at the time of arrival in the PET clinic. Oral diazepam was occasionally administered one hour prior to tracer injection to reduce brown fat uptake. Oral diluted contrast (e.g., Gastografin or 2% barium sulfate) could be administered, according to institutional guidelines. Intravenous contrast could also be administered, provided this was done by a technique that avoided deterioration of the CT images by streak artifacts due to a high-concentration iv. contrast bolus.

Detailed scanning protocol

1. 260 - 555 MBq (7-15mCi) of ^{18}F- FDG was administered.
2. The emission part of the scan was started no earlier than 60 minutes and no later than 80 minutes after injection.
3. The same period of uptake was used for staging and response scans – within 15 minutes.
4. Attenuation corrected 'half-body' PET-CT scans were performed to cover the area from the base of the skull to mid-thigh. This was done with the arms above the head.
5. A separate head and neck scan was done with arms down, ONLY IF this was the only site of disease.
6. Attenuation correction of PET emission data was based on the low dose CT from the PET/CT.

7. It was considered critical that follow-up PET/CT scans be performed in an identical fashion to the baseline scan, with the same PET/CT scanner, same scan direction (skull to thighs or thighs the skull), and consistent arm positioning (arms up or arms down).

Acquisition was performed using the institution's standard protocol, i.e. with regard to time per bed position, 2D or 3D, CTAC parameters, reconstruction parameters etc. Images were reconstructed using OSEM or a similar iterative reconstruction algorithm. Both attenuation-corrected and non attenuation-corrected images were reconstructed. The proposed data acquisition/reconstruction protocol (including details of all the parameters above) had to be discussed with the core lab prior to the start of the study.

Centralized PET/CT Review and Reporting

To ensure the highest standards and consistency between different centers, all FDG-PET/CT scans (baseline, interim, and end of treatment PET/CT scans) were required to be submitted to the CALGB Imaging Core Laboratory at Ohio State University for centralized review. Response determinations and treatment decisions (e.g. continuation of ABVD or switch to BEACOPP) were based on the centralized review of the FDG-PET scan and NOT on scan assessments by local physicians. The crucial FDG-PET scan conducted after the 2nd cycle of ABVD was performed on Day 22-25 of Cycle 2 (i.e. 7-10 days after the Day 15 doses of ABVD during Cycle 2). The second PET/CT scan was scheduled at the start of Cycle 2 of treatment to ensure appropriate timing of response scans. The PET/CT images were electronically uploaded to the CALGB Imaging Core Laboratory on the day of examination (no later than 24 hours

after scanning) using either the CALGB FTP data transfer or AG Mednet service. The following image files were required:

• Attenuation corrected half body images (skull base to mid thigh)

• Non-attenuation corrected half body images

• Half body CT scan

• Attenuation corrected view of head and neck (if performed)

• Non-attenuation corrected view of head and neck (if performed)

• Head and neck CT scan (if performed)

Projection images (MIPs) are not required

The CALGB Imaging Core Laboratory transmitted the scans to the expert reviewers for response determination and then transmitted the results to the SWOG statistical center and to the sites primary contact via email within 72 hours of image receipt .Centralized review was performed by a member of a team of five PET/CT readers. There was one adjudicator in the CALGB Core Lab, for cases where major discrepancies existed between the local site and central PET interpretation. The CALGB Imaging Core Laboratory transmitted the scans to expert reviewers for response determination and then transmitted the results to the SWOG Statistical Center and to the site's primary contact within 72 hours of image receipt (not including weekends). The central PET/CT expert review only focused on the assessment of Hodgkin lymphoma disease sites.

Cycle 3 of chemotherapy could not be administered until the results of the second PET/CT scan were available. Determination of FDG-PET positivity or negativity was

performed using the Deauville 5 point scoring system. According to these guidelines, scans were judged to be positive if lesions were more hypermetabolic than the liver by visual, qualitative inspection. Borderline metabolism in a lesion was considered negative as determined by the international harmonization conference and in concordance with the policies of Gallamini and Hutchinson whose studies established the value of early interim FDG-PET imaging. Absolute and relative standard uptake values (SUVs) were recorded for research purposes but were not used to determine scan positivity because of inter-institution variations in scan performance and the acknowledged lack of standardization for SUV values.

WebEx Conferences and Training

The CALGB Imaging Core Lab enabled Internet based Visual & Virtual conferences that allow the simultaneous display of images (desktop presentations/desktop applications such as PowerPoint) and mutual communication between participating sites and the core lab in a secure manner (SSL-encoded). The Imaging Core Lab organized WebEx meetings for problem shooting, site training and important issue discussions as necessary.

Initial Analysis of the first 10 patients and Monthly Monitoring Calls

The CALGB Imaging Core Lab database tracked all information of site accrual, patient accrual, study compliance/non-compliance and released a monthly report to the SWOG trial committee. After the first 10 patients had completed baseline and interim scans and these scans had been graded by the expert readers, a phone conference was held

among the PET expert readers. Using WebEx, the expert readers jointly assessed these first 10 cases to assure inter-observer agreement. In addition, monthly phone conferences were held among PET expert readers to monitor study progress, address any issues with data transfer, online access to the core lab, scan interpretation, feed-back from core lab or local sites etc. The leader of the PET expert team (H. Schoder), or his designee was available to answer immediate questions from the core lab or other expert readers on a daily basis.

Details of Response Assessments

All measurable lesions up to a maximum of 6 lesions were identified as target lesions at baseline. If there were more than 6 measurable lesions, the remaining were identified as non-target lesions and included as non-measurable disease. The 6 largest lesions were selected, and were chosen to represent disparate regions of the body, including mediastinal and retroperitoneal areas if these sites had measurable lesions. Complete Response (CR) was defined as complete disappearance of all measurable and non-measurable disease with the exception of the following: In patients with a positive PET scan before therapy, a post-treatment residual mass of any size was permitted as long as it was PET negative. If the PET scan was negative before therapy, all nodal masses > 1.5 cm in greatest transverse diameter (GTD) at baseline must have regressed to ≤ 1.5 cm in GTD and all nodal masses > 1 cm and ≤ 1.5 cm in GTD and > 1 cm in their short axis before treatment must have regressed to ≤ 1 cm in their short axis. No new lymphoma lesions could be visible on PET/CT scan or by any other imaging studies. The spleen and/or liver, if considered enlarged at baseline based on physical

examination or imaging study (other than PET), must have regressed in size and not be palpable. If bone marrow was positive at baseline, it had to be negative based on biopsy and aspirate at end of treatment. All disease sites had to be assessed using the same techniques as at baseline. Partial Response (PR) was assigned to patients with at least one lesion that did not qualify for a CR. For patients with measurable disease, ≥ 50% decrease in the sum of the product of the diameters (SPD) of up to six dominant lesions identified at baseline was required. No new lesions and no increase in the size of the liver, spleen, or other nodes was permitted. Splenic and hepatic nodules had to regress by ≥ 50% in SPD. In patients with a positive PET scan before therapy, PET had to be positive in at least one previously involved site. Stable Disease (SD) included patients who did not qualify for CR, PR, or Relapsed/Progressive Disease. Persistent abnormalities seen on CT scans must have been FDG-avid on PET scans. Relapsed Disease (after CR)/Progressive Disease (after PR, SD) was assigned to patients exhibiting at least 50% increase in the SPD of measurable target nodal lesions over the smallest sum observed (over baseline if no decrease during therapy), or ≥ 50% increase in the GTD of any node > 1 cm in shortest axis, or ≥ 50% increase in the SPD of other target measurable lesions (e.g., splenic or hepatic nodules) over the smallest sum observed. In addition, appearance of any new bone marrow involvement or appearance of any new lesion > 1.5 cm in longest axis, or ≥ 50% increase in GTD of any previously involved node with a diameter ≤ 1 cm in the short axis such that its longest axis was >1.5 cm qualified as progressive disease. Lymph nodes were considered abnormal for relapse or progressive disease only if the long axis was > 1.5 cm, or if both the long and

short axes were > 1 cm. In patients with a positive PET scan before therapy, lesions had to be PET positive.

Statistical Analysis

This study pursued two co-primary objectives: 1) to estimate the 2-year PFS rate in HIV-negative patients with advanced stage HL treated with response-adapted therapy; 2) to estimate the 2-year PFS rate in the subset of these patients who were FDG-PET-positive after 2 cycles of ABVD and were subsequently treated with escalated dose BEACOPP. The error rates for the testing associated with the two objectives were split equally between the two hypotheses. Since the hypothesis within FDG-PET-positive patients was nested within the hypothesis for all HIV-negative patients, testing each hypothesis at the 1-sided 0·037 level resulted in an overall 1-sided level of 0.05 (determined via simulation studies). Accrual continued until 60 eligible patients were enrolled in the FDG-PET-positive subgroup. With an estimated PET-positive rate of 20% and an estimated ineligibility rate of 7%, the total sample size was initially estimated to be 300 eligible HIV-negative patients. (Ultimately, 358 HIV-negative patients were accrued to achieve the PET-positive goal with the lower than expected PET+ rate of 18% observed.) Two hundred seventy-eight eligible HIV-negative patients were judged sufficient to estimate the 2-year PFS rate to within 6% (95% confidence interval). In the entire HIV-negative cohort, the historical 2-year PFS estimate of 70% was tested against an alternative hypothesis of 78%. We considered an observed 2-year PFS estimate of 75% or greater to indicate that further investigation of this risk-adapted therapy was warranted, provided other factors such as toxicity appeared

favorable. This hypothesis test had 89% power. With 60 patients in the FDG-PET-positive group, the 2 year PFS rate could be estimated in this subgroup to within 13% (95% confidence interval). In the FDG-PET-positive subgroup, we tested a 2-year PFS estimate of 30% against an alternative hypothesis of 48%, with 87% power. We considered an observed 2-year PFS estimate of 42% or greater to indicate further investigation of this therapy would be warranted, provided toxicity was acceptable. With 278 total HIV-negative patients (of whom 22% patients were projected to be FDG-PET-positive), the overall rates of response, toxicity, and PET positivity could be estimated to within 6% (95% confidence interval). Any toxicity occurring with at least 5% probability was likely to be seen at least once (> 99% chance). An exploratory study was also conducted in a cohort of HIV+ HL patients receiving response-adapted therapy using $BEACOPP_{standard}$ for patients who were PET-positive after 2 cycles of ABVD (rather than $BEACOPP_{escalated}$ as in the HIV-negative cohort). This cohort was analyzed separately from the HIV-negative cohort, using descriptive statistics, and will be reported separately. Toxicity and accrual monitoring was performed by the Study Coordinator, Study Statistician and the Disease Committee Chair. Endpoint monitoring was done by the Study Statistician and Study Coordinator. Accrual reports were generated weekly and formal toxicity reports generated every 6 months. In addition, the Statistical Center, Adverse Event Coordinator at the Operations Office, SAE Physician Reviewer, and Study Coordinator monitored toxicities on an ongoing basis.

Supplemental Figure Legends

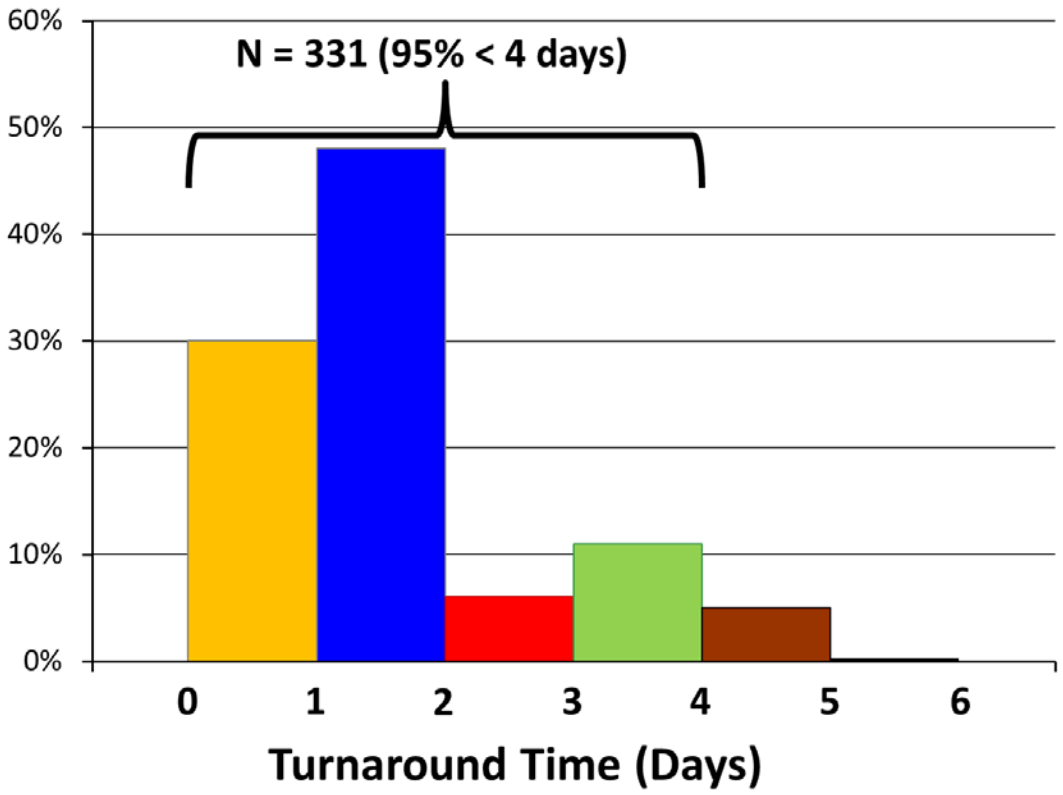
Supplemental Figure S1: Turnaround Time for Reporting of Centralized FDG-PET2 Imaging on SWOG S0816 HIV-negative Patients.

Supplemental Figure S2: Response Rates of 325 HIV-negative patients with HL treated with response-adapted therapy on SWOG S0816. ABVD: CR 96% (258/270), PR 4% (12/270); eBEACOPP: CR 55% (30/55), PR 38% (21/55), Stable Disease 5% (3/55), Non-Assessable 2% (1/55).

Supplemental Figure S3: Severe Toxicities by Treatment Arm on Protocol S0816. The percentages of patients on each treatment arm experiencing any grade 4-5 toxicity, grade 3-5 non-hematologic toxicities, grade 4-5 neutropenia, grade 4-5 thrombocytopenia, grade 3-5 anemia, grade 3-5 febrile neutropenia, and grade 3-5 infection are indicated. ANC = absolute neutrophil count. Yellow bars = Patients allocated to the ABVD arm. Blue Bars = patients allocated to the eBEACOPP arm. All differences were statistically significant at p values <0.0001 by two-sided Fisher's exact test.

Supplemental Figure S4: Ongoing Trials of Interim FDG-PET Imaging for Advanced Stage HL.[5]

Supplemental Figure S1



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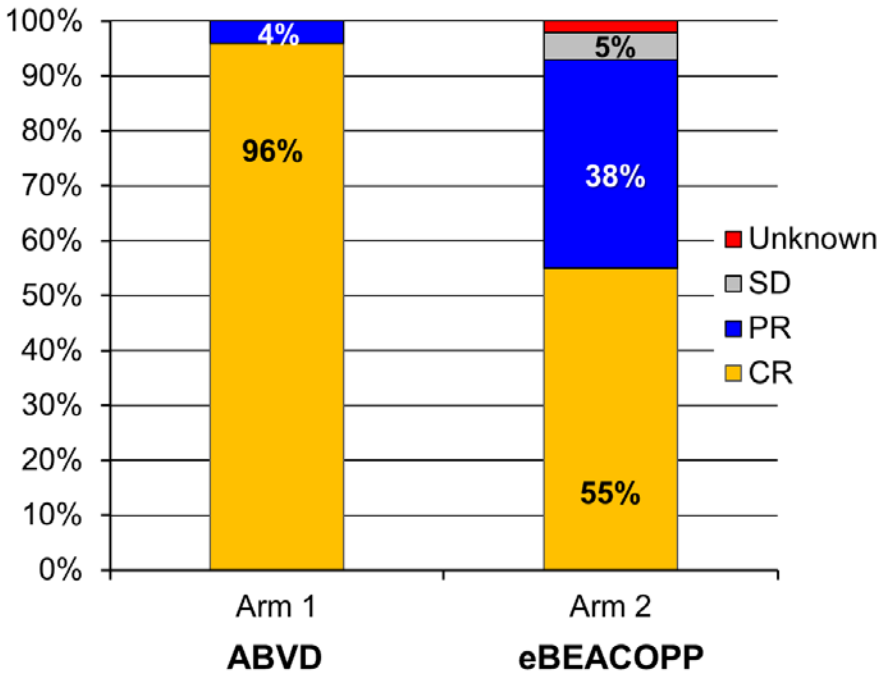
Supplemental Figure S2



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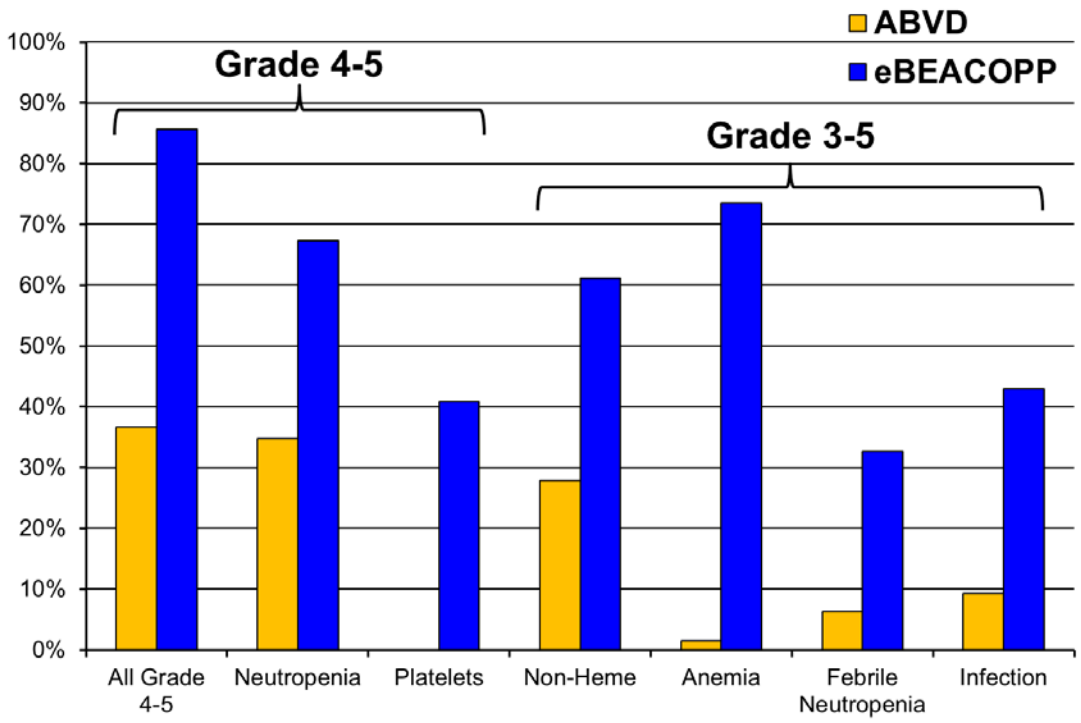
Supplemental Figure S3



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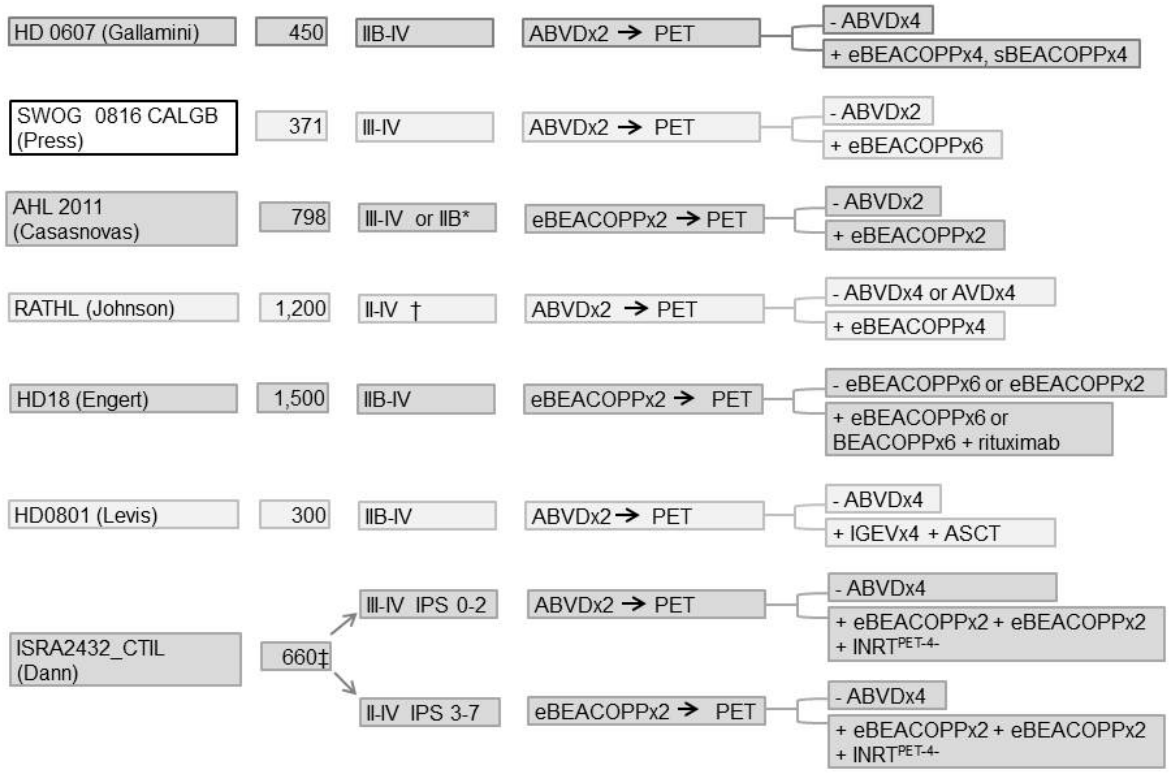
Supplemental Figure S4



Supplemental Figure S4: Ongoing Trials of Interim FDG-PET Imaging for Advanced Stage HL.[5]

Supplemental Table SI:

Drug Doses and Schedules of the BEACOPP baseline and escalated regimens.

Supplemental Table I: Drug doses and schedules of the BEACOPP baseline and escalated regimens																			
Day of Study		Baseline [mg/m^2]	Escalated [mg/m^2]	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	22
B	Bleomycin	10	10								▼								**restart**
E	Etoposide	100	200	▼	▼	▼													
A	Doxorubicin (Adriamycin™)	25	35	▼															
C	Cyclophosphamide	650	1250	▼															
O	Vincristine	1.4	1.4								▼								
P	Procarbazine	100	100	■	■	■	■	■	■	■									
P	Prednisone	40	40	■	■	■	■	■	■	■	■	■	■	■	■	■	■		
	G-CSF subcutaneously										►	►	►	►	►	►			

Supplemental Table SII:

Relative Dose Delivery of Drugs on Protocol S0816 (HIV-negative patients only)

Supplemental Table II: Relative dose delivery of drugs on Protocol S0816 (HIV-negative patients only)								
ABVD	**N**	**Doxorubicin**	**Bleomycin**	**Vinblastine**	**Dacarbazine**			
Step 1 (Cycles 1-2)	336	99.3 ± 3.6%	98.4 ± 7.0%	98.4 ± 5.1%	99.4 ± 3.6%			
Step 2* (Cycles 3-6)	271	95.8 ± 12.5%	86.6 ± 24.1 %	93.4 ± 15.3%	96.1 ±12.3%			
eBEACOPP		**Doxorubicin**	**Bleomycin**	**Cyclophosphamide**	**Etoposide**	**Vincristine**	**Procarbazine**	**Prednisone**
(Cycles 1-6)†	60	82.3 ± 32.5%	74.1 ± 39.5%	76.0 ± 38.1%	74.8 ± 37.7%	74.0 ± 39.2%	72.1 ± 38.7%	73.5 ± 39.1%

*One patient did not register to step 2; the total actual dose delivered was considered to be 0 for each agent for this patient. An additional 3 patients did not receive any bleomycin in step 2 due to pulmonary toxicities in cycles 1-2. Eleven patients received less than 30% of the planned bleomycin due to toxicities.

†Five HIV-negative, PET2-positive patients did not register to step 2 and another 3 withdrew prior to the start of receiving any step 2 treatment. The total actual dose delivered for each agent was counted as 0 for these nine patients. Another 3 PET-positive patients registered to step 2 but received 4 cycles ABVD instead of 6 cycles BEACOPP; the total actual dose for Bleomycin and Doxorubicin was the sum of actual dose delivered at each cycle for 4 cycles, the total actual dose for other agents was counted as 0. In addition, another 3 patients did not receive bleomycin due to pulmonary toxicities or severe hypersensitivity reactions.

Supplemental Table SIII:

Progression-Free Survival According to Stage of Patients with Advanced Hodgkin Lymphoma Treated on Selected Studies with ABVD regimens.

Supplemental Table III: Progression-free survival according to stage of patients with advanced Hodgkin lymphoma treated on selected studies with ABVD regimens							
Author	**Cooperative Group**	**N**	**Regimen**	**PFS (Stage III-IV Only)**	**PFS ("Unfavorable" Stage I-II)**	**PFS (All Patients)**	**Median Follow Up (Months)**
Press, 2015	US S0816	271	Response-Adapted ABVD	82% (2 yr)	NA	82% (2 yr)	39.7
Gordon[6], 2013	US E2496	793	ABVD or Stanford V	~65%* (5 yr)	~85%* (5 yr)	74%* (5 yr)	76.8
Tao[7], 2014	China	118	ABVD	68.6%	91%	81.4%	62
Diehl[8], 1989	German Hodgkin Study Group HD1 & HD3	89 + 137	COPP-ABVD + radiotherapy	65%§ (2 yr) (stages IIIB-IV on HD3)	80%§ (2 yr) (stages I-IIIA with risk factors on HD1)	NA	20 (HD1) 15 (HD3)
Djeridane[9], 2002	Groupe Ouest et Est des Leucemies et Autres Maladies de Sang H90-A/B	162	Epirubicin Vinblastine Bleomycin Vincristine Cyclophosphamide Methotrexate Methylprednisolone	51.4% (10 yr) (IV only)	74.9% (10 yr) (I-III bulky)	63.9% (10 yr)	120

*Failure-free survival
†Event-free survival
§Freedom-from progression
NA = Not applicable

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